Endocarditis

Prosthetic valve infective endocarditis (PVE) is the most worrisome complication after valve replacement, as it still carries high mortality and morbidity rate.

1. Introduction

Interventional treatment of aortic stenosis is currently based on two different approaches: transcatheter aortic valve implantation/replacement (TAVI/TAVR) and surgical aortic valve replacement (SAVR) [1].

The results from randomized controlled trials (RCTs) and observational/retrospective studies pointed out the evolution of bioprostheses that are used in TAVR, as compared to SAVR, in patients with low- to moderate-high risk for surgical intervention and the need for carefully opting between the two procedures [2][3].

Furthermore, the use of biological prosthetic valves in first place should induce physicians to carefully think about the right indications for adopting TAVR, rather than SAVR. In fact, a recent meta-analysis showed that patients that were treated with bioprosthetic valves demonstrated a 60% higher risk for infective endocarditis as compared to those who underwent cardiac valve replacement treatment with mechanical prostheses [4].

Infective endocarditis (IE) is the most worrisome complication after valve replacement, as it still carries high mortality and morbidity, despite the general improvement in diagnosis, medical, and surgical treatment [5].

A meta-analysis from Abegaz et al. reported a mortality rate that ranged from 20 to 37% at short- and up to five-year follow-up, while the rate of complications due to septic embolisms, cardiac, and/or renal involvement ranged between 19 and 39% [6]. Furthermore, about 25% of patients already treated for IE might be re-hospitalized, due to recurrent cardiac valve infection [7].

Comparisons between SAVR and TAVR in terms of IE incidence and outcomes are still under investigation [3][8]. However, initial evidence showed a similar risk of IE after TAVR or SAVR.

2. SAVR Endocarditis: Epidemiology, Pathogens, Medical Treatment

Prosthetic Valve Endocarditis (PVE) is one of the most dreadful complications after surgical aortic valve replacement (SAVR) [9].

The epidemiological outline of PVE after SAVR is challenging and it quite differs in relation to data from different international registries/studies (Table 1); in particular, the different works show great variability in the reported incidence rates, and this has an impact on proposing a definite value. Because SAVR still remains the most performed cardiac surgical intervention with more than 200,000 procedures per year worldwide, the risk for developing PVE is comparably higher [10][11][12].

Table 1. Characteristics of the main studies dealing with infective endocarditis in surgical aortic valve replacement (SAVR).

Reference	Study Design	SAVR Population (n)	Period	Epidemiological Data	Outcomes	Associated Conditions
Moriyama et al. (2019) [13]	Retrospective (FinnValve registry)	4333	2008–2017	Incidence IE: 2.9/1000 person-yrs	In-hospital death: 32.1%	-Male gender (HR 1.73, 95% CI: 1.04–2.89) -Deep sternal wound infection/vascular access-site infection (HR 5.45, 95% CI: 2.24–13.2) -Hospital death (HR 0.34, 95% CI: 0.21–0.61)
Luehr et al. (2019) [14]	Retrospective, observational	103	2005–2015	IE incidence 2005–2010: 7.4 ± 3.9 cases/yrs IE incidence 2011–2015: 11.4 ± 5.4 cases/yrs	Overall mortality: 47.6% In-hospital mortality: 22.3% Follow-up mortality: 25.2%	Mortality risk factors: Urgent surgery; Mitral regurgitation II; Previous cardiac operation with homograft; LVEF < 40%
Fauchier et al. (2020) [15]	Retrospective, propensity matched (French registry)	60,253 (propensity: 16,291)	2010–2018	UNMATCHED Incidence IE: 1.40/100 person-yrs MATCHED-PROPENSITY Incidence IE: 1.71/100 person-yrs	MATCHED-PROPENSITY All-cause death 32.8%	Male gender, Charlson comorbidity index, frailty index, obesity, alcohol abuse and presence cardiac implantable electronic device
Summers et al. (2019) [16]	Cohort study PARTNER RCTs and registries	1257	2007–2016	Incidence IE: 4.10/1000 person-yrs	All-cause mortality risk: HR 12.03, 95% CI, 5.15-23.51	Cirrhosis Significant pulmonary disease CKD
Kolte et al. (2018) [17]	Retrospective, propensity matched (U.S. Nationwide Readmissions Databases)	66,077 (propensity: 6942)	2013–2014	UNMATCHED Incidence IE: 2.5/100 person-yrs MATCHED Incidence IE: 1.9/100 person-yrs	In-hospital mortality: 15.6%	Younger age History heart failure Need permanent PM Cardiac arrest Major bleeding Sepsis
Butt et al. (2019) [18]	Nationwide observational cohort study	3777	2008–2016	Incidence IE: 1.2/100 person-yrs 5-year IE risk: 5.1% (95% CI: 4.4% to 6.0%),	In-hospital mortality: 14.0% 1-year mortality 23.1%	Male sex and diabetes

