



**HAL**  
open science

## Infective Endocarditis After Transcatheter Versus Surgical Aortic Valve Replacement

Vassili Panagides, Guillermo Cuervo, Jaume Llopis, Mohamed Abdel-Wahab, Norman Mangner, Gilbert Habib, Ander Regueiro, Carlos Mestres, Pilar Tornos, Eric Durand, et al.

► **To cite this version:**

Vassili Panagides, Guillermo Cuervo, Jaume Llopis, Mohamed Abdel-Wahab, Norman Mangner, et al.. Infective Endocarditis After Transcatheter Versus Surgical Aortic Valve Replacement. *Clinical Infectious Diseases*, 2023, pp.ciad464. 10.1093/cid/ciad464 . hal-04196618

**HAL Id: hal-04196618**

**<https://univ-rennes.hal.science/hal-04196618>**

Submitted on 15 Sep 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

**MAJOR ARTICLE**

**Infective Endocarditis After Transcatheter versus Surgical Aortic Valve Replacement**

Vassili Panagides<sup>1\*</sup>, MD, Guillermo Cuervo MD PhD<sup>2\*</sup>, Jaume Llopis MD PhD<sup>3\*</sup>, Mohamed Abdel-Wahab, MD<sup>4</sup>, Norman Mangner, MD<sup>5</sup>, Gilbert Habib, MD, PhD<sup>6</sup>, Ander Regueiro, MD, PhD<sup>2</sup>, Carlos Mestres, MD, PhD<sup>7</sup>, Pilar Tornos, MD, PhD<sup>8</sup>, Eric Durand, MD, PhD<sup>9</sup>, Christine Selton-Suty, MD<sup>10</sup>, Nikolaj Ihlemann, MD<sup>11</sup>, Niels Bruun, MD<sup>12</sup>, Marina Urena, MD, PhD<sup>13</sup>, Enrico Cecchi, MD<sup>14</sup>, Holger Thiele, MD<sup>4</sup>, Emanuele Durante-Mangoni, MD, PhD<sup>15</sup>, Costanza Pellegrini, MD<sup>16</sup>, Helene Eltchaninoff, MD, PhD<sup>9</sup>, Eugene Athan, MD, PhD<sup>17</sup>, Lars Søndergaard, MD, PhD<sup>11</sup>, Axel Linke, MD<sup>5</sup>, Pierre Tattevin, MD, PhD<sup>18</sup>, David del Val, MD, PhD<sup>1</sup>, Quintana, Eduard, MD, PhD<sup>2</sup>, Chu, Vivian, MD<sup>18</sup>, Josep Rodés-Cabau, MD, PhD<sup>1,2\*\*</sup>, Jose. M. Miro, MD, PhD<sup>2,20\*\*</sup> on behalf of TAVI Infective Endocarditis International Registry and ICE investigators

<sup>1</sup>Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada; <sup>2</sup>Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain; <sup>3</sup>Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Spain; <sup>4</sup>Heart Center Leipzig at University of Leipzig, Leipzig, Germany; <sup>5</sup>Herzzentrum Dresden, Department of Internal Medicine and Cardiology, Technische Universität Dresden, Germany; <sup>6</sup>Cardiology Department, APHM, La Timone Hospital, Marseille, France; <sup>7</sup>Department of Cardiac Surgery, University Hospital Zürich, Zürich, Switzerland; <sup>8</sup>Department of Cardiology, Hospital Quiron Barcelona, Spain; <sup>9</sup>Normandie Univ, UNIROUEN, U1096, Department of Cardiology, CHU Rouen, France; <sup>10</sup>Department of Cardiology, University Hospital of Nancy, Nancy, France; <sup>11</sup>Righospitalet, Copenhagen, Denmark; <sup>12</sup>Zealand University Hospital, Roskilde, Denmark; <sup>13</sup>Cardiology

\*Co-primary authorship: these 3 authors equally contributed to this work \*\* These authors contributed equally as senior authors.

**Corresponding authors:** Jose M. Miro, MD, PhD, Hospital Clinic, Villarroel, 170, 08036-Barcelona, Spain; Josep Rodés-Cabau, MD, PhD, Quebec Heart and Lung Institute, Laval University, Quebec City, QC, Canada

Department, Bichat Hospital, Paris, France; <sup>14</sup>Cardiology Department, Hospital Maria Vittoria, Turin, Italy; <sup>15</sup>Internal Medicine, University of Campania 'L Vanvitelli', and AORN dei Colli-Monaldi Hospital, Napoli, Italy; <sup>16</sup>Deutsches Herzzentrum München, Munich, Germany; <sup>17</sup>Department of Infectious Disease, Barwon Health, Deakin University, Geelong, VIC, Australia; <sup>18</sup>Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France; <sup>19</sup>Duke University School of Medicine, Durham, North Carolina, U.S.A.; <sup>20</sup>CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain

**Background:** Scarce data are available comparing infective endocarditis (IE) following surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR). This study aimed to compare the clinical presentation, microbiological profile, management, and outcomes of IE after SAVR vs. TAVR.

**Methods:** Data were collected from the “Infectious Endocarditis after TAVR International” (enrollment from 2005 to 2020) and the “International Collaboration on Endocarditis” enrollment from 2000 to 2012) registries. Only patients with an IE affecting the aortic valve prosthesis were included. A 1:1 paired matching approach was used to compare patients with TAVR and SAVR.

