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JOSÉ CARLOS ROCHA PIRES FERREIRA

# *Incidence of infective endocarditis after transcatheter aortic valve implantation versus aortic valve replacement surgery: a systematic review and meta-analysis*

ARTIGO DE REVISÃO SISTEMÁTICA

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Trabalho realizado sob a orientação de:

PROF. DOUTOR ROGÉRIO PAIVA CARDOSO TEIXEIRA

DR. GONÇALO NUNO FERRAZ COSTA

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# INCIDENCE OF INFECTIVE ENDOCARDITIS AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION VERSUS AORTIC VALVE REPLACEMENT SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS

José Carlos Pires Ferreira[1]; Gonçalo Costa[2], MD; Rogério Teixeira[1,2], MD, PhD

1 – Faculdade de Medicina, Universidade de Coimbra, Portugal

2 – Serviço de Cardiologia, Centro Hospitalar e Universitário de Coimbra, Portugal

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**Abstract**

**Introduction:** Infective endocarditis (IE) after transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) is a rare but life-threatening complication.

**Objective:** To compare the risk of IE between TAVI and SAVR.

**Methods:** We performed a systematic searched PubMed, Embase and Cochrane database, between July and August 2023, to identify observational and interventional studies that reported the event rate of IE in both TAVI and SAVR. A Mantel-Haenszel method and a random-effects model was used to calculate the odds ratio (OR) and 95% confidence interval (CI).

**Results:** Forty-one studies were included in which seventeen were randomised clinical trials. A total of 170720 patients were included, providing 4062 pooled infective endocarditis events (854 in TAVI and 3208 in SAVR), resulting in an incidence of 2% and 2,5% in TAVI and SAVR, respectively. Our meta-analysis revealed a lower incidence of IE in TAVI patients compared to SAVR (pooled odds ratio [OR], 0.72; 95% confidence interval [CI] 0.58, 0.89, $P < 0.01$; $I^2 = 63\%$). However, sub-analysis of randomized controlled trials showed no significant difference between TAVI and SAVR (pooled OR, 0.93; 95% CI [0.66, 1.31], $P = 0.68$, $I^2 = 21\%$). Sub-analysis of surgical risk revealed no significant difference across the surgical risk (low, intermediate, and high), but a trend was noted favouring TAVI in higher surgical risk patients (pooled OR 0.55; 95% CI [0.28, 1.11], $P = 0.09$, $I^2 = 50\%$). Studies reporting IE incidence at 1 year follow-up showed a similar result between groups (pooled OR 0.87; 95% CI [0.59, 1.30], $P = 0.51$, $I^2 = 5\%$), as well at 5-year follow-up (pooled OR 0.76; 95% CI [0.41, 1.41], $P = 0.38$, $I^2 = 78\%$).

**Conclusions:** Our study suggests a lower incidence of IE in TAVI compared to SAVR patients, albeit no significant difference was obtained in randomized controlled trials. These findings possibly highlight discrepancy between real world experience and clinical trials.

**PROSPERO registration number** CRD42023391169.

**Abbreviations**

AS – aortic stenosis

IE – infective endocarditis

TAVI – transcatheter aortic valve implantation

SAVR – surgical aortic valve replacement

ESC – European society of cardiology

## Introduction

Aortic stenosis (AS) is the most common primary valve lesion requiring valvular intervention in Europe and North America. It is most often of degenerative aetiology. Therefore, its prevalence is rising rapidly because of the ageing population.[1]

Surgical aortic valve replacement (SAVR) has long been the gold standard for treatment of aortic valve disease, with well-documented benefits in terms of symptom improvement and survival.[2] In the last decades, transcatheter aortic valve implantation (TAVI) has been developed, and it is increasingly used for patients across surgical risk profiles, leading to an expanded population with prosthetic valves.[3,4] Multiple studies have demonstrated TAVI to be either noninferior or even superior to SAVR.[4–7]

Prosthetic valve endocarditis is the most severe form of infective endocarditis (IE) and occurs in 1–6% of patients with valve prostheses, with an incidence of 0.3–1.2% per patient-year.[8] Although the risk of IE after SAVR is well-characterized, data on the risk of this complication in the setting of TAVI is sparse and limited by either lack of long-term follow-up or a small number of patients.[9] Considering some characteristics of patients eligible for TAVI (i.e., advanced age and high burden of comorbidities), there is an hypothesis that these patients may be more likely to develop IE than those undergoing SAVR, although the former is less invasive and has a shorter hospitalization duration than the latter.[6]

Therefore, we aim to perform a systematic review and meta-analysis comparing patients that underwent TAVI versus SAVR, targeting the rate of post-procedural IE, all-cause mortality, and stroke.

## Methods

### Protocol and registration

This systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (**supplemental Table 1 and 2**) and was registered in the PROSPERO database (CRD42023391169).

### Literature search

We systematically searched PubMed, Embase and Cochrane Controlled Register of Trials (CENTRAL), between July and August 2023, for full-length, and both interventional and observational studies that reported the event rate of IE in both TAVI and SAVR in patients with symptomatic severe AS. The search did not include date or language limits. The full search strategy is presented in **Table 1**.