Abbreviations: CI: confidential interval; HR: hazard ratio; IE: Infective endocarditis; PARTNER: Placement of Aortic Transcatheter Valves trial; RCT: Randomized Controlled Trial; SAVR: surgical aortic valve replacement; U.S.: United States; Yrs: years.

The FinnValve Registry [13] enrolled more than 6400 patients who underwent TAVR or SAVR between 2008 and 2017. Among the 4333 patients who underwent bioprosthesis implantation via SAVR, the occurrence of PVE was about 2.9 per 1000 person-years during a mean follow-up period of 4.2 ± 2.6 years [13].

Luehr et al. [14] evaluated native valve endocarditis (NVE) vs. PVE after SAVR in a ten-year observational study (2005–2015); they recognized a 48.7% increase in PVE incidence (from 7.4 ± 3.9 to 11.4 ± 5.4 cases/year) within the last five years (2010–2015). According to patients' characteristics, most of them were males (87.4% vs. 75.3%; p = 0.015) and older (67.9 ± 12.1 vs. 60.7 ± 14.7 years; p < 0.001) when compared to NVE patients; moreover, the PVE group showed a higher rate of single valve endocarditis (83.5% vs. 74.7%; p < 0.001) than NVE group [14].

A large retrospective French study analysed more than 100,000 patients undergoing isolated SAVR or TAVR for aortic stenosis (AS) from January 2010 to December 2018 [15]. Among the 60,253 patients who underwent isolated SAVR, PVE incidence was 1.40 (95% CI 1.34–1.46) events per 100 person-years with a lower global risk of developing IE after the procedure as compared with TAVR (RR 1.35, 95% CI 1.26–1.45) when considering unmatched populations [15].

Nonetheless, after adjusting the results by means of propensity score match analysis, the incidence rate of PVE was 1.71 (95% CI 1.58–1.85) events per 100 person-years in SAVR patients and there was no difference when compared to TAVR populations (RR 1.09, 95%CI 0.96–1.23) [15].

A sub-analysis from the randomized Placement of Aortic Transcatheter Valves (PARTNER)-I and -II trials and dedicated registries evaluated the occurrence of PVE in patients who underwent TAVR or SAVR procedures [16]. Among 8530 enrolled patients, there were 107 total cases of PVE: the incidence of PVE after SAVR was 4.10 per 1000 person-years, with no statistically significant difference with PVE after TAVR (p = 0.44) and a calculated incidence rate ratio (IRR) that is equal to 1.27, with SAVR being the reference point [16]. The authors also split data in relation to the timing of PVE occurrence after SAVR: most of the events (more than 60%) were during the period ranging from the 31st day to one year after the procedure; less than 10% of SAVR patients developed PVE within the first month after surgery, while the remaining patients suffered PVE after one year from the index surgical event [16]. In particular, the analysis from Kolte et al. [17] revealed an incidence of 2.5% (95% CI 2.3–2.9%) per person-year for the occurrence of early onset PVE after SAVR.

Indeed, after gathering the results from RCTs, Ando et al. [8] observed long-term incidence in PVE after SAVR that ranged from 0.6% after 2.0 years follow-up to 1.3% after 3.4-years follow-up.

PVE is considered to be the worst complication after heart valve surgery, since it is still weighted with high early and late mortality, despite therapeutic and diagnostic improvements over time [19][20]. Luehr et al. [14] demonstrated overall in-hospital mortality for SAVR PVE equal to 22.3% (4.6% for elective cases and 17.5% for urgent/emergent cases), which increased until 25.2% during the follow-up period. Such percentages were influenced by the occurrence of post-operative complications, such as permanent renal failure (20.4%), sepsis and/or systemic inflammatory response syndrome (SIRS) (27.2%), low cardiac output syndrome (LCOS) (15.5%), and the need for ECLS/ECMO support (12.6%) [14].