**Results:** A total of 1688 patients were included. Of them, 602 (35.7%) had a surgical bioprosthesis (SB), 666 (39.5%) a mechanical prosthesis, 70 (4.2%) a homograft, and 350 (20.7%) a transcatheter heart valve. In the SAVR vs. TAVR matched population, the rate of new moderate or severe aortic regurgitation was higher in the SB group (43.4% vs. 13.4%, $p<0.001$ ), and fewer vegetations were diagnosed in the SB group (62.5% vs. 82%, $p<0.001$ ). Patients with a SB had a higher rate of perivalvular extension (47.9% vs. 27%, $p<0.001$ ) and *Staphylococcus Aureus* was less common in this group (13.4% vs. 22%, $p=0.033$ ). Despite a higher rate of surgery in patients with SB (44.4% vs. 26.8%, $p<0.001$ ), 1-year mortality was similar (SB: 46.5%, TAVR: 44.8%, log-rank  $p=0.697$ ).

**Conclusions:** Clinical presentation, type of causative microorganism and treatment differed between patients with an IE located on SB compared to TAVR. Despite these differences, both groups exhibited high and similar mortality at 1-year follow-up.

**KEYWORDS:** Infective endocarditis, TAVR, SAVR, heart surgery, prognosis.

#### ABBREVIATIONS LIST

IE: infective endocarditis

IQR: interquartile range

PVE: prosthetic valve endocarditis

SAVR: surgical aortic valve replacement

SB: surgical bioprosthesis

TAVR: transcatheter aortic valve replacement

THV: trans-catheter heart valve

## INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of severe aortic valve stenosis over the past decade [1,2]. In recent years, there has been a notable shift in the preference for TAVR over surgical aortic valve replacement (SAVR), with an increasing number of patients, including those at low surgical risk. One could expect that a less invasive procedure such as TAVR would be associated with a lower rate of infective complications compared to SAVR. However, randomized trials showed similar annual rates of infective endocarditis (IE) following SAVR and TAVR [3,4]. Also, patients treated with TAVR have a different profile, as they have more co-morbid and frail conditions than those undergoing SAVR. Furthermore, some post-procedural complications which are more frequently observed in patients with TAVR such as the need for permanent pacemaker implantation may predispose to bacterial infections over time. Lastly, the specific design of the transcatheter heart valve (THV) with a stent frame and a high amount of metal around the valve may also influence the presentation, management, and outcomes of these patients. Differences in IE presentations after surgical versus percutaneous procedures may help to better understand their pathophysiology and define the most appropriate preventive measures and management. The evolving landscape and changing trend reflect the need for comprehensive research comparing these populations. We therefore sought to compare the clinical presentation, microbiological profile, management, and outcomes of IE after SAVR versus TAVR.

## METHODS

### Study population

Data were collected from two registries: “The Infectious Endocarditis after TAVR International Registry” and the “International Collaboration on Endocarditis (ICE) registry”. Details of the design of these registries have been previously reported [5,6].

The “Infectious Endocarditis after TAVR International Registry” included data from 604 patients with definite IE determined by the modified Duke criteria after TAVR from 59 centers in 11 countries across Europe, North America, and South America between June 2005 and November 2020 (**Figure 1**). A dedicated uniform database was used at all sites. Informed consent was obtained before the procedure and the individual anonymized data sharing was performed according to the local ethics committee of each participating center.

The ICE Prospective Cohort Study (ICE-PCS) database contains prospective data on 5,591 patients with definite and possible IE collected between 1<sup>st</sup> January 2000 and 31<sup>st</sup> December 2006. The

ICE-Plus database contains prospective data on 2,124 patients with IE collected between 1<sup>st</sup> September 2008 and 31<sup>st</sup> December 2012. Overall, sites from 30 countries participated in both cohorts. Data for each patient were collected prospectively on a standardized case report form by site investigators. Both databases are maintained at the Duke University School of Medicine, which serves as the coordinating center for the ICE studies, and approvals were obtained from the institutional review boards of the Duke University School of Medicine. Only 1,338 patients with a prosthetic valve endocarditis located on the aortic valve were included in this study.

### **Study definitions**

The definition of definite IE was based on the modified Duke criteria [7]. Outcomes were defined according to the Valve Academic Research Consortium-2 criteria [8]. Persistent bacteremia was defined as positive blood cultures despite appropriate antibiotic therapy for > 7 days. Early IE was defined as IE occurring within 1-year after surgery according to the European guidelines [7].

### **Statistical analysis**

Categorical variables were expressed as absolute number and percentages. Continuous variables were expressed as mean (SD) or medians (interquartile range [IQR]) for normal and non-normal distributions, respectively. Differences between groups were assessed using the  $\chi^2$  test, Fisher exact test, Student t-test, or Mann-Whitney U test, as appropriate. A 1:1 paired matching approach was used (between patients treated with SAVR and TAVR) to create comparable populations based on different baseline variables. By using this approach, we aimed to balance the distribution of covariates between two groups reducing potential confounding factors and making the population more comparable. The following variables were included for matching: age, sex, diabetes, chronic renal failure, and previous IE episode. Patients were selected by 1:1 matching without replacement using the nearest neighbor method. A caliper width of 0.2 of the pooled standard deviation of logit propensity scores was used for matching. The balance of the distribution of the baseline characteristics between the 2 groups was assessed by evaluating the absolute standardized differences. The risk of all-cause 1-year mortality was evaluated with the use of logistic regressions. The multivariable analysis was performed using all significant variables in univariable analyses ( $p < 0.05$ ). Kaplan-Meier survival curves were compared using log-rank test. Statistical significance was 2-sided for all comparisons, and a  $p < 0.05$  was considered significant. Stata v.15.0 (College Station, TX) was used for all analyses.

