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CONTEMPORARY REVIEW

Infective Endocarditis After Surgical and Transcatheter Aortic Valve Replacement: A State of the Art Review

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ABSTRACT: Prosthetic valve endocarditis (PVE) after surgical aortic valve replacement and transcatheter aortic valve replacement (TAVR) carries significant morbidity/mortality. Our review aims to compare incidence, predisposing factors, microbiology, diagnosis, management, and outcomes of PVE in surgical aortic valve replacement/TAVR patients. We searched PubMed and Embase to identify published studies from January 1, 2015 to March 13, 2020. Key words were indexed for original reports, clinical studies, and reviews. Reports were evaluated by 2 authors against a priori inclusion/exclusion criteria. Studies were included if they reported incidence and outcomes related to surgical aortic valve replacement/TAVR PVE and excluded if they were published pre-2015 or included a small population. We followed the Cochrane methodology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for all stages of the design and implementation. Study quality was based on the Newcastle-Ottawa Scale. Thirty-three studies with 311 to 41025 patients contained relevant information. The majority found no significant difference in incidence of surgical aortic valve replacement/TAVR PVE (reported as 0.3%–1.2% per patient-year versus 0.6%–3.4%), but there were key differences in pathogenesis. TAVR has a specific set of infection risks related to entry site, procedure, and device, including nonstandardized protocols for infection control, valve crimping injury, paravalvular leak, neo-leaflet stress, intact/calcified native leaflets, and intracardiac hardware. With the expansion of TAVR to lower risk and younger patients, a better understanding of pathogenesis, patient presentation, and guideline-directed treatment is paramount. When operative intervention is necessary, mortality remains high at 20% to 30%. Unique TAVR infection risks present opportunities for PVE prevention, therefore, further investigation is imperative.

Key Words: endocarditis ■ prosthetic valve infection ■ transcatheter aortic valve implantation

Surgical prosthetic valve endocarditis (PVE) is a well-studied morbid condition that accounts for 10% to 30% of all cases of infective endocarditis (IE).[1,2] The initial infectious nidus on the prosthetic valve is typically the sewing ring, which can lead to dehiscence and/or leaflet dysfunction.[1] Despite improvements in the diagnosis and management of early PVE, it still carries a high surgical mortality of 20% to 30%.[1]

PVE occurs at the rate of 0.3% to 1.2% per patient-year in surgical aortic valve replacement (SAVR) and can have devastating sequelae of destruction of the valvular apparatus, abscess formation, pseudoaneurysms, fistulas, perforations, heart block, and stroke, many promoted by the elevated pressures of the aortic root.[1,3] PVE has been studied in SAVR for decades and is currently being investigated in transcatheter aortic valve replacement (TAVR). The incidence of TAVR PVE is reported as 0.6% to 3.4%.[3] Although TAVR is most often performed via the femoral artery in a less invasive manner than conventional sternotomy, it is offset with a specific set of infection risks related to the entry site and device/procedure: nonstandardized protocols for infection control outside of a standard/hybrid operating room, valve crimping

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Nonstandard Abbreviations and Acronyms

CT	computed tomography
HR	hazard ratio
IE	infective endocarditis
PVE	prosthetic valve endocarditis
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement
TEE	transesophageal echocardiography

injury, paravalvular leak turbulence, neo-leaflet stress with malaligned commissures, intact/calcified native leaflets, and intracardiac hardware (ie, pacemaker leads).[4,5]

The aim of our review is to compare incidence, predisposing factors, microbiology, diagnostic modalities, studies, management, and outcomes of PVE in SAVR and TAVR to better understand the pathology, as TAVR is now approved in lower risk, younger patients.