Fauchier et al. [15] reported 32.78%/year all-cause mortality for PVE after SAVR; in particular, when analysing the timing after PVE diagnosis, the all-cause mortality was 14.81% after 30 days and 30.13% after one year. Similar results were obtained by Leontyev et al. [21]: among 313 patients undergoing redo SAVRs from December 1994 to April 2008, 48.6% was affected with PVE, showing a mean hospital mortality rate that is equal to 24.3%, which was increased in the case of clinical/post-procedural complication (complicated 30.9% vs. uncomplicated 12.7%; p = 0.01). Periannular abscess, for example, dramatically increased mortality (40.6% vs. 12.5%; p < 0.001) [21]. Finally, the mortality rate after surgical intervention for PVE still persists higher both within the first year (about 48%) and after ten years follow-up (about 69%) [21].

2.1. Pathogens in SAVR-IE

The identification of the causal infective agent of surgical PVE is a further challenging issue. Beyond the limitations deriving from IE related to fastidious microorganisms (i.e., HACEK bacteria) and/or intra-cellular bacteria—which can notably provoke the negative result of the analysis, most of patients suffering PVE underwent empirical antibacterial treatments, which are able to further promote difficulties in correctly identifying pathogens [22].

The direct culture of specimens from surgical biopsies may promote a better and more reliable identification of the outer microorganism.

Literature portrays different microbiological profiles for SAVR and TAVR PVE [13][14][16][17]. According to SAVR, data from registries and international trials provide insights about the causative agent (Table 2) [13][14][16][21].

Table 2. Characteristics of the main studies dealing with infective endocarditis in surgical aortic valve replacement (SAVR).

Reference	Staphylococcus Aureus	Coagulase Positive Staphylococcus	Coagulase Negative Staphylococcus	Enterococcus	Streptococcus	Others
Moriyama et al. (2019) [13]	/	15.1%	26.4%	17.0%	42.6%	18.9%
Fauchier et al. (2020) [15]	/	17.3%	15.5%	21.2%	24.3%	8.6%
Summers et al. (2019) [16]	58.3%	/	/	/	8.3%	/

Reference	Staphylococcus Aureus	Coagulase Positive Staphylococcus	Coagulase Negative Staphylococcus	Enterococcus	Streptococcus	Others
Luehr et al. (2019) [14]	32.2%	/	/	14.2%	21.5%	/

A dedicated sub-analysis from PARTNER trial outlined that 58.3% of SAVR-PVE were caused by Staphylococcus, followed by Enterococcus (25%) and Streptococcus (8.3%) [16]. Indeed, the pathogen was not identified in approximatelt 8% of the cases [16].

The FinnValve Registry [13] revealed that Staphylococci were the most frequent cause of PVE after SAVR (41.5% of cases), with Coagulase-Negative (CoN) species being equal to 26.4%. Furthermore, Streptococci were responsible in 22.6% of cases, while Enterococci in 17%. A further seventeen percent were finally due to other causes (including blood culture negative IE) [13].

A retrospective study from Leontyev et al. [21] focused on causative agents also in relation to PVE timing: Staphylococcus species (spp), especially Aureus and CoNs, were mostly observed in both early (49%) and late (34%) PVE, as well as Enterococcus spp (21% vs. 18%), while Gram-negatives could only be found in a few cases (7%) of late PVE; Streptococci were more likely to be the cause for late PVE (16% vs. 8% for early PVE) [21].

This etiological distribution has been confirmed in a recent retrospective study from Luehr et al. [14], as these authors observed that Staphylococci (37.9%), Enterococci (15.5%), and Streptococci (12.6%) were the most common etiologic agents.

2.2. Medical Approach and Prognosis in SAVR-IE

The final management of PVE after SAVR needs a multidisciplinary approach by a dedicated "Endocarditis" team—in agreement with international guidelines—in order to individualize intervention in a tailored-suited manner [5]. Many aspects of the antimicrobial management are on empirical bases, given the lack of clinical trials testing medical treatments, especially for PVE caused by resistant pathogens.