## **RESULTS**

## Study population baseline characteristics

A total of 1688 patients were included (**Figure 1**). IE involved a SB, a mechanical prosthesis, a homograft, or a THV in 602 (35.7%), 666 (39.5%), 70 (4.2%), and 350 (20.7%) patients, respectively. The baseline characteristics of the population are presented in **Table 1**. Patients with IE located on a mechanical valve, or a homograft were younger (64.6 years IQR [53.2-72.9] and 50.2 years IQR [38-64.9] respectively) compared to those with a SB or a THV (73.8 years IQR [66.1-78.5] and 80 years IQR [74.6-84] respectively),  $p < 0.001$ . Patients with IE on the THV had more comorbidities (chronic obstructive pulmonary disease, cerebrovascular disease, and chronic kidney disease) compared with the remaining groups. A previous IE episode was more frequent in patients with SB (20.0%), mechanical valve (20.6%) and homograft (51.4%), compared to patients post-TAVR (1.4%). IE after TAVR affected respectively 159 (45.4%) and 191 (54.6%) self and auto-expandable THV. The mean STS score of patients before TAVR was 7.2 (SD: 6.5).

## Infective endocarditis episode

Early IE ( $\leq 12$  months) was more frequently found in patients after TAVR (65.3%) than in patients with SB (40.8%), mechanical prosthesis (41.5%) or homograft (50.0%) ( $p < 0.001$ ). The rate of new moderate or severe aortic regurgitation was higher in SB (39.4%), mechanical valve (36.3%), and homograft (63.8%) compared to patients with a THV (15.7%). However, the presence of a vegetation was more common in patients with IE post-TAVR (83.4%) compared to patients with SB (62%), mechanical valve (60.2%) or homograft (68.6%) ( $p < 0.001$ ). Perivalvular extension was also more prevalent in patients with IE following SAVR (bioprosthesis: 38.8%, mechanical valve: 35.4%, homograft: 39.4%) compared to patients with IE post TAVR (26.0%) ( $p < 0.001$ ). The main causative micro-organism was coagulase negative staphylococci (19.4%) in the SB population, *Staphylococcus aureus* (21.2%) in the mechanical valve population, *Streptococcus viridans* (28.6%) in the homograft population, and enterococcus species in the THV group (24.7%). Clinical presentation was characterized by a lower incidence of stroke and systemic embolism but more heart failure episodes and persistent positive blood cultures in the TAVR group compared to the patients who had SAVR.

## Outcomes

During the index endocarditis hospitalization, patients with an infected SB, mechanical valve or homograft had more frequent cardiac surgery (46.5%, 44.2%, 49.3%, respectively) than those with an infected THV (24%) ( $p < 0.001$ ). Before propensity match adjustment, in-hospital mortality ( $p = 0.006$ ) and 1-year all-cause mortality was higher in patients after TAVR compared to SAVR (log-rank  $p = 0.0002$ ) (**Figure 2**).

## Propensity matched cohorts

The main characteristics and outcomes of the propensity matched cohorts (SB and THV) are shown in **Table 2**. After matching, early IE was more frequent after TAVR than in patients with a SB (64.8% vs. 44.8%,  $p=0.006$ ). IE episodes  $\leq 3$  months were similar between groups ( $p=0.374$ ). Patients with a SB had higher rates of moderate or severe aortic regurgitation (43.4% vs. 13.5%,  $p<0.001$ ). Perivalvular extension was also more frequent in patients with a SB (47.9%) compared to THV (27%),  $p<0.001$ . Causative microorganisms were similar except for a higher incidence of *Staphylococcus aureus* in the THV group (13.4% vs. 22%,  $p=0.03$ ). Patients with IE on a SB had a higher rate of stroke (16.6% vs. 8.9%,  $p=0.023$ ) compared to TAVR-IE patients. Despite a higher rate of patients managed surgically in the SB group (44.4% vs. 26.8%,  $p<0.001$ ), patients with a SB had a similar in-hospital (38.0 vs. 31.8%,  $p=0.196$ ) and 1-year estimated mortality (46.5% vs. 44.8%, log-rank  $p=0.697$ ) compared to patients with a THV (**Figure 3**). After matching, the THV cohort consisted of 93 (46.5%) patients who received a self-expandable THV and 107 (53.5%) patients with an auto expandable THV. The rate of moderate to severe aortic regurgitation was similar between these prostheses: 15.1% patients with self-expandable THV vs. 12.3% with auto expandable THV ( $p=0.549$ ). Mean STS score of the TAVR cohort was 6.1 (SD: 5.8). A description of early IE cohort in the propensity matched population ( $n=156$ ) is available in **Supplemental Table 1** and show similar results except for comparable rate of perivalvular extension between the two populations. The description of a matched mechanical valve population ( $n=130$ ) and THV population ( $n=130$ ) is available in **Supplemental Table 2**. These matched cohorts exhibit comparable disparities in terms of aortic regurgitation, peri-annular damage, vegetation, rates of surgical intervention, and comparable mortality echoing the findings observed between the matched SB and THV cohorts.

### Patients treated with surgery

A description of the surgically treated patients in the matched population is available in the **Supplemental Table 3**. Among patients undergoing surgical therapy for IE, intracardiac complications were more common in both SB and THV group, respectively: new moderate or severe aortic regurgitation (55.8% and 28.3%,  $p=0.002$ ), intracardiac vegetation (69.8% and 90.6%,  $p=0.004$ ), perivalvular extension (67.4% and 43.4%,  $p=0.005$ ) and heart failure (51.7% and 62.3%,  $p=0.636$ ). Among this subgroup of surgically treated patients, the most frequent causative organism was coagulase negative staphylococcus (40.8%) in patients with SB and enterococcus species in the THV group (24.8%). Death after surgery was high in both SAVR and TAVR groups (42.5% and 32.7% respectively,  $p=0.250$ ).

### Factors associated with death

In the propensity-matched cohort, factors associated with one year mortality in the TAVR population were: perivalvular extension (ORadj: 1.73 95% CI (1.04-2.87),  $p=0.035$ ), heart failure during IE hospitalization (ORadj: 2.50 95% CI (1.50-4.14),  $p<0.001$ ), stroke (ORadj: 2.61 95% CI (1.22-5.61),  $p=0.014$ ) and persistent bacteremia (ORadj: 3.68 95% CI (2.04-6.64),  $p<0.001$ ) (**Table 3**). Factors associated with 1-year mortality in the SB population were: heart failure during

IE hospitalization (ORadj: 2.26 95% CI (1.17-4.35), p=0.015) and stroke (ORadj: 3.32 95% CI (1.34-8.19), p=0.015) (**Table 4**).