**Table 1**. Search Strategy.

| Database - MESH | | **Number of results** | | |
|---|---|---|---|---|
| **PubMed Search** | | **Individual Search Results** | **Total Results** | **Date** |
| ((((Endocarditis[Title/Abstract] OR Endocarditides[Title/Abstract] OR Infective endocarditis[Title/Abstract] OR Endocarditides, Infective[Title/Abstract] OR Endocarditis, Infective[Title/Abstract] OR Infective Endocarditides[Title/Abstract]) OR ("Endocarditis"[Mesh])) AND (Transcatheter aortic valve replacement[Title/Abstract] OR Transcatheter aortic valve implantation[Title/Abstract])) OR ("Transcatheter Aortic Valve Replacement"[Mesh])) AND (Surgical aortic valve replacement[Title/Abstract] OR Surgical aortic valve implantation[Title/Abstract] OR Surgical aortic valve repair[Title/Abstract]) | | 1431 | 2403 | 07/07/2023 |
| # | **Embase search** | | | |
| 1 | 'endocarditis'/exp OR endocarditis OR endocarditides OR 'infective endocarditis'/exp OR 'infective endocarditis' OR (infective AND ('endocarditis'/exp OR endocarditis)) | | | |
| 2 | 'surgical aortic valve replacement'/exp OR 'surgical aortic valve replacement' OR (surgical AND aortic AND ('valve'/exp OR valve) AND ('implantation'/exp OR implantation)) OR 'surgical aortic valve repair' OR (surgical AND aortic AND ('valve'/exp OR valve) AND ('repair'/exp OR repair)) OR savr | | | |
| 3 | 'transcatheter aortic valve replacement'/exp OR 'transcatheter aortic valve replacement OR | | | |

| | | | | |
|---|---|---|---|---|
| | (transcatheter AND aortic AND ('valve'/exp OR valve) AND ('replacement'/exp OR replacement)) OR tavr OR 'transcatheter aortic valve implantation'/exp OR 'transcatheter aortic valve implantation' OR (transcatheter AND aortic AND ('valve'/exp OR valve) AND ('implantation'/exp OR implantation)) OR 'tavi'/exp OR tavi | | | |
| 4 | #1 AND #2 AND #3 | 955 | | |
| **CENTRAL search** | | | | |
| Endocarditis OR Endocarditides OR Infective endocarditis AND Transcatheter aortic valve replacement OR Transcatheter aortic valve implantation AND Surgical aortic valve replacement OR Surgical Aortic valve implantation OR Surgical aortic valve repair | | 17 | | |

**Eligibility criteria**

Studies that fulfilled the following criteria were included: (1) patients with severe or very severe AS; (2) comparison between TAVI and SAVR; (3) information on post-procedural outcomes during follow-up was reported, mainly the rates of IE. We excluded studies that didn´t report the outcome of interest, studies that didn´t compare TAVI and SAVR, case reports or editorial material.

**Primary and secondary outcomes**

The primary outcome was the rate of IE. Secondary endpoints were all-cause mortality and stroke.

**Data collection and management**

Two authors (J. Ferreira, G. Costa) systematically screened titles and abstracts of publications retrieved according to a search strategy to select studies that met the inclusion criteria outlined above. Second, identified articles were subjected to full-text review. Any disagreement between them over the eligibility of studies was resolved through discussion and involvement of a third author (R. Teixeira), when necessary. Data were extracted on the study population, main demographics and baseline characteristics, interventions and the outcomes described above. The number of patients in each arm was defined according to the type of intervention (TAVI versus SAVR).

**Risk of bias assessment**

Two review authors (J. Ferreira, G. Costa) independently assessed the risk of bias in the included articles, following the Cochrane Collaboration`s ´risk of bias` tool for randomised controlled trials (RCTs).

The risk of bias in the included observational studies was assessed by a Newcastle-Ottawa Scale for observational studies.

RCTs were assessed as having a ´low`, ´high` or ´unclear` risk for the following biases: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The quality assessment for each study is presented in the ´risk of bias summary` (**supplementary Table 3**) and Newcastle-Ottawa Scale summary (**supplementary Table 4**).

Publication bias was assessed visually using funnel plots. A p value <0.05 was considered statistically significant. Subgroup analysis of randomized controlled trials for primary outcome was performed to assess the intervention effect with the least amount of bias and confounding factors inherent to the study design.

Additionally, a sub-analysis of surgical risk (low, intermediate, and high) and studies reporting IE at 1-, 2- and 5-year follow-up was elaborated.

**Statistical analysis**

To perform statistical analysis, we used Review manager 5.4 from the Cochrane Collaboration, computing meta-analysis of the studies for the endpoints defined (rate of endocarditis, all-cause mortality, and stroke). We pooled dichotomous data using ORs to describe effect sizes and a Mantel-Haenszel procedure in a random-effects model. The mean effect was considered significant if its 95% CI did not include zero. Heterogeneity was assessed statistically using an $I^2$ index (<25% low, 25%-50% moderate, >50% high heterogeneity).