METHODS/LITERATURE SEARCH

A comprehensive database search of the past 5 years was performed on PubMed and Embase. To ensure that only contemporary data were included, search parameters were from January 1, 2015 to March 13, 2020. Keywords "infective endocarditis" OR "prosthetic valve endocarditis" AND "aortic valve replacement" OR "aortic valve implantation" OR "TAVR" OR "TAVI" OR "SAVR" OR "SAVI" were indexed in all combinations for original reports and clinical studies (cross-sectional/observational/clinical trial studies) and reviews. Reference lists of other published reviews/relevant reports were cross-checked to identify any additional studies. These reports were evaluated by 2 authors against a priori inclusion/exclusion criteria. Quality was evaluated with the Newcastle-Ottawa Scale (Tables S1 and S2) with a third party for discordant ratings. Studies were included if they reported incidence/outcomes of IE after SAVR/TAVR and excluded if they had data published pre-2015 or had a smaller number of patients (<300). We conducted a search on PVE after TAVR before 2015 and found only 4 entries meeting our criteria. Given that we wanted to examine more contemporary outcomes comparing PVE with SAVR versus TAVR, we decided to exclude historical data. We followed the Cochrane methodology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for all stages of the design and implementation (Figure S1).

Our initial search in PubMed and Embase yielded 1044 articles. Thirteen studies were added after a search of bibliographies and recent conferences. After electronic/manual deduplication, 622 articles remained, 66 of which were relevant and selected for full-text review. After full-text review, 33 studies were selected. Studies on TAVR PVE by Puls et al,[6] Makkar et al,[7] Shi et al,[8] Shehada et al,[9] Rodriguez-Vidigal et al,[10] and studies from the Nordic Aortic Valve Intervention trial were either excluded based on older data or smaller number of participants. A recent study by Summers et al was excluded on the basis of composite data that we have included from individual PARTNER trials.[11]

DISEASE MECHANISMS

Pathophysiology and Microbiology

Early SAVR PVE is likely the result of peri-procedural bacteria: *Staph. aureus*, *Staph. epidermidis*, Gram-negative bacteria, and fungi, whereas late SAVR PVE organisms can mimic those of native valve endocarditis with Streptococci/Staphylococci.[1] The microorganisms for intermediate SAVR PVE may be because of hospital-acquired infections of lower pathogenicity or community-acquired infections similar to late PVE.

In addition to surgical valves, Staphylococci and Streptococci have a penchant for transcatheter valves. Interestingly, with TAVR PVE, Enterococci has also been a prominent causative agent in the peri-procedural period.[2] It is likely that this is secondary to femoral access in the groin.

With suspicion of PVE, it is critical that blood cultures are drawn before antibiotic/antifungal administration to prevent false negatives.[12,13] Identifying the culprit agent allows for sensitivity testing. If bacteremia persists without evidence of PVE, there is a high probability of recurrent endocarditis.[12,13]

With negative cultures, serologic and polymerase chain reaction testing should be initiated for *Brucella*, *Coxiella*, *Bartonella*, *T. whipplei*. *Mycoplasma*, *Legionella*, and fungi.[14] If results remain inconclusive, even after testing of excised valvular material, the patient may have a rare case of autoimmune or malignant PVE. The aortic complex, including the sinuses, annulus, left ventricular outflow tract, and mitral valve should be inspected for periannular/intramyocardial abscesses, defects, pseudoaneurysms, and fistulae by imaging.

Clinical Presentation, Risk Factors, and Natural History

There are several risk factors for SAVR PVE, including male sex, prolonged cardiopulmonary bypass time, previous native valve endocarditis, and type of valve

prosthesis implanted.[15] Modifiable sources of infection in the postoperative period are sternal wound infections, intravascular catheter infections, urinary tract infections, and pneumonia. Patients present with the vague stigmata of fever (90% of the time), chills, murmurs (85%), and emboli.[16,17]