## DISCUSSION

The main findings of this study including 1688 patients with an IE after surgical or transcatheter aortic valve replacement are: (i) clinical presentation of the IE episode, causative microorganism and in-hospital complications differed between different aortic valve prostheses; (ii) after paired matching on baseline characteristics, a higher rate of perivalvular extension and new moderate or severe aortic regurgitation was found in the SB group compared to the THV group along with a higher rate of *Staphylococcus aureus* in the THV group; (iii) in-hospital complications and treatment strategies differed between the matched surgical and transcatheter groups; (iv) in-hospital and 1-year mortality were high and similar in both groups.

### Clinical presentation

Numerous studies have investigated factors associated with the occurrence of IE in patients after TAVR [9], and compared the incidence of IE in SAVR vs TAVR [10–12]. However, this study is the first to provide a description of the differences that can be seen in clinical presentation among aortic valves implanted surgically or catheter-based. The number of patients with early IE was higher in patients after TAVR compared to patients with SAVR. This finding may be related to a higher risk of health-care associated IE. A previous work has shown a worrying prevalence of IE  $\leq 30$  days after TAVR [13]. The resistance of causative microorganisms to the antibiotic prophylaxis regimen has been described and could be a potential explanation [13,14]. Interestingly, in the early IE subgroup of the matched population, fewer perivalvular extension (26.9%) were found in patients with SB compared with the global matched cohort merging early and late IE (47.9%). This finding suggests a higher incidence of this complication in patients with SB with late IE. Nevertheless, in this same sub-population, the rate of aortic regurgitation was higher in the SB group and outcomes remained similar between groups. However, caution must be taken concerning these findings given the number of missing data surrounding the timing of the IE episode in patients after SAVR.

The rate of moderate or severe newly diagnosed aortic regurgitation and perivalvular extension differed substantially between subgroups. Indeed, these aortic valve and aorta root complications were higher in SAVR compared to TAVR. These findings may be related to a greater vulnerability of the periaortic structures in patients after SAVR. The surgical manipulation of the aortic tissues and the sutures may explain this susceptibility to the infection. Since differences in the timing of the IE episode have been noticed, this factor could also have influenced the occurrence of these complications. Given the severe impact on the prognosis of perivalvular extension in both surgical valves [15] and THV [16], a better understanding of these differences is of clinical interest.



Patients with an IE on the aortic THV presented with a higher rate of vegetations than patients with SB. The stent frame of the THV could be more favorable for vegetation development than bioprosthetic leaflets. THV endocarditis has been reported to be more obstructive than others [17]. This can be related to the more frequently observed vegetations in this subgroup. Paradoxically, the rate of stroke or systemic embolism was lower in TAVR recipients. A previous work investigating stroke episodes in patients with IE after TAVR suggested that the low rate of embolic events in the TAVR population may be related to the misleading clinical presentation of such events in an elderly and highly comorbid population [18]. Also, vegetations at the level of the stent valve frame may be less prone to systemic embolization than those on valve leaflets. Specific studies with routine cerebrovascular imaging techniques and a precise description of the vegetations are warranted to better investigate these findings.

### **Causative microorganisms**

The causative bacteria implicated in the IE are usually related to the presumed source of entry. The various profile of patients receiving different aortic valves may explain the heterogeneity of causative microorganisms in our population. After adjustment for baseline characteristics, the microbiological profile was similar in the matched cohorts, except for a predominance of *Staphylococcus aureus* in the THV group compared to SB. Del Val et al. found that several factors were associated with *Staphylococcus aureus* IE after TAVR: major bleeding, sepsis complicating TAVR, neurological symptoms or systemic embolism at admission and IE with cardiac device involvement [19]. Therefore, the higher rate of *Staphylococcus aureus* may be related to the higher risk of diagnostic and therapeutic invasive procedures after TAVR-related complications. Interestingly, the rate of enterococcus was similar in both groups after propensity matching suggesting that the high observed rate of this bacteria in TAVR series [20] is probably related the patient's frailty rather than the TAVR procedure itself.

### **Choice of treatment and outcomes**

Cardiac surgery was performed in nearly half of the patients after SAVR, and this was in accordance with the results previously described in the literature [21,22]. The role of surgery in native valve IE has been well investigated and clear recommendations have been established in this setting [23]. However, in the presence of a prosthetic valve, the role of cardiac surgery compared to medical therapy alone has been more controversial [22,24]. In our study, after adjusting for age, sex and comorbidities, patients with a SB were more prone to have surgery to remove the infected material than patients with a THV. These discrepancies may be related to the aforementioned differences in clinical presentation. Indeed, patients with SB had more aortic root complications and embolic episodes with an indication for surgery compared to patients with a THV. The only indication for surgery that was predominant in the THV group was persistent bacteremia in blood cultures. The persistence of bacteremia despite an effective antibiotic therapy can be related to antibiotic resistance or the greater capability of biofilm formation on THV prostheses. However, it is important to consider the impact of the matching process on our findings.

Given the predominance of elderly and potentially frail patients in the TAVR-IE group, similar characteristics were selected in the SB group. Consequently, it is unsurprising that the outcomes including those related to surgical intervention were similar between groups. While our study underlines the high mortality associated with endocarditis, these results do not reflect the overall mortality of SB recipients or patients treated with surgery in a broader sense. Therefore, the impact of our matching process does not allow us to draw definitive conclusions regarding the role of surgery in patients prognosis.