The current guidelines do not significantly differentiate the medical managements of both NVE and PVE, except for PVE, due to Staphylococci, where the therapy should include rifampicin whenever indicated [5].

Bille [23] suggested a combination of three antibiotics (vancomycin or oxacillin, gentamicin and rifampicin) for staphylococcal PVE for at least six weeks. A case report from de Feiter et al. [24] reported the successful use of linezolid for the treatment of Staphylococcus epidermidis PVE after the failure of treatment with oxacillin, gentamicin, rifampicin, vancomycin, and fusidic acid regimens.

More recently, some authors focused on the prognostic assessment, in order to identify the high risk categories that may need more aggressive strategies [13][14][21].

Leontyev et al. [21] identified sepsis (odds ratio [OR]: 6.5), left ventricle ejection fraction (LVEF) less than 30% (OR: 5.8), concomitant coronary artery bypass grafting (CABG) (OR: 3.3), and aortic root abscess (OR: 2.7) as independent predictors of perioperative mortality for SAVR PVE, whereas sepsis (OR: 3.1) and unstable preoperative status (OR: 1.8) were shown to be predictors of long-term mortality. In this study, the patients with PVE showed a higher risk profile, as they were older, with more urgent/emergency cases and a higher incidence of preoperative neurologic dysfunction, thromboembolic events, renal failure, diabetes, and congestive cardiac failure. All of these conditions may explain the lower five-year survival rate reported [21]. Luehr et al. identified urgent surgery as an independent risk factor for in-hospital mortality (OR 6.461), while the identification of the causal pathogen was considered to be a protective condition for the positive outcome of the patients [14].

Indeed, Moriyama et al. [13] outlined the protective role of surgical intervention against the risk of mortality in patients with aortic PVE. Roughly, all of these results can be mainly attributed to the fast identification of the correct anti-microbial therapy—thus explaining the protective role of early identification of pathogens by means of preoperative blood cultures [14]—and the early indication to surgical intervention before patients' decompensation [13].

Such findings were in line with Grubitzsch et al. [25], who stated that prompt diagnosis and subsequent treatment were fundamental in reducing morbidity, mortality, and, consequently, costs after PVE surgery.

3. TAVR Endocarditis: Epidemiology, Pathogens, Medical Treatment

The occurrence of IE on transcatheter-implanted prostheses is a rare complication, although the impact on prognosis is devastating [5].

The incidence and prevalence of IE after TAVR is difficult to determine, due to the recent introduction of the procedure in clinical management of aortic stenosis; indeed, data regarding incidence are quite uneven amongst the different studies (Table 3). Large cohort registries and observational studies provided a first glance of the impact of IE after the TAVR procedure [13][16][17][18][26][27][28].

Table 3. Characteristics of the main studies dealing with infective endocarditis in transcatheter aortic valve replacement (TAVR).

Reference	Study Design	Population (n)	Period	Epidemiological Data	Outcomes	Associated Conditions
Moriyama et al. (2019) [13]	Retrospective (FinnValve registry)	2.130	2008–2017	Incidence IE: 3.4/1000 person-yrs	In-hospital deah: 20.0%	-Male gender (HR 1.73, 95% CI: 1.04–2.89) -Deep sternal wound infection/vascular access-site infection (HR 5.45, 95% CI: 2.24–13.2)
Regueiro et al. (2016) [33]	Retrospective (Infectious Endocarditis after TAVR International Registry)	20,006	2005–2015	Incidence IE 1.1% per person-yrs Incidence early IE 0.9% per person-yrs	-Surgery during index hospitalization: 14.8%, 95% CI, 10.4–19.2% -Surgical transcatheter valve explantation: 10.8%, 95% CI, 6.9–14.6% -TAVR valve-in-valve: 1.2%, 95% CI, 0–2.5% -Antibiotic therapy alone: 82.0%, 95% CI, 77.2–86.8% In-hospital death: 36%, 95%CI, 30.0–41.9%. 2-year mortality: 66.7%, 95% CI, 59.0–74.2%	-Male gender (HR, 1.69; 95% CI, 1.13–2.52) -Age (HR, 0.97; 95% CI, 0.94–0.99) -Diabetes (HR, 1.52; 95% CI, 1.02–2.29) -residual moderate/severe aortic regurgitation (HR, 2.05; 95% CI, 1.28–3.28)
Latib et al. (2014) [26]	Retrospective on multicenter registry	2572	2008–2013	Incidence IE: 1.13% [95% CI: 0.76% to 1.62%] According to IE onset: -Early (<60 days): 28% -Intermediate (60–365 days): 52% -late (>365 days): 20%	Overall mortality: 62% In-hospital mortality: 45% Follow-up mortality: 17%	N/A
Fauchier et al. (2020) [15]	Retrospective, propensity matched (French registry)	47,553 (propensity: 16,291)	2010–2018	UNMATCHED Incidence IE TAVR: 1.89/100 person-yrs MATCHED-PROPENSITY Incidence IE TAVR: 1.86/100 person-yrs	MATCHED-PROPENSITY All-cause death: 43.0%	Male sex, Charlson comorbidity index, frailty index, AF and anaemia
Summers et al. (2019) [16]	Cohort study of PARTNER RCTs and registries	7273	2007–2016	Incidence IE: 5.21/1000 person-yrs	All-cause mortality risk: HR 4.09, 95% CI, 3.09–5.41	Cirrhosis; significant pulmonary disease; CKD