Because TAVR is predominantly performed via a percutaneous femoral approach, one would expect a very low incidence of early PVE, but many factors can explain its pathogenesis. One issue of paramount concern is the sterility of the procedural environment with transcatheter procedures.[18,19] Many studies fail to indicate the hospital location of TAVR, and multiple studies have suggested that similar outcomes can be achieved at a lower cost by performing the procedure in a standard catheterization laboratory.[20,21] Unfortunately, there is sometimes less attention paid to infection prevention guidelines in catheterization laboratories, often resulting in substandard maintenance of sterility compared with operating rooms or hybrid suites. Hubble et al studied conventional plenum positive pressure ventilation versus vertical laminar-flow ventilation in procedural rooms and found that regardless of sterile protective gear used by operators, positive pressure labs had consistently high bacterial counts as measured by colony forming units.[18]

Additional risks may be associated with the TAVR procedure itself: crimping of valve leaflets during valve loading and postdilatation following deployment can lead to microscopic cellular damage that predisposes to inflammation and bacterial organism adhesion.[22] Paravalvular leak can also serve as a nidus for infection because turbulence between the transcatheter prosthesis and native valve can augment platelet aggregation and thrombus formation[23,24]; this facilitates bacterial seeding because the adhesive platelet-fibrin environs are used by organisms to produce the matrix of vegetations.[1,12] (Table 1).

Table 1. Nonmodifiable and Modifiable Risk Factors Involved in the Pathogenesis of Transcatheter Aortic Valve Replacement vs Surgical Aortic Valve Replacement Prosthetic Valve Endocarditis

Risk Factors	TAVR	SAVR
Nonmodifiable		
Male sex	Yes	Yes
Younger age	Yes	No
Groin access	Yes	No
Crimping of valve leaflets	Yes	No
Modifiable		
Urinary tract infection	No	Yes
Pneumonia	No	Yes
Intravascular catheter infections	No	Yes
Prolonged cardiopulmonary bypass	No	Yes
Sternal wound infections	No	Yes
Suboptimal sterility	Yes	No
Paravalvular regurgitation	Yes	No

SAVR indicates surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

Assessment and Diagnostic Strategies

Definite IE is outlined by the Modified Duke Criteria as 2 major criteria (positive blood cultures meeting specific definitions, endocardial involvement), 1 major and 3 minor criteria, or 5 minor criteria (predisposition/predisposing heart condition/IV drug use, fever, vascular phenomena, immunologic phenomena, microbiologic evidence).[1] PVE has also been defined for TAVR in the Valve Academic Research Consortium-2 document as: fulfillment of the Duke criteria, evidence of abscess/paravalvular leak/pus/vegetation on reoperation, or the aforementioned findings during autopsy.[25] PVE can be categorized as early (within 2 months), intermediate (between 2 and 12 months), or late (>12 months).[26]

Echocardiography and computed tomography angiography are used to diagnose PVE. Transesophageal echocardiography (TEE) has shown an 86% to 94% sensitivity and 88% to 100% specificity for vegetation diagnosis versus transthoracic echocardiography with a sensitivity of 28% to 69%.[27–32] Transthoracic echocardiography is the logical first step, but because it is limited in assessing PVE, TEE is additionally recommended for patients with at least "possible IE" by clinical criteria or with complicated IE (ie, paravalvular abscess). It should be repeated after 1 week in the setting of non-diagnostic results and a high likelihood.[14,16,33] A negative TEE does not preclude PVE. Adjunctive imaging ie, leukocyte scanning, magnetic resonance imaging, and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography hould be considered.[16,34]

Recent studies have shown that ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography uptake around surgical valves is an accurate indicator of PVE[34,35] and can be used to detect transcatheter valve PVE.[16,36] In non-PVE patients, lower levels of ^{18}F-fluorodeoxyglucose and maximal standardized uptake in the valve have been reported (standardized uptake value$_{max}$ 3.2 versus 5.8).[34] ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography can improve PVE diagnosis because normal/inconclusive echocardiography results occur in almost 30% of cases.[37] In 1 study, abnormal ^{18}F-fluorodeoxyglucose uptake increased sensitivity of the modified Duke criteria from 70% to 97% (P=0.008).[37] (Figure 1).