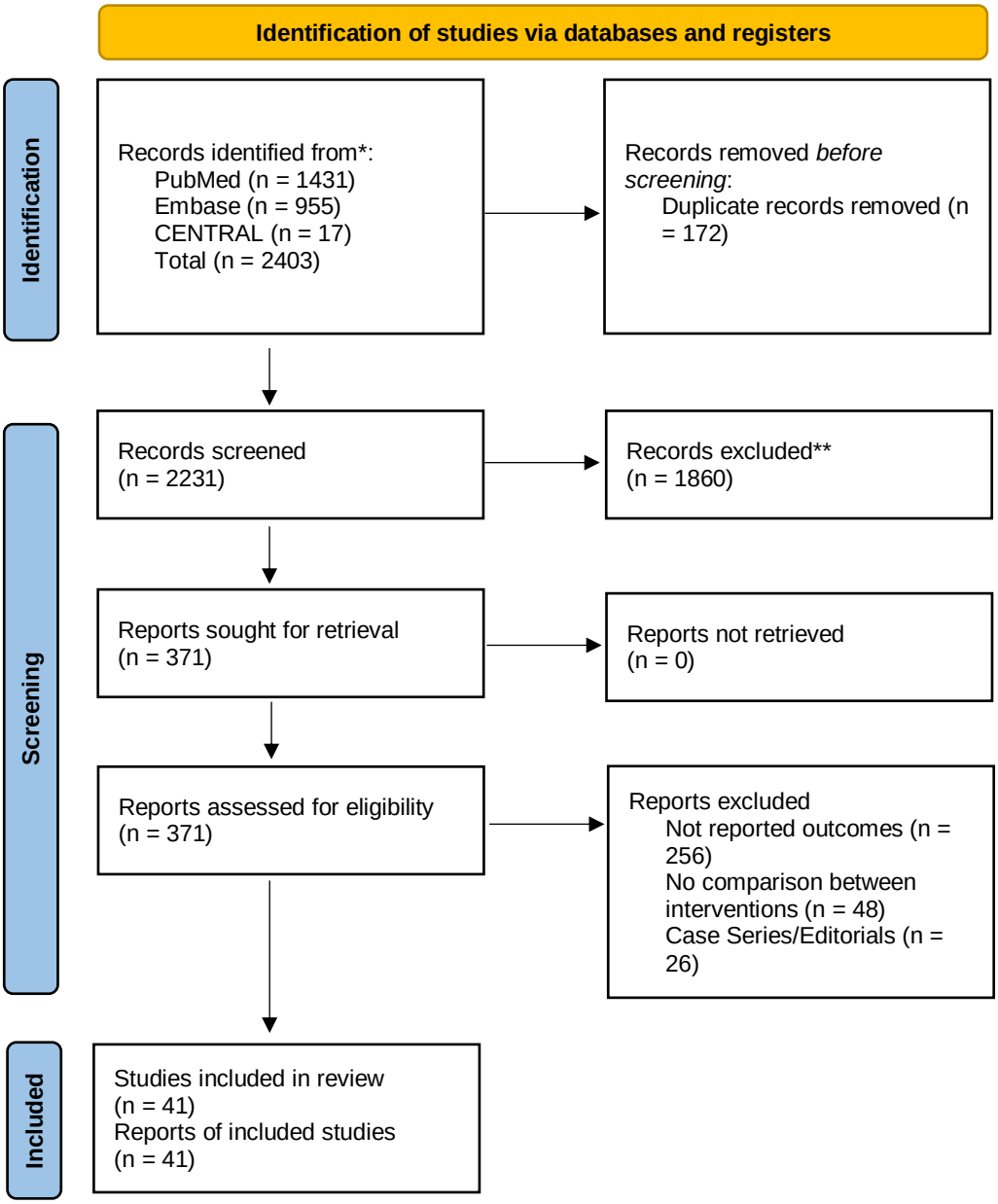



**Figure 1** Flow diagram of literature search. * No automation tools were used in identification of records.

## Results

### Search results

The literature search identified 2403 articles. After removal of duplicates, we excluded 1860 publications according to title and abstract assessment, study type and study population.

Forty-one publications were included (17 RCTs and 24 observational studies) (**Figure 1**), providing a total of 170720 patients, of which 4062 were pooled infective endocarditis events (854 in TAVI and 3208 in SAVR). Study characteristics related to the included studies are described in **Table 2** and demographics and baseline characteristics

of the included patients are summarised in **supplementary Table 5**. IE was adjudicated according to the modified Duke criteria and Valve Academic Research Consortium in most of the studies.

The most common microorganisms are summarised in **supplementary Table 6**. Enterococci and Streptococci are the two most common microorganisms involved in IE post-TAVI, followed by Staphylococcus aureus and Coagulase-negative staphylococci. For IE post-SAVR, Streptococci and Enterococci are the two most common, followed by Coagulase-negative staphylococci and Staphylococcus aureus.

**Table 2.** Study Characteristics.

| | | | | | **EuroSCORE II, %** | | **STS Score, %** | | **Number of patients, n** | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Desing** | **Prosthetic valve endocarditis criteria** | **Study period** | **Follow-up time** | TAVI | SAVR | TAVI | SAVR | TAVI | SAVR |
| Abdelfattah et al 2021[10] | Retrospective cohort | Adjudicated by the investigation team | 2012-2017 | 30 days | NR | NR | NR | NR | 762 | 1278 |
| Amrane et al 2019[11] | Post hoc analysis | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2012-2016 | 1 year | 11.9+-7.6 | 11.6+-8.0 | 4.4+-1.5 | 4.5+-1.6 | 864 | 791 |
| Bianco et al 2019[13] | Retrospective cohort | Based on diagnostic admissions codes. | 2011-2017 | 5 years | NR | NR | 7.96+-4.71 | 2.73+-2.93 | 1034 | 1345 |
| Brízido et al 2021[14] | Retrospective cohort | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2009-2017 | Mean follow-up: 4.5-years | 2.43 (1.71-3.03) | 2.11 (1.49-3.0) | NR | NR | 79 | 79 |
| Butt et al 2019[9] | Retrospective cohort | According to the modified Duke criteria[15] | 2008-2016 | Mean follow-up: 3.6-years | NR | NR | NR | NR | 2632 | 3777 |
| Cahill et al 2022[4] | Retrospective cohort | Adjudicated by the investigation team | 2007-2016 | Mean follow-up TAVI 24.5 months SAVR 53.9 months | 16.1 (10.7-25.3) | 5.8 (3.3-10.1) | NR | NR | 14195 | 91962 |
| Calderón-Parra et al 2023[3] | Prospective cohort | According to the modified Duke criteria[15] | 2015-2020 | Mean follow-up: TAVI 41 months SAVR 38 months | 5.5 (3.2–8.8) | 1.4 (0.8–2.3) | NR | NR | 278 | 355 |
| Conte et al 2016[16] | Post hoc analysis | Adjudicated according to the Valve Academic Research Consortium-1[17] | 2011-2012 | 1 year | 25.6+-16.2 (22.6) | 24.2+-15.8 (21.2) | 7.3+-2.7 (7.0) | 8.0+-3.5 (7.4) | 115 | 111 |