### **Limitations**

This study has some limitations. Due to the retrospective design of the TAVR registry, some data were not available. It is important to acknowledge the temporal disparity between the two cohorts included in this study. The ICE cohort encompasses data collected from 2000 to 2012 while the other cohort included data from 2005 to 2020. This substantial time gap introduces the potential for variations in diagnosis and management patterns over time. Consequently, these differences could introduce time-related bias which may affect the generalizability and interpretation of our findings. Numerous patients had missing data concerning the timing of the IE episode and the hypotheses surrounding this point of interest remain therefore largely uncertain. Scarce data are available about imaging modalities used to define each diagnosis and the differences observed may result from difference in imaging methods. Another limitation could be the primary cause of aortic valve replacement that was not captured in our study and could have influenced our findings. Lastly, due to its multicenter design, diagnosis and treatment modalities of patients may have been different between participating centers.

### **CONCLUSION**

This study underlines differences in clinical presentation, microbiology, complications, treatment, and outcomes of the infectious episode in various transcatheter and surgical aortic valves. After propensity matching, the main differences were the higher rate of valve dysfunction and perivalvular extension in the patients with SAVR and the predominance of *Staphylococcus aureus* in TAVR patients. Despite a higher rate of cardiac surgery in patients with SAVR, their 1-year prognosis was similar compared to their TAVR counterparts. These differences observed suggest that the IE episode characteristics are largely influenced by the type and the method of aortic valve replacement.

### **ACKNOWLEDGMENTS**

We would like to acknowledge the *Infectious Endocarditis after TAVR International Registry Investigators* and the International Collaboration on Endocarditis (ICE) investigators for their substantial contribution to data collection and research (the list of investigators is available in the supplemental material).

Dr Rodés-Cabau holds the Research Chair "*Fondation Famille Jacques Larivière*" for the Development of Structural Heart Disease Interventions.

Dr Panagides has received a research grant from the "*Mediterranean Academic Research and Studies in Cardiology*" association (MARS Cardio).

Dr. Jose M. Miro received a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–23.

**FUNDING:** No specific funding for the TAVI database. No current funding for the ICE registry

**CONFLICT OF INTEREST:** Josep Rodés-Cabau has received institutional research grants, consulting fees, and honoraria for speaking engagements from Edwards Lifesciences, Medtronic, and Boston Scientific. Vassili Panagides has received received institutional research grants from Medtronic, Boston scientific and Microport. Jose M. Miro has received consulting honoraria and/or research grants from Angelini, Contrafect, Cubist, Genentech, Gilead Sciences, Jansen, Lysovant, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside the submitted work. Niels Bruun has received institutional research grants from The Novo Nordisk Foundation, The Augustinus Foundation, The Kaj Hansen Foundation, and Health Insurance Denmark, outside the submitted work. Norman Mangner has received personal fees from Edwards Lifesciences, Medtronic, Biotronik, Novartis, Sanofi Genzyme, AstraZeneca, Pfizer, Bayer, Abbott, Abiomed, and Boston Scientific outside the submitted work. Guillermo Cuervo reports travel support from Angelini Pharma Spain to attend national and international scientific conferences. Emanuele Durante-Mangoni reports grants or contracts from Pfizer, Angelini, Shionogi, Advanzpharma, and Infectopharm; consulting fees from Roche, Genentech, and Pfizer; payment or honoraria for speaking engagements from Pfizer, Angelini, and Shionogi; and travel support from Biotest. The remaining authors have nothing to disclose.

**DATA AVAILABILITY STATEMENT:** The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## REFERENCES

1. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *New England Journal of Medicine* 2019; 380:1706–1715.
2. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *New England Journal of Medicine* 2019; 380:1695–1705.

3. Ando T, Ashraf S, Villablanca PA, et al. Meta-Analysis Comparing the Incidence of Infective Endocarditis Following Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement. *The American Journal of Cardiology* 2019; 123:827–832.
4. Ullah W, Khan MS, Gowda SN, Alraies MC, Fischman DL. Prosthetic Valve Endocarditis in Patients Undergoing TAVR Compared to SAVR: A Systematic Review and Meta-Analysis. *Cardiovasc Revasc Med* 2020; 21:1567–1572.
5. Regueiro A, Linke A, Latib A, et al. Association Between Transcatheter Aortic Valve Replacement and Subsequent Infective Endocarditis and In-Hospital Death. *JAMA* 2016; 316:1083–1092.
6. Wang A. Statement from the International Collaboration on Endocarditis on the current status of surgical outcome in infective endocarditis. *Ann Cardiothorac Surg* 2019; 8:678–680.
7. Habib G, Lancellotti P, Antunes MJ, 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.
8. Kappetein AP, Head SJ, G en ereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012; 60:1438–1454.
9. Stortecky S, Heg D, Tueller D, et al. Infective Endocarditis After Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol* 2020; 75:3020–3030.
10. Cahill TJ, Raby J, Jewell PD, et al. Risk of infective endocarditis after surgical and transcatheter aortic valve replacement. *Heart* 2022; 108:639–647.
11. Bjursten H, Rasmussen M, Nozohoor S, et al. Infective endocarditis after transcatheter aortic valve implantation: a nationwide study. *Eur Heart J* 2019; 40:3263–3269.
12. Fauchier L, Bisson A, Herbert J, et al. Incidence and outcomes of infective endocarditis after transcatheter aortic valve implantation versus surgical aortic valve replacement. *Clin Microbiol Infect* 2020; 26:1368–1374.
13. Panagides V, Abdel-Wahab M, Mangner N, et al. Very early infective endocarditis after transcatheter aortic valve replacement. *Clin Res Cardiol* 2022;
14. Conen A, Stortecky S, Moreillon P, et al. A review of recommendations for infective endocarditis prevention in patients undergoing transcatheter aortic valve implantation. *EuroIntervention* 2021; 16:1135–1140.
15. Chan K-L. Early clinical course and long-term outcome of patients with infective endocarditis complicated by perivalvular abscess. *CMAJ* 2002; 167:19–24.
16. Panagides V, Del Val D, Abdel-Wahab M, et al. Perivalvular Extension of Infective Endocarditis after Transcatheter Aortic Valve Replacement. *Clin Infect Dis* 2021; :ciab1004.
17. Salaun E, Sportouch L, Barral P-A, et al. Diagnosis of Infective Endocarditis After TAVR: Value of a Multimodality Imaging Approach. *JACC Cardiovasc Imaging* 2018; 11:143–146.
18. Del Val D, Abdel-Wahab M, Mangner N, et al. Stroke Complicating Infective Endocarditis After Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol* 2021; 77:2276–2287.
19. Del Val D, Abdel-Wahab M, Mangner N, et al. Infective Endocarditis Caused by *Staphylococcus aureus* After Transcatheter Aortic Valve Replacement. *Can J Cardiol* 2022; 38:102–112.
20. Regueiro A, Linke A, Latib A, et al. Association Between Transcatheter Aortic Valve Replacement and Subsequent Infective Endocarditis and In-Hospital Death. *JAMA* 2016; 316:1083–1092.

21. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA* 2007; 297:1354–1361.
22. Lalani T, Chu VH, Park LP, et al. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. *JAMA Intern Med* 2013; 173:1495–1504.
23. Kang D-H, Kim Y-J, Kim S-H, et al. Early Surgery versus Conventional Treatment for Infective Endocarditis. *New England Journal of Medicine* 2012; 366:2466–2473.
24. Mangner N, Val D del, Abdel -Wahab Mohamed, et al. Surgical Treatment of Patients With Infective Endocarditis After Transcatheter Aortic Valve Implantation. *Journal of the American College of Cardiology* 2022; 79:772–785.

Table 1: Baseline characteristics, infective endocarditis description and outcomes in the whole population.

Variable	<b>Bioprosthesi s</b> N= <b>602</b> ( <b>35.7%</b> )	<b>Mechanical prosthesis</b> N= <b>666</b> ( <b>39.5%</b> )	<b>Homograft</b> N= <b>70</b> ( <b>4.2%</b> )	<b>THV</b> N= <b>350</b> ( <b>20.7%</b> )	p-value
<b>Demography</b>					
Europe, n (%)	291 (49.7)	365 (56.7)	30 (42.9)	287 (82.5)	
North America, n (%)	65 (11.1)	54 (8.4)	10 (14.3)	50 (14.3)	
South America, n (%)	120 (20.5)	82 (12.7)	6 (8.6)	11 (3.1)	<0.001
Asia/Mid East, n (%)	11 (1.9)	32 (5.0)	4 (5.7)	0 (0)	
Australia / New Zealand / Africa, n (%)	98 (16.8)	111 (17.2)	20 (28.6)	0 (0)	
<b>Baseline characteristics</b>					
Year of the episode, median (IQR)	2006 (2003-2009)	2005 (2003-2009)	2005 (2002-2006)	2015 (2013-2017)	
Age, median (IQR)	73.8 (66.1-78.5)	64.6 (53.2-72.9)	50.2 (38-64.9)	80 (74.6-84)	<0.001
Sex (Male), n (%)	429 (71.6)	494 (74.3)	52 (74.3)	237 (67.7)	0.162
Chronic obstructive pulmonary disease, n (%)	70 (18.4)	48 (12.3)	0 (0)	95 (27.1)	<0.001
Cerebrovascular disease, n (%)	33 (8.6)	48 (12.3)	0 (0)	47 (13.4)	0.050
Diabetes mellitus, n (%)	124 (21.1)	141 (21.6)	16 (24.6)	123 (35.1)	<0.001
Mild to severe renal insufficiency	67 (18.0)	58 (15.9)	4 (16.0)	162 (46.7)	<0.001

Previous IE episode, n (%)	119 (20.0)	136 (20.6)	36 (51.4)	5 (1.4)	<0.001
<b>Timing of the IE episode</b>					
Month between prosthesis implantation and IE, mean (SD)	50.8 (59.5)	48.7 (63.1)	38.9 (55.6)	12.3 (14.5)	<0.001
Early IE ( $\leq 12$ months), n (%)	80/196 (40.8)	76/183 (41.5)	13/26 (50)	228/349 (65.3)	<0.001
IE $\leq 3$ months, n (%)	37/196 (18.9)	38/183 (20.8)	7/26 (26.9)	102/349 (29.2)	0.029
<b>Echocardiographic findings</b>					
Mitral valve involvement, n (%)	93 (16.1)	145 (22.4)	7 (10.6)	49 (14.0)	0.001
New moderate or severe aortic regurgitation, n (%)	232 (39.4)	238 (36.3)	44 (63.8)	55 (15.7)	<0.001
Intracardiac vegetation, n (%)	362 (62.0)	393 (60.2)	48 (68.6)	292 (83.4)	<0.001
<b>Perivalvular extension</b>	227 (38.8)	233 (35.4)	26 (39.4)	91 (26.0)	0.001
Abscess, n (%)	222 (38.9)	226 (35.6)	22 (33.9)	75 (21.4)	<0.001
Fistula, n (%)	30 (5.0)	30 (4.5)	3 (4.3)	6 (1.7)	0.087
Nosocomial, n (%)	171 (30.4)	148 (24.1)	7 (10.8)	145 (41.4)	<0.001
<b>Causative micro-organism</b>					
<i>Staphylococcus aureus</i> , n (%)	85 (15.2)	129 (21.2)	12 (19.1)	71 (20.3)	0.058
Coagulase-negative staphylococci, n (%)	108 (19.4)	85 (14.0)	7 (11.1)	67 (19.1)	0.032
<i>Streptococcus Viridans</i> , n (%)	83 (14.9)	66 (10.9)	18 (28.6)	47 (14.0)	0.001
<i>Streptococcus bovis</i> , n (%)	42 (7.5)	48 (7.9)	1 (1.6)	13 (3.9)	0.029
Other streptococci, n (%)	31 (5.6)	28 (4.6)	2 (3.2)	14 (4.2)	0.704
Enterococci, n (%)	105 (18.2)	92 (15.1)	8 (12.7)	83 (24.7)	0.002
<b>In hospital complications</b>					
Fever, n (%)	473 (86.0)	559 (89.0)	51 (83.6)	264 (77.0)	<0.001
Stroke, n (%)	83 (14.0)	119 (18.1)	8 (11.8)	31 (9.3)	0.001
Systemic embolism, n (%)	96 (16.2)	92 (14.1)	17 (24.6)	39 (11.8)	0.031
Heart failure, n (%)	210 (35.9)	186 (28.4)	26 (38.2)	152 (45.8)	<0.001