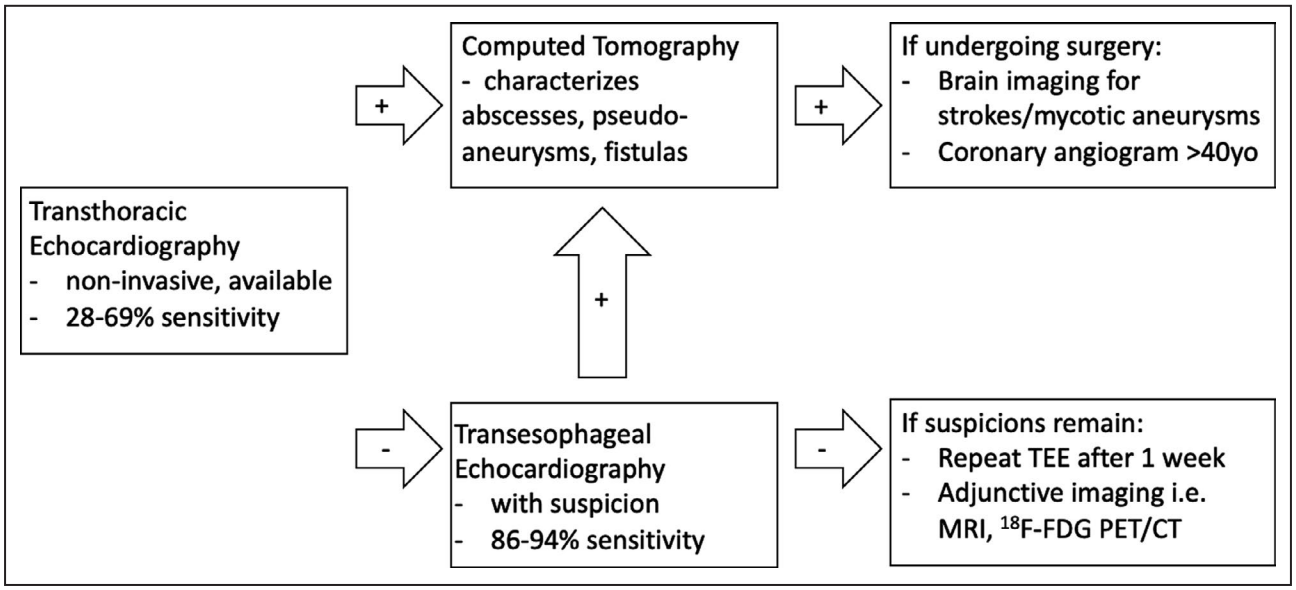

Figure 1. Imaging algorithm for prosthetic valve endocarditis.
(+) is positive findings on imaging. (–) is negative/inconclusive findings on imaging. The first step is to start with transthoracic echocardiography (TTE), given its availability and noninvasive nature. With positive findings, one can undergo computed tomography (CT) and consider brain imaging/coronary angiography (depending on age) if there is a plan for surgery. With negative TTE findings, one can perform transesophageal echography (TEE). If that is negative, repeat TEE 1 week later if suspicions remain or consider adjunctive imaging, such as magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG-PET/CT). If TEE has positive findings, one should obtain a CT to characterize abscesses, pseudoaneurysms, and fistulas.