Reference	Study Design	Population (n)	Period	Epidemiological Data	Outcomes	Associated Conditions
Kolte et al. (2018) [17]	Retrospective, propensity matched (U.S. Nationwide Readmissions Databases)	29,306 (propensity: 6942)	2013–2014	UNMATCHED -Incidence IE: 1.7/100 person-yrs MATCHED -Incidence: 1.7/100 person-yrs	In-hospital mortality: 15.6%	Younger ag History heart failure Need permanent PM Cardiac arrest Major bleeding Sepsis
Butt et al. (2019) [18]	Nationwide observational cohort study	2632	2008–2016	IncidenceIE: 1.6/100 person-yrs 5-year IE risk: 5.8% [95% CI: 4.7% to 7.0%]	In-hospital mortality: 20.9% 1-year mortality: 40.0%	Male sex and CKD
Stortecky et al. (2020) [27]	Retrospective (SwissTAVI Registry)	7203	2011–2018	INCIDENCE -Peri-procedural (<100 days): 2.59/100 person-yrs -Delayed-early (100–365 days): 0.71/100 person-yrs -Late (>365 days): 0.40/100 person-yrs Overall 5-years incidence: 1.0/100 person-yrs	All-cause mortality risk: -Overall: HR: 6.55 (95% CI: 4.44–9.67) -Peri-procedural IE: HR: 7.19 (95% CI: 3.69–14.03) -Delayed IE: HR: 5.05 (95% CI: 2.10–12.16) -Late IE: HR: 7.34 (95% CI: 4.13–13.05) Stroke risk: -Overall: HR: 4.03 (95% CI: 1.54–10.52) -Peri-procedural IE: HR: 1.28 (95% CI: 0.23–7.24) -Delayed IE: 0 -Late IE: HR: 11.92 (95% CI: 2.76–51.53)	-Younger age -Male gender -Lack predilatation balloon aortic valvuloplasty before valve implantation -Treatment in cath-lab as opposed to hybrid
Mangner et al. (2016) [28]	Retrospective	1820	2006–2014	Cumulative incidence: 1.82/100 patient-yrs	In-hospital mortality:63.6% 1-year mortality: 74.5%	-Chronic hemodialysis -PAD
Bjursten et al. (2019) [30]	Retrospective (TAVI registry SWENTRY)	4336	01/2018–06/2018	Incidence • 1 year: 1.42% (1.03–1.80%) • 1–5 yrs: 0.80% (0.60–1.06%) • 5–10 yrs: 0.52% (0.20–1.32%)	1-year survival: 58% 5-year survival was 29%	Body surface area; eGFR < 30 mL/min/1.73 m^2; Critical pre-operative state; mean pre-procedural valve gradient; Amount contrast dye; Transapical access; A.F.