**Continued**

| | | | | | EuroSCORE II, % | | STS Score, % | | Number of patients, n | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Desing** | **Prosthetic valve endocarditis criteria** | **Study period** | **Follow-up time** | TAVI | SAVR | TAVI | SAVR | TAVI | SAVR |
| Deeb et al 2016[18] | Randomised clinical trial | Adjudicated according to the Valve Academic Research Consortium-1[17] | 2011-2012 | 3 years | 17.7+-13.0 | 18.8+-13.2 | 7.3+-3.0 | 7.5+-3.3 | 391 | 359 |
| Dubois et al 2013[19] | Prospective cohort | Adjudicated according to the Valve Academic Research Consortium-1[17] | 2008-2011 | Mean follow-up: TAVI 25 months SAVR 38 months | 7.8 (4.8–12.9) | 7.7 (4.2–13.6) | 7.3 (5.7–10.6) | 6.6 (5.3–10.8) | 73 | 35 |
| Falcon et al 2014[20] | Prospective cohort | According to the modified Duke criteria[15] | 2009-2012 | 1 year | NR | NR | NR | NR | 51 | 102 |
| Fauchier et al 2020[6] | Retrospective cohort | Based on diagnostic admissions codes | 2010-2018 | Mean follow-up: 2.0 years | 3.57 ± 1.04 | 3.55 ± 1.01 | NR | NR | 16291 | 16291 |
| Fernandez-Aviles et al 2022[21] | Prospective cohort | Adjudicated by the investigation team | 2012-2020 | 8 anos | NR | NR | NR | NR | 520 | 652 |
| Forrest et al 2022[22] | Randomised clinical trial | Adjudicated according to Valve Academic Research Consortium-3[23] | 2016-2019 | 2 years | NR | NR | 2.0+-0.7 | 1.9+-0.7 | 725 | 678 |
| Forrest et al 2023[24] | Randomised clinical trial | Adjudicated according to Valve Academic Research Consortium-3[23] | 2016-2019 | 3 years | NR | NR | 2.0+-0.7 | 1.9+-0.7 | 730 | 684 |
| Gleason et al 2018[25] | Randomised clinical trial | Adjudicated according to the Valve Academic Research Consortium-1[17] | 2011-2012 | 5 years | 17.7+-13.0 | 18.8+-13.2 | 7.3+-3.0 | 7.5+-3.3 | 391 | 359 |
| Jorgensen et al 2021[26] | Randomised clinical trial | According to the modified Duke criteria[27] | 2009-2014 | 8 years | NR | NR | 2.9+-1.7 | 2.9+-1.6 | 145 | 135 |
| Leon et al 2016[28] | Randomised clinical trial | According to the modified Duke criteria[27] | 2011-2013 | 2 years | NR | NR | 5.8±2.1 | 5.8±1.9 | 1011 | 1021 |
| Leon et al 2021[5] | Randomised clinical trial | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2016-2017 | 2 years | 1.5 ± 1.2 | 1.5 ± 0.9 | 1.9 ± 0.7 | 1.9 ± 0.6 | 496 | 454 |

**Continued**

| | | | | | EuroSCORE II, % | | STS Score, % | | Number of patients, n | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Desing** | **Prosthetic valve endocarditis criteria** | **Study period** | **Follow-up time** | TAVI | SAVR | TAVI | SAVR | TAVI | SAVR |
| Mack et al 2015[29] | Randomised clinical trial | According to the modified Duke criteria[27] | 2007-2009 | 5 years | NR | NR | 11.8 ± 3.3 | 11.7 ± 3.5 | 358 | 351 |
| Madhavan et al 2023[30] | Retrospective cohort | Adjudicated according to the Valve Academic Research Consortium-2[12] | NR | Mean follow-up: 4.70 years | NR | NR | 5.5+-1.30 | 5.5+-1.54 | 783 | 783 |
| Makkar et al 2020[31] | Randomised clinical trial | According to the Duke's criteria[27] | 2011-2013 | 5 years | NR | NR | 5.8±2.1 | 5.8±1.9 | 1011 | 1021 |
| Moriyama et al 2019[7] | Retrospective cohort | According to the modified Duke criteria[15] | 2008-2017 | Mean follow-up: 3.5±2.6 years | 5.4±5.6 | 5.6±6.6 | 3.9±2.6 | 4.1±3.7 | 2130 | 4333 |
| Muneretto et al 2015[32] | Retrospective cohort | Adjudicated by the investigation team | 2007-2014 | 2 years | 19.5+-6.7 | 19.2+-7.4 | 8.2+-4.2 | 8.3+-4.4 | 367 | 336 |
| Popma et al 2019[33] | Randomised clinical trial | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2016-2018 | 2 years | NR | NR | 1.9±0.7 | 1.9±0.7 | 725 | 678 |
| Ramlawi et al 2022[34] | Retrospective cohort | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2016-2018 | 2 years | NR | NR | 1.9+-0.7 | 1.9+-0.7 | 722 | 680 |
| Reardon et al 2015[35] | Randomised clinical trial | Adjudicated according to the Valve Academic Research Consortium-1[17] | 2011-2012 | 2 years | 17.7+-13.0 | 18+-13.2 | 7.3+-3.0 | 7.5+-3.3 | 391 | 359 |
| Robertson et al 2022[36] | Retrospective cohort | Adjudicated by the investigation team | 2010-2020 | Mean follow-up: TAVI 1.5 years SAVR 3.8 years | NR | NR | NR | NR | 16 | 30 |
| Saito et al 2022[2] | Retrospective cohort | Adjudicated by the investigation team | 2015-2019 | 4 years | NR | NR | 6.7±4.6 | 5.7±6.6 | 230 | 195 |