The diagnosis of TAVR PVE is more complicated than SAVR PVE, and a low threshold for clinical suspicion is warranted.[12,19] Pinpointing vegetations on echocardiography can be challenging with the acoustic shadowing of the stented frame abutting the native valve leaflets.[12,19] (Figure 2A and 2B) It can also be challenging to distinguish between postoperative paravalvular leak and prosthetic valve dehiscence.[19] Diagnosis of definite versus probable TAVR PVE is limited by lower sensitivity to diagnosis by modified Duke criteria with the absence of echocardiographic findings.[38] The structural peculiarities of TAVR PVE can impede diagnosis and have even led to postmortem diagnosis.[12,19,39–41]

Another modality that can be used for diagnosis of PVE is computed tomography (CT). The American College of Cardiology and American Heart Association guidelines have given a Class IIA recommendation to multidetector CT to diagnose TAVR PVE; the European Society of Cardiology has followed suit.[16,42] CT is valuable in characterizing abscesses/pseudoaneurysms with comparable diagnostic accuracy to TEE. Gomes et al performed a study looking at multiple imaging modalities for endocarditis and found that the sensitivity of echocardiography and multidetector computed tomography angiography were both 75% for prostheses; regurgitation and valve dehiscence were also detected at the same rate.[43] On CT, one can size perivalvular lesions and the aortic valve/root/ascending aorta to plan surgical intervention.[16]

Treatment Approaches and Prognosis

Pharmacotherapy

Targeted antibiotic treatment is vital for PVE and requires ≈6 weeks of bactericidal multidrug therapy secondary to vegetation/biofilm tolerance and resistance to host defenses.[16] Empiric antibiotics for PVE, before culture speciation, should cover Staphylococci, Streptococci, Enterococci, and Gram-negative pathogens. Specific recommendations from the European Society of Cardiology suggest vancomycin (30 mg/kg per day intravenous in 2 doses) and gentamicin (3 mg/kg per day intravenous/intramuscular in 1 dose) with rifampin to be added 3 to 5 days after treatment to target dormant bacteria.[16] In late PVE (after 1 year), vancomycin/gentamicin is preferred in patients who are allergic to penicillin, but in patients who are penicillin tolerant, instead of vancomycin, ampicillin with (flu) cloxacillin/oxacillin (12 g/day intravenous in 4–6 doses) can be used.[16]

For blood culture-negative pathogens, specific regimens with doxycycline and levofloxacin are suggested. For fungal infections, which can occur in intravenous drug users and immunocompromised patients, amphotericin B should be used for *Candida* with fluconazole, and voriconazole should be used for