Abbreviations: AF: Atrial fibrillation; CI: confidential interval; CKD: history chronic kidney disease; eGFR: estimated glomerular filtration rate; HR: hazard ratio; IE: Infective endocarditis; N/A: not applicable; PAD: peripheral artery diseases; PARTNER: Placement of Aortic Transcatheter Valves trial; PM: pacemaker; RCT: Randomized Controlled Trial; SWENTRY: SWEdish traNscatheter cardiac intervention registry; TAVR: transcatheter aortic valve implantation; TAVR: transcatheter aortic valve replacement; U.S.: United States; Yrs: years.

A pooled cohort of all patients in PARTNER-I and PARTNER-II trials and registries observed a PVE incidence equal to 5.21 per 1000 person-years in patients who underwent TAVR, with most of them occurring during the first year after implantation (56.8% within one year vs. 43.2% after one year) [16]. The same results were reported by a large multicentre Italian registry, which enrolled 2572 consecutive patients who underwent TAVR, with no difference [26] in the incidence of PVE according to the type of transcatheter aortic prosthesis (i.e., balloon-expandable or self-expandable) [26]. Indeed, Stortecky et al. [27] showed a higher incidence in PVE after TAVR during the peri-procedural period with a 2.59 events per 100 person-years.

The FinnValve registry outlined an incidence of PVE that is equal to 2.4 per 1000 person-years among 2130 individuals who were treated with TAVR [13]. An incidence rate of early PVE equal to 1.7% was noted in a cohort of 29,306 patients collected by Kolte et al. [17].

Butt et al. [18] calculated a cumulative one-year risk of PVE equal to 2.3% in TAVR patients, with a cumulative five-year risk of IE that is equal to 5.8%. Similar results came from a retrospective analysis involving 1820 patients who underwent TAVR: the cumulative incidence rate of PVE was 3.02%, while most of them (74.5%) were within the first year after the procedure [28].

A recent meta-analysis from Wang et al. [29] reported an incidence rate ratio of 0.69 of IE after TAVR as compared to SAVR (p = 0.011), with the one-year post-TAVR incidence of IE being equal to 0.9%.

Data from the national TAVI registry SWENTRY (SWEdish traNscatheter cardiac intervention regisTRY), which is a sub-registry of SWEDEHEART (Swedish Websystem for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies), found a 1.4% increased risk for PVE after TAVR within the first year, which lessened to 0.8% thereafter [30].

Finally, a comprehensive meta-analysis from Khan et al. [31] pointed out a mean incidence in PVE after TAVR of 3.25% (range interval: 0–14.3%).

IE in patients with valvular prostheses, surgical or transcatheter, is strictly associated with an increased burden of mortality during the follow-up [16]. The in-hospital mortality of PVE after TAVR is still high and above 60% than in patients who had an uncomplicated TAVR procedure [26][28][31][32]. Data from the SwissTAVI Registry reported a 6.55-fold higher risk for all-cause death in patients with PVE, with most of them occurring within 30-days after hospital admission (6.20-fold risk increase) [27]. The great impact on prognosis was mostly related to the time of PVE onset: peri-procedural PVE accounted for the majority of death (7.19-fold risk increase) when compared to delayed- or late-onset PVE [27].

Moreover, TAVR PVE was responsible of 4.03-fold risk increase in stroke, which reached higher values in late-onset IE after TAVR (11.92-fold risk increase) [27].

Indeed, the FinnValve Registry reported a cumulative increase in mortality rate related to TAVR PVE, ranging from 37.7% within 30-days after diagnosis to 52.5% one-year after [13]. Interestingly, the surgical approach to TAVR PVE seemed dramatically improving the in-hospital mortality rate of the patients by providing a 66% decrease in death rate [13].

Similar results were observed in a recent meta-analysis, which demonstrated a 37.8% rate of in-hospital mortality [29], mainly driven by heart failure during hospitalization, stroke during hospitalization, prior valve surgery, and Staphylococcus-associated PVE.

A systematic analysis from Khan et al. [31] outlined in-hospital mortality due to TAVR PVE that ranged from 11% to 47.2%, mortality rate at follow-up from 11% to 75%, and heart failure occurrence from 20% to 67.9% [31].

It is hard to define the final determinants that are able to predict the risk for TAVR PVE and the occurrence of negative outcomes. The bias in studies that tried to determine PVE predictors were mainly related to the highest burden of comorbidities of patients who underwent TAVR. However, gender and age can effectively impact the occurrence of TAVR PVE and possibly death [27][29]. Comorbidities, such as peripheral artery disease [29] and/or chronic kidney disease [18], revealed a two-fold increase in adverse outcomes in patients with PVE.