**Continued**

| | | | | | EuroSCORE II, % | | STS Score, % | | Number of patients, n | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Desing** | **Prosthetic valve endocarditis criteria** | **Study period** | **Follow-up time** | TAVI | SAVR | TAVI | SAVR | TAVI | SAVR |
| Sehatzadeh et al 2012[37] | Post hoc analysis | According to the modified Duke criteria[27] | 2007-2011 | Mean follow-up: 1.4 years | NR | NR | 11.8 ± 3.3 | 11.7 ± 3.5 | 333 | 300 |
| Shehada et al 2018[38] | Prospective cohort | According to the Duke's criteria[27] and confirmed by echocardiography | 2014-2015 | 2 years | 23.1+-13.8 | 8.7+-9.5 | NR | NR | 100 | 100 |
| Sondergaard et al 2019[39] | Randomised clinical trial | According to the modified Duke criteria[27] | 2009-2013 | 6 years | 2.0+-1.3 | 2.0+-1.2 | 3.0+-1.7 | 3.0+-1.6 | 139 | 135 |
| Takeji et al 2020[40] | Retrospective cohort | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2013-2016 | 2 years | NR | NR | 6.2 (4.6–9.3) | 4.7 (3.4–6.3) | 153 | 153 |
| Thourani et al 2016[41] | Prospective cohort | Adjudicated according to the Valve Academic Research Consortium-2[12] | NR | 1 year | NR | NR | 5.2 (4.3-6.3) | 5.4(4.4-6.7) | 1077 | 944 |
| Thyregod et al 2015[42] | Randomised clinical trial | According to the modified Duke criteria[27] | 2009-2013 | 1 year | 1.9+-1.2 | 2.0+-1.3 | 2.9+-1.6 | 3.1+-1.7 | 145 | 135 |
| Thyregod et al 2019[43] | Randomised clinical trial | According to the modified Duke criteria[27] | 2009-2013 | 5 years | 1.9+-1.2 | 2.0+-1.3 | 2.9+-1.6 | 3.1+-1.7 | 145 | 135 |
| Toff et al 2022[44] | Randomised clinical trial | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2014-2018 | 2 years | 2.0 (1.4-3.0) | 2.0 (1.5-3.3) | 2.6 (2.0-3.5) | 2.7 (2.0-3.4) | 458 | 455 |
| Useini et al 2021[45] | Retrospective cohort | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2012-2018 | Mean follow-up: 19.2 months | NR | NR | 4.4 ± 1.5 | 4.3 ± 3.2 | 199 | 182 |
| Vejpongsa et al 2017[46] | Retrospective cohort | Based on diagnostic admissions codes. | 2013 | 30 days | NR | NR | NR | NR | 888 | 3053 |
| Virtanen et al 2020[47] | Retrospective cohort | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2008-2017 | Mean follow-up: 3.6+-2.1 | 5.0+-5.2 | 4.9+-5.9 | 3.5+-2.2 | 3.5+-2.8 | 308 | 308 |
| Waksman et al 2018[48] | Randomised clinical trial | Adjudicated according to the Valve Academic Research Consortium-2[12] | 2016-2018 | 30 days | NR | NR | 1.8 ± 0.5 | 1.6 ± 0.6 | 200 | 719 |

**Concluded**

**Primary outcome**

Our meta-analysis showed that the pooled incidence of post-TAVI IE was 28% lower than that of post-SAVR IE, although with a high amount of heterogeneity in the magnitude of effect between studies (pooled odds ratio [OR], 0.72; 95% confidence interval [CI] 0.58, 0.89, P < 0.01; $I^2$ = 63%) (**Figure 2**). The overall incidence of IE was 2% for TAVI and 2.5% for SAVR.

Restricting the analysis to RCTs, no significant difference was observed between TAVI and SAVR, with low heterogeneity (pooled odds ratio [OR], 0.93; 95% confidence interval [CI] 0.66, 1.31, P = 0.68; $I^2$ = 21%) (**Figure 3**).

Sub-analysis of surgical risk revealed no significant difference across the surgical risk (low, intermediate, and high), with low, no, and moderate heterogeneity (pooled OR 0.76; 95% CI [0.46, 1.23], P = 0.26, $I^2$ = 13%) (pooled OR 1.23; 95% CI [0.86, 1.76], P = 0.26, $I^2$ = 0%) (pooled OR 0.55; 95% CI [0.28, 1.11], P = 0.09, $I^2$ = 50%), respectively. Studies reporting IE at 1 year, 2-year, and 5-year follow-up did not show difference between TAVI and SAVR, with low, moderate, and high heterogeneity (pooled OR 0.87; 95% CI [0.59, 1.30], P = 0.51, $I^2$ = 5%) (pooled OR 0.76; 95% CI [0.48, 1.22], P = 0.26, $I^2$ = 37%) (pooled OR 0.76; 95% CI [0.41, 1.41], P = 0.38, $I^2$ = 78%), respectively (**Figure 4 and 5**).

The funnel plots analysis showed no evidence of publication bias (**supplementary Figure 1**).