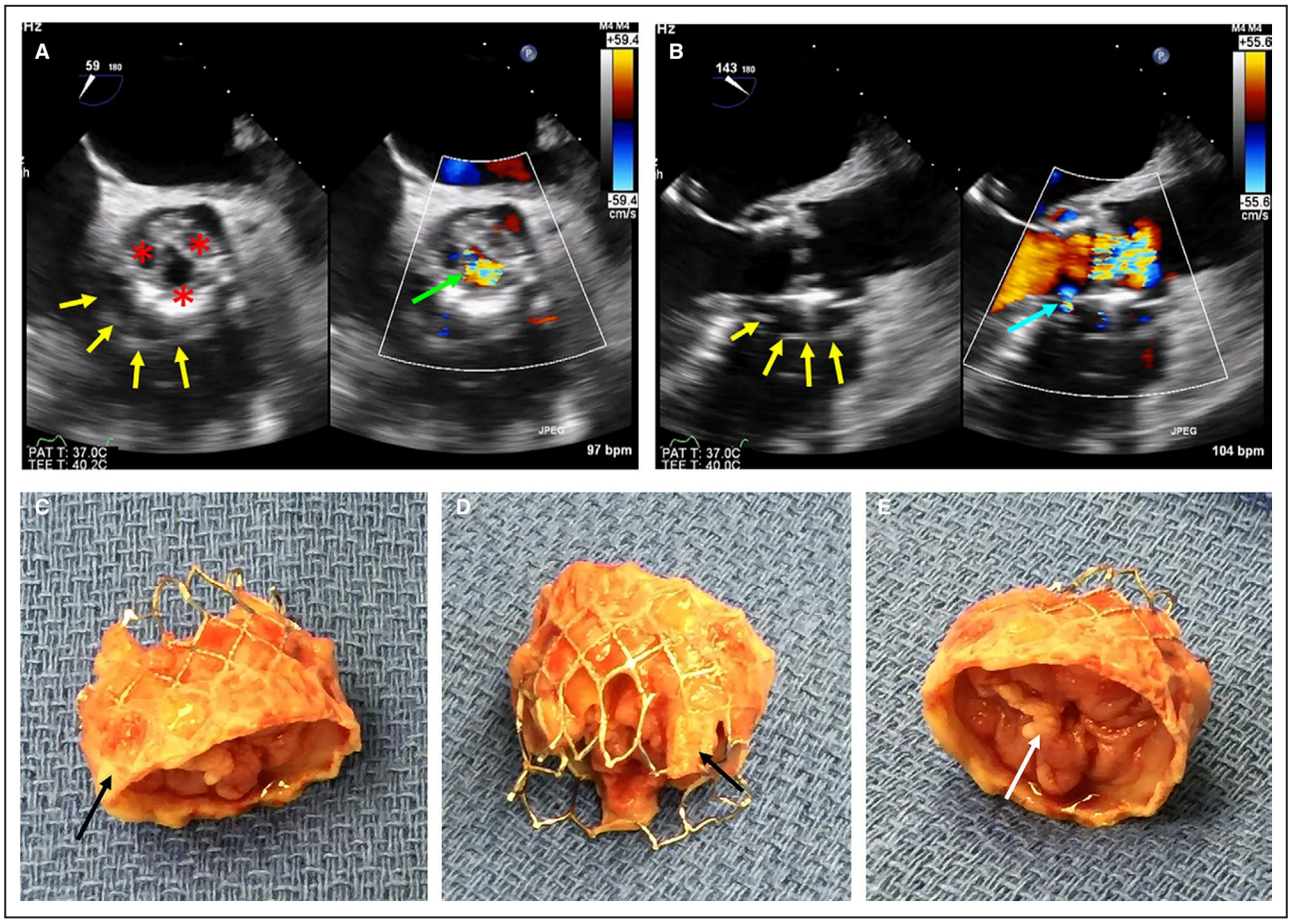

Figure 2. Images of transcatheter aortic valve endocarditis.
Transesophageal echocardiography showing simultaneous 2-dimensional and color Doppler short-axis view (**A**) of a balloon-expandable transcatheter valve with severe thickening of the leaflets (red *) and severe aortic regurgitation (green arrow). A mitral-aortic intervalvular fibrosa abscess cavity (yellow arrows) is also seen. Two-dimensional and color Doppler long-axis view (**B**) of the same valve showing the mitral-aortic intervalvular fibrosa abscess cavity (yellow arrows) with color Doppler revealing flow from the left ventricle to the cavity (blue arrow) representing a fistula and pseudoaneurysm formation. Explanted Edwards SAPIEN 3 (Edwards Lifesciences LLC, Irvine, CA) transcatheter valve because of Enterococcus endocarditis (**C** through **E**). Note the extensive vegetation infiltration on all aspects of the valve (arrows), including the sealing skirt (**C**), metal frame (**D**), and leaflets (**E**).

Aspergillus.[16] If the infection persists after a week of treatment, one needs to evaluate all lines and search for another source before surgery.

Current European perioperative antibiotic prophylaxis guidelines for TAVR/SAVR include dosing antibiotics (ie, intravenous cefazolin) before incision with redosing if necessary and termination within 2 days (Class IIa). They also recommend preoperative screening and treatment of nasal *Staph. aureus* (Class I).