For sure, technical features that are related to the procedure may promote the occurrence of IE. Paravalvular aortic regurgitation [34], the need for implantable cardiac devices [34], heart failure history [17], use of non-hybrid surgical room [27], sepsis, cardiac arrest, and/or major bleeding during TAVR hospitalization [17] are further conditions that are able to favour the occurrence of TAVR PVE.

Indeed, the type of implanted prosthesis seemed not to affect the rate of IE occurrence: a meta-analysis from Tinica et al. [32] showed no difference in terms of time-interval between prosthesis implantation and IE occurrence between the two types of valves (i.e., self expandable or balloon-expandable). The same results were found by Summer et al. [16] in their analysis from the PARTNER trials: the occurrence of TAVR PVE is not linked to the type of valve, while other comorbidities may promote the infection of the device.

Pathogens in TAVR-IE

Studies tried to report the most frequent microorganisms that are responsible for TAVR PVE (Table 4). The Italian multicentre study from Latib et al. [26] found that staphylococci and enterococci were commonly involved in TAVR PVE (about 50%), while negative cultures were reported in about 30% of cases. While staphylococci were mostly responsible for early onset IE, late IE were mainly related to staphylococci and enterococci [26]. The SwissTAVI Registry [27] confirmed these data: early, peri-procedural, and late onset IE were mostly related to infections from staphylococci and enterococci, although the authors observed the Viridans-group streptococci as able to determine the occurrence of valvular infection in late IE after TAVR. The Nationwide Readmissions Databases (NRD) reported that Staphylococci (30.4%), Streptococci (29.9%), and Enterococci (20.5%) were usually involved in TAVR PVE [17].

Table 4. Characteristics of the main studies dealing with infective endocarditis in transcatheter aortic valve replacement (TAVR).

Reference	*Staphylococcus aureus*	Coagulase Positive *Staphylococcus*	Coagulase Negative *Staphylococcus*	*Enterococcus*	*Streptococcus*	Others
Moriyama et al. (2019)	/	20%	6.8%	26.7%	46.7%	0%
Regueiro et al. (2016)	23.8%	/	16.8%	24.6%	/	/
Latib et al. (2014)						
-Early-onset group	50%	/	50%	/	/	/
-Intermediate-onset group	/	20%	/	20%	20%	/
-Late-onset group	/	33%	/	33%	/	/
Fauchier et al. (2020)	/	15.8%	13.2%	22.7%	29%	7.1%
Summers et al. (2019)	28.4%	/	/	/	28.4%	/
Kolte et al. (2018)	30.4%	/	/	20.5%	29.9%	11.1%
Stortecky et al. (2020)	21.5%	/	/	26.2%	28.9%	/
Mangner et al. (2016)	/	38.2%	9.1%	/	3.6%	18.2%
Bjursten et al. (2019)	22.3%	34%	6.8%	20.4%	/	16.6%

The FinnValve Registry pointed out that streptococci were the microorganisms mostly involved in TAVR PVE (46.7%), followed by staphylococci and enterococci (26.7% and 26.7%, respectively). These data were confirmed by the analysis of PARTNER trials: as compared to SAVR, patients with TAVR PVE were infected by streptococci (28.4% vs. 8.3%) .

Gathering the results from literature, Khan et al. [31] finally demonstrated that Enterococci (25.9%), Staphylococcus aureus (16.1%), and coagulase-negative Staphylococcus species (14.7%) were the causative microbiological agents that are involved in TAVR PVE.

The approach to TAVR PVE is challenging. Antibiotic prophylaxis was explored as a possible option for minimising the occurrence of IE after TAVR. Data from the SwissTAVI registry reported higher prevalence (92.6%) in antibiotic prophylaxis in patients who developed IE [27]. Indeed, such prophylaxis was ineffective: most of the patients (77.2%) were

on 1st or 2nd generation cephalosporins, which are efficient on staphylococci and streptococci. Nevertheless, enterococci might not be neutralized by such a kind of drug, just as Gram negative agents. Therefore, the need for widening the spectrum of antibiotics is crucial in preventing PVE.

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