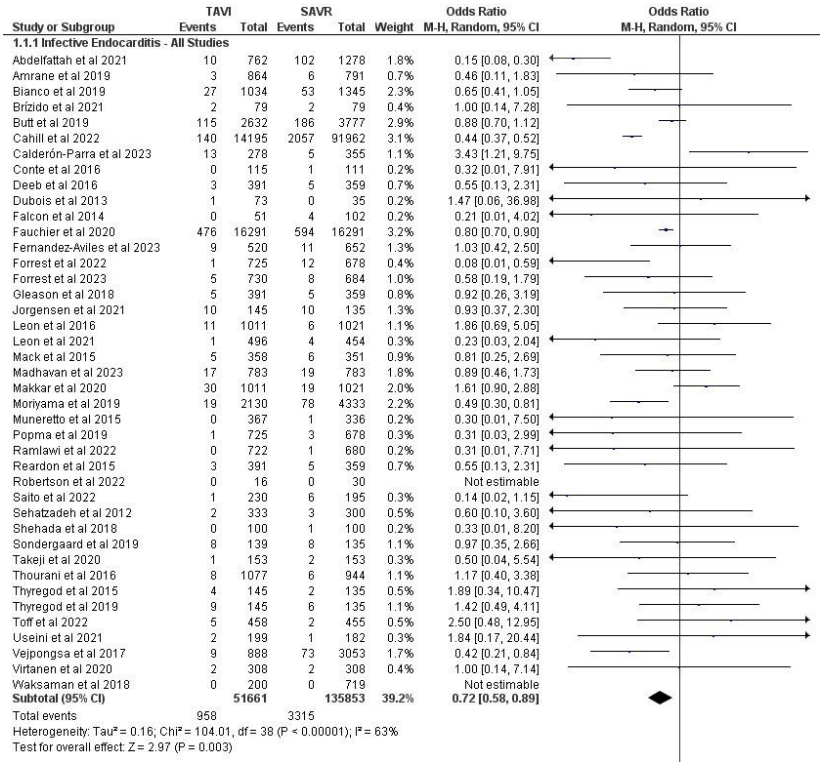



**Figure 2** Forest plot comparing TAVI versus SAVR prosthetic valve endocarditis; M-H, Mantel-Haenszel.

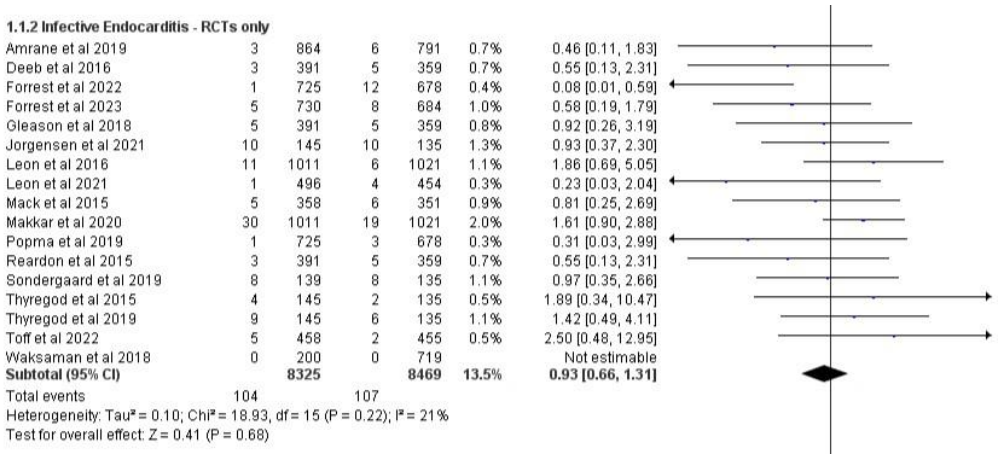



**Figure 3** Forest plot comparing TAVI versus SAVR prosthetic valve endocarditis, only using RCTs; RCTs, randomised controlled trials; M-H, Mantel-Haenszel.

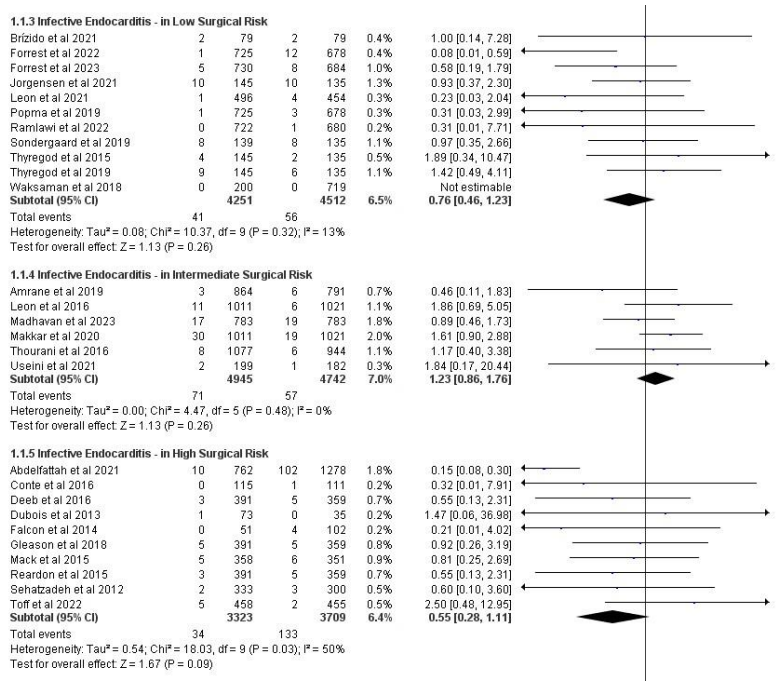



**Figure 4** Forest plot of infective endocarditis in low, intermediate, and high surgical risk patients comparing TAVI versus SAVR prosthetic valve endocarditis; M-H, Mantel-Haenszel.