Persistent positive blood cultures, n (%)	52 (9.1)	51 (8.3)	7 (10.3)	103 (33.9)	<0.001
<b>Treatment / outcomes</b>					
In-hospital surgical therapy (%)	275 (46.5)	293 (44.2)	34 (49.3)	82 (24.0)	<0.001
In-hospital death (%)	154 (25.9)	153 (23.0)	13 (18.6)	110 (32.5)	0.006
One-year mortality (%)	206 (41.1)	194 (35.7)	23 (36.5)	155 (44.3)	0.062
Estimated one-year mortality (95% CI)	37.0 (33.1-41.2)	31.4 (27.8-35.2)	34.5 (24.4-47.3)	47.4 (42.1-53.1)	0.0002*

\*by log-rank test

Table 2: Baseline characteristics, infective endocarditis description and outcomes after propensity matching of the SB and the THV cohorts.

Variable	SB N= 200	THV N=200	p-value
<b>Baseline characteristics</b>			
Age, mean (SD)	75.8 (7.6)	76.3 (8.1)	0.570
Sex (Male), n (%)	135 (67.5)	138 (69.0)	0.747
Chronic obstructive pulmonary disease, n (%)	37 (19.1)	54 (27.0)	0.062
Cerebrovascular disease, n (%)	20 (10.3)	24 (12.0)	0.594
Diabetes mellitus, n (%)	54 (27.0)	57 (28.5)	0.738
Mild to severe renal insufficiency	42 (21.0)	41 (20.5)	0.902
Previous IE episode, n (%)	6 (3.0)	5 (2.5)	0.760
<b>Timing of the IE episode</b>			
Month between prosthesis implantation and IE	50.8 (59.5)	12.3 (14.5)	<0.001
Early IE ( $\leq 12$ months), n (%)	26/58 (44.8)	130/199 (64.8)	0.005
IE $\leq 3$ months, n (%)	14/58 (24.1)	60/199 (29.7)	0.374
<b>Echocardiographic findings</b>			
Mitral valve involvement, n (%)	35 (18.4)	29 (14.5)	0.296
New moderate or severe aortic regurgitation, n (%)	86 (43.4)	27 (13.5)	<0.001
Intracardiac vegetation, n (%)	120 (62.5)	164 (82.0)	<0.001

<b>Perivalvular extension</b>	92 (47.9)	54 (27.0)	<0.001
Abscess, n (%)	91 (47.4)	44 (22.0)	<0.001
Fistula, n (%)	19 (9.5)	4 (2.0)	0.001
Nosocomial, n (%)	74 (39.2)	75 (37.5)	0.737
<b>Causative micro-organism</b>			
Staphylococcus aureus, n (%)	24 (13.4)	44 (22.0)	0.030
Coagulase-negative staphylococci, n (%)	39 (21.8)	35 (17.5)	0.293
<i>Streptococcus Viridans</i> , n (%)	27 (15.1)	24 (12.5)	0.470
<i>Streptococcus bovis</i> , n (%)	9 (5.0)	9 (4.7)	0.879
Other streptococci, n (%)	14 (7.8)	10 (5.2)	0.307
Enterococci, n (%)	38 (21.2)	44 (22.9)	0.695
<b>In hospital complications</b>			
Fever, n (%)	169 (84.5)	156 (80.4)	0.286
Stroke, n (%)	33 (16.6)	17 (8.9)	0.023
Systemic embolism, n (%)	30 (15.3)	23 (12.1)	0.361
Heart failure, n (%)	84 (42.6)	86 (45.0)	0.636
Persistent positive blood cultures, n (%)	21 (10.9)	57 (32.5)	<0.001
<b>Treatment / outcomes</b>			
In-hospital surgical therapy (%)	87 (44.4)	53 (27.3)	<0.001
In-hospital death (%)	76 (38.0)	62 (31.8)	0.196
One-year mortality (%)	93 (46.5)	82 (41.0)	0.268
Estimated one-year mortality (95% CI)	46.5 (39.9-53.7)	44.8 (37.9-52.4)	0.696*

\* by log-rank test

Table 3: Univariate and multivariate analysis of factors associated with 1-year mortality in the THV matched-population (only variables with a p-value <0.2 are displayed).