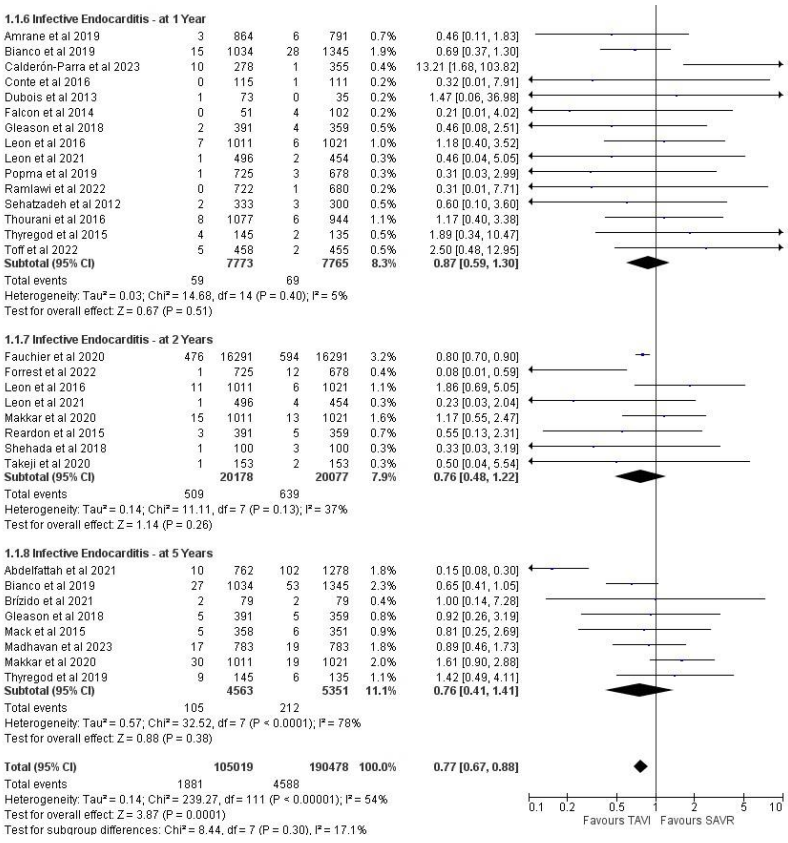
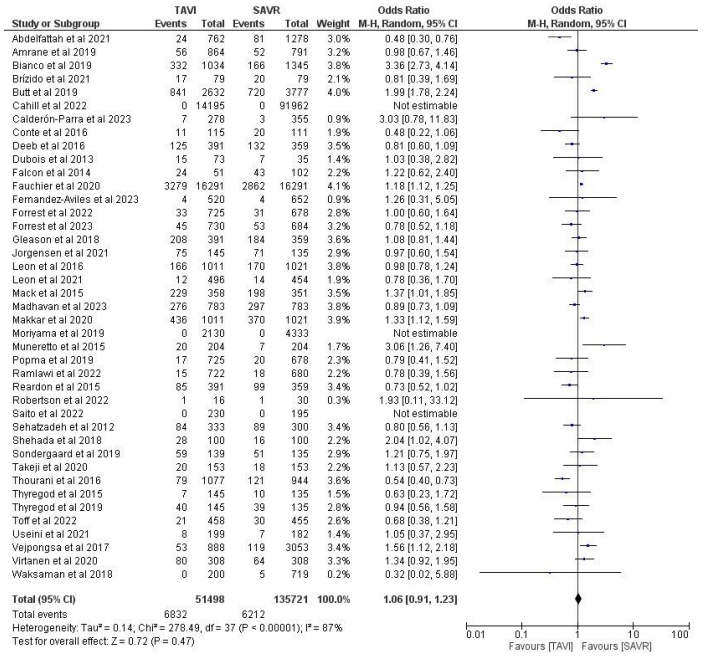



**Figure 5** Forest plot of infective endocarditis at 1-, 2- and 5-years comparing TAVI versus SAVR prosthetic valve endocarditis; M-H, Mantel-Haenszel.

## Secondary outcomes

Regarding secondary end points, no significant differences were noted between TAVI and SAVR for all-cause mortality (pooled OR 1.06; 95% CI [0.91, 1.23], P = 0.47, $I^2$ = 87%) and stroke (pooled OR 0.91 [0.79, 1.05], P = 0.19, $I^2$ = 39%) (**Figure 6**).

(A)




(B)

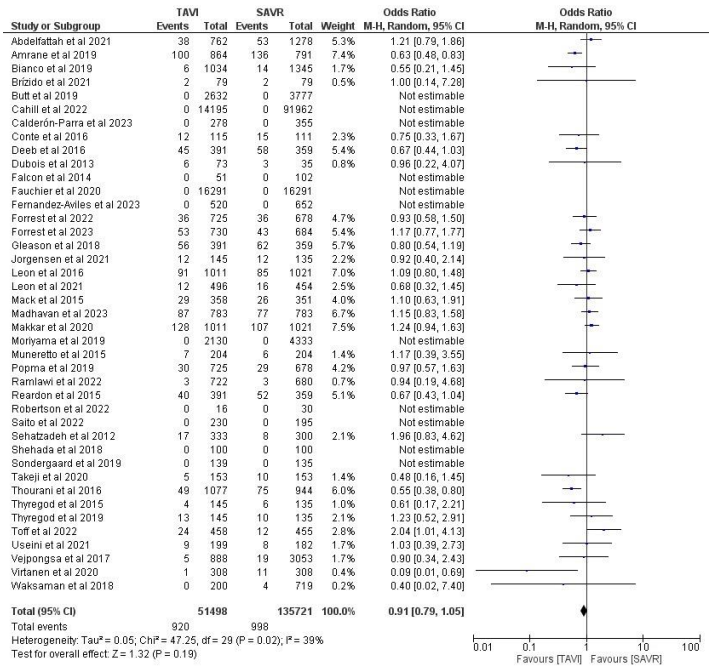



**Figure 6** Forest plot comparing TAVI versus SAVR prosthetic valve endocarditis, (A) all-cause mortality; (B) stroke; M-H, Mantel-Haenszel.

## Discussion

Our key findings are (1) the incidence of post-TAVI IE was 28% lower than that of post-SAVR IE, with an overall incidence of 2% and 2.5%, respectively; (2) sub-analysis of randomized controlled trials showed no significant difference between TAVI and SAVR; (3) Enterococci and Streptococci are the two most common microorganisms involved in IE post TAVI, followed by Staphylococcus aureus and Coagulase-negative staphylococci. For IE post SAVR, Streptococci and Enterococci are the two most common, followed by Coagulase negative staphylococci and Staphylococcus aureus.