	<b>Unadjusted Odds ratios</b>	<b>Unadjusted <i>p</i>-value</b>	<b>Adjusted Odds Ratios</b>	<b>Adjusted <i>p</i>-value</b>
<b>Baseline characteristics</b>				
Age	1.02 (0.99-1.05)	0.120		
Male sex	0.64 (0.42-0.98)	<b>0.042</b>	0.67 (0.40-1.14)	0.140
Chronic obstructive pulmonary disease	0.78 (0.49-1.26)	0.318		



Mild to severe renal insufficiency	1.51 (0.93-2.45)	0.098		
<b>Echocardiographic findings</b>				
Mitral valve involvement	2.01 (1.17-3.47)	<b>0.012</b>	1.20 (0.63-2.29)	0.584
New moderate or severe aortic regurgitation	1.46 (0.94-2.26)	0.089		
Intracardiac vegetation	1.70 (1.08-2.69)	<b>0.022</b>	1.34 (0.74-2.42)	0.340
Perivalvular extension	1.74 (1.15-2.64)	<b>0.009</b>	1.73 (1.04-2.87)	<b>0.035</b>
<b>Causative microorganisms</b>				
<i>Staphylococcus aureus</i>	2.12 (1.23-3.63)	<b>0.007</b>	1.25 (0.64-2.43)	0.340
<i>Streptococcus bovis</i>	0.34 (0.11-1.07)	0.065		
<b>Complications during IE hospitalization</b>				
Heart failure	2.63 (1.74-3.98)	<b>&lt;0.001</b>	2.50 (1.50-4.14)	<b>&lt;0.001</b>
Stroke	2.70 (1.46-4.99)	<b>0.001</b>	2.61 (1.22-5.61)	<b>0.014</b>
Systemic embolism	2.12 (1.18-3.81)	<b>0.012</b>	1.65 (0.79-3.47)	0.186
Persistent bacteremia	3.76 (2.21-6.40)	<b>&lt;0.001</b>	3.68 (2.04-6.64)	<b>&lt;0.001</b>

Table 4 – Univariate and multivariate analysis of factors associated with one year mortality in the SB matched-population (only variable with a p-value <0.2 are displayed).

	<b>Unadjusted Odds ratios</b>	<b>Unadjusted p-value</b>	<b>Adjusted Odds Ratios</b>	<b>Adjusted p-value</b>
<b>Baseline characteristics</b>				
Age	1.03 (0.99-1.07)	0.098		
Male sex	0.65 (0.36-1.17)	0.149		
<b>Echocardiographic findings</b>				
Mitral valve involvement	2.02 (0.96-4.27)	0.065		

Intracardiac vegetation	1.90 (1.05-3.46)	<b>0.034</b>	1.50 (0.76-2.95)	0.245
Perivalvular extension	1.57 (0.88-2.78)	0.128		
<b>Causative microorganisms</b>				
<i>Staphylococcus aureus</i>	2.56 (1.03-6.33)	<b>0.042</b>	2.06 (0.79-5.41)	0.140
<b>Complications during IE hospitalization</b>				
Heart failure	2.07 (1.16-3.67)	<b>0.013</b>	2.26 (1.17-4.35)	<b>0.015</b>
Stroke	3.23 (1.45-7.22)	<b>0.004</b>	3.32 (1.34-8.19)	<b>0.009</b>
Systemic embolism	2.01 (0.91-4.43)	0.085		
Persistent bacteremia	2.10 (0.83-5.33)	0.118		

Figure 1: Study flowchart

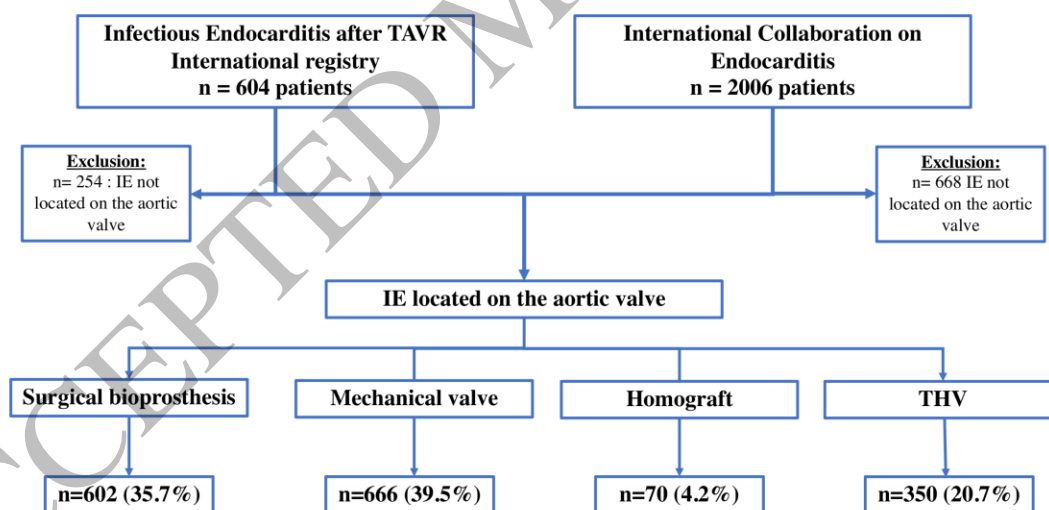


Figure 2: Kaplan-Meier curves comparing survival stratified into the type of valve in the whole population.

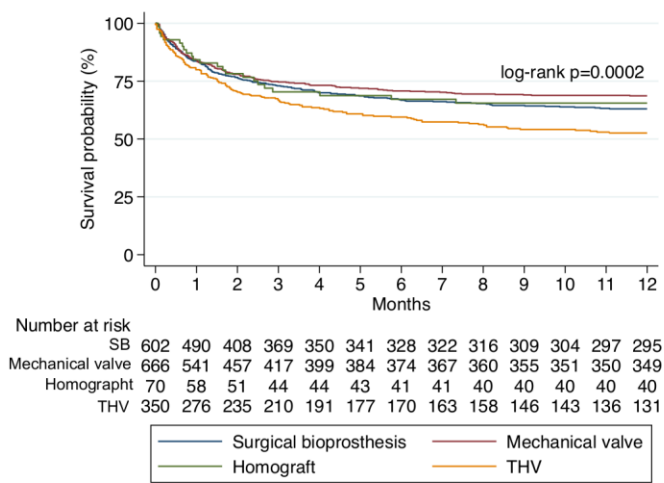


Figure 3: Kaplan-Meier curves comparing survival stratified into the type of valve in the propensity-matched population.