To the best of our knowledge this is the first meta-analysis comprising >170 000 patients comparing post-TAVI IE with post-SAVR IE.

Two previous meta-analysis has also compared the incidence of IE between TAVI and SAVR. One including 10 001 patients from 7 studies, showed an incidence of post-TAVI IE 31% lower than that of post-SAVR IE.[49] The other one including 84 288 patients from 19 studies showed no significant difference between TAVI and SAVR patients, at 30-day, 1-year, 2-year and 5-year follow-up.[50]

Prior studies, including RCTs and observational studies, have compared the incidence of post-TAVI IE with post-SAVR IE. In line with our findings, a previous retrospective cohort using the NICOR databases in England reported a cumulative incidence of IE lower after TAVI than after SAVR (1.5% [95% CI 1.3 to 1.8] vs 2.4% [95% CI 2.3 to 2.5], HR 1.60, p<0.001) over a follow-up period of 60 months.[4]

On the other hand, some retrospectives cohort studies like those using data from the Finn Valve Registry, or the Danish National Patient Registry, identified no difference in the incidence of IE.[7,9] Some RCTs, such as the more recent PARTNER 3 trial and the NOTION trial have suggested a similar incidence of IE after TAVI or SAVR.[5,22,24,26,33]

Regardless of whether the incidence of IE after TAVI is lower or similar to that after SAVR, the hypotheses explaining these results could be the same. One possible explanation is that although TAVI population are usually older and with more comorbidities, its less invasive nature, shorter hospitalization duration, the absence of an open sternotomy wound, the reduced need for blood transfusions and self-transfusions, as well as the absence of many other risk factors associated with surgical procedures, means that the patient is at less risk of direct contamination.

The evolution of TAVI over the last decades has shown its increasing applicability to different surgical risk profiles, mainly in high and intermediate risk patients.[1] Some studies like the more recent PARTNER 3 and Evolut Low Risk trials have even shown that TAVI is non-inferiority to SAVR in low surgical risk patients.[5,22,24,33] Our study showing a lower incidence of post-TAVI IE compared to post-SAVR IE, together with the studies showing comparable incidence rates of IE between TAVI and SAVR patients, underlines the potential for expanding TAVI as a primary modality for severe symptomatic AS across surgical risk profiles.

According to the 2023 ESC Guidelines for the management of endocarditis, IE is associated with invasive procedures, which could increase the risk for bacteraemia.[8] Our results indeed suggest that the less-invasive nature of TAVI compared with SAVR may reduce the incidence of post-operative infection like IE.

Identification of modifiable risk factors, including patient-related and procedure-related, may allow for preventive measures to avoid post-TAVI IE, as used in cardiac devices implantation, outlined in the European Heart Rhythm Association international consensus document.[51] For example, in patients who have fever or signs of active infection, the procedure should be delayed until the patient has been afebrile for at least 24 hours.[52] The development of haematoma increases the risk for infection,[53] therefore in patients who are not at high risk for thrombo-embolic events (e.g. $CHA_2DS_2VASc$ score <4), holding anticoagulation for the procedure and restarting when the bleeding risk is reduced seems prudent.[51] Therapeutic low-molecular-weight-heparin should be avoided and antiplatelet agents, especially P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) significantly increase the risk for bleeding and should (unless clearly indicated) preferably be discontinued for 5-10 days before the intervention, especially if they are combined with oral anticoagulation.[54–57]

Prophylactic systemic antibiotics may be used with the aim of reducing the risk of prosthetic valve infection, as observed in the prevention of cardiac implantable electronic device infection.[58] Antibiotics must be completed within 1 hour of incision for cefazolin and flucloxaciline, or in case of allergy to cephalosporins, Vancomycin within 90-120 minutes. On the other hand, as there are no data supporting this practice, it is not recommended to administer postoperative antibiotic therapy.[51]

Alcoholic 2% chlorhexidine for skin preparation prior to intra-vascular catheter insertion is superior to povidone-iodine (with or without alcohol).[59] Early re-intervention dramatically increases the risk of infection, delay, or reconsider indication for re-intervention if possible. Furthermore, continuous surveillance programs of infection rates and associated microbiology should be adopted at the level of each implanting centre.[51]

Of course, this will have to be studied, but these data do not have any limitations on the application of these preventive measures to avoid post-TAVI IE.

**Limitations**

Our study has several limitations: i) the meta-analysis was mainly based on observational studies, so the pooled estimates cannot be free of the influence of selection bias; ii) the inclusion of open- label trials, where ascertainment bias is inherent to the trial design. Because event adjudication was not blinded and clinical diagnoses were coded with knowledge of the assigned trial group, the risk of ascertainment bias is probably higher; iii) we found high heterogeneity between the studies, which might be explained by the different study designs and sample sizes; iv) most of the included studies did not report the different microorganisms involved in post-TAVI IE and post-SAVR IE, thus limiting the power of our results in these topic; v) the results obtained for our secondary outcomes may not be as reliable because the incidence of all-cause mortality and stroke was not the primary endpoint of our study, and therefore the sample size was not calculated based on the estimation of all-cause mortality and stroke.

**Conclusion**

The results of our study suggest a lower incidence of IE in TAVI compared to SAVR patients, with no significant difference obtained when analysis was limited to randomized controlled trials. These findings highlight discrepancy between real world experience and clinical trials.

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**Competing interests**

None declared.

**Supplementary Material**

Supplementary material to this paper is available at:

https://drive.google.com/drive/folders/1-AHpUFjoLuTdGBgU1rDYgwFIxCHxjHVZ?usp=drive_link

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