Recommendations for antibiotic prophylaxis of IE for other procedures have become more restricted, and there has been a dramatic shift in guidelines.[1] The American Heart Association updated their level of evidence from B (moderate quality) to C-LD (limited data) in 2017 with regard to IE prophylaxis in TAVR patients.[42] Patients with surgical and transcatheter valves are still at highest risk of IE; therefore, antibiotic prophylaxis is justifiable with gingival/periapical teeth manipulation or breeching of the oral mucosa.[1,16,42]

Surgery

There are certain situations where antibiotic therapy has not been able to treat PVE. Emergent (intervention needed within 24 hours) indications for PVE are acute severe regurgitation or fistula obstruction leading to pulmonary edema/shock. Urgent (intervention needed within days) indications include severe aortic regurgitation/obstruction with heart failure, abscess/fistula/pseudoaneurysm/enlarging vegetation, new conduction abnormalities, positive fevers/blood cultures for over 1 week without cause, fungal/multiresistant/Staphylococci/gram-negative agents, embolization on appropriate therapy, and vegetations >1 cm with sequelae or >1.5 cm without sequelae.[1]

Before surgery, there should be a discussion over whether invasive coronary angiography or noninvasive computed tomography angiography would be beneficial in patients >40 years old, considering the risks of vegetation dislodgment, renal toxicity, and delay in management. Brain imaging is reasonable because ischemic/hemorrhagic stroke or mycotic aneurysm will delay intervention and may require treatment.[1,44]

During surgery, care must be taken to avoid contamination of the field with items that contact purulence. Complete removal of all foreign tissue is necessary before replacement with a valve or an allograft (Figure 2C through 2E). In a systematic review looking at freedom from infection, reoperation, and mortality, there was no significant difference between the use of homograft versus conventional prosthesis for SAVR PVE,[45] and an allograft can be used when there is aortic root damage secondary to large TAVR stent frames. If the anterior leaflet of the mitral valve is also destroyed, it is possible to use a combined aortic/anterior mitral leaflet homograft. Operative technique to remove infected material must evolve because transcatheter devices encompass tissue in the supra-/subannular planes. With extensive debridement, placement of epicardial leads should be considered. Operative mortality remains high at 20% to 30%.[1]

DISCUSSION

TAVR Versus SAVR PVE Data

There is a limited amount of literature that provides a direct comparison between TAVR and SAVR PVE. In the FinnValve Registry, no significant difference in PVE was appreciated with TAVR (3.4/1000 person-years) versus SAVR (2.9/1000 person-years)[46] in 6463 consecutive patients enrolled from 2008 to 2017. Of note, TAVR demonstrated an increase in PVE with vascular access site infections, as did SAVR with deep sternal wound infections. Male sex was a risk factor (hazard ratio [HR], 1.73; 95% CI, 1.04–2.89), but unlike Regueiro's TAVR study, surgical treatment decreased 1-year mortality, even though it was high at 52.5% (HR, 0.34;, 95% CI, 0.21–0.61).[46]

Kolte and colleagues also found no difference between TAVR and SAVR PVE with an incidence of 1.7% versus 1.9% per person-year when they propensity-matched 15 138 and 15 030 patients from 2013 to 2014 in the United States.[4] TAVR PVE risk factors included younger age, history of heart failure, and need for permanent pacemaker; mortality was 15.6% with readmission.

Butt et al had findings consistent with the FinnValve Registry and Kolte's group when studying 6409 TAVR and SAVR patients in Denmark.[47] There was no difference in PVE (HR, 1.12; 95% CI, 0.84–1.49) between the 2 and male sex was a significant risk factor for both (overall HR, 1.78; 95% CI, 1.38–2.29), similar to previous studies. Mortality remained high for those with PVE at 1 year (40% with TAVR and 23% with SAVR).[47]

Interestingly, when observing timing of PVE, Kuttamperoor et al found that early PVE was more common in TAVR (80%) versus SAVR (40%), but noted that larger studies overall still demonstrated similar incidence.[26] Viquez et al also found 30 and 90 day readmission rates for PVE to be higher in TAVR versus SAVR.[48]

SAVR PVE Data

Glaser and colleagues conducted one of the most robust studies in SAVR PVE, reporting the incidence from national registries in Sweden from 1995 to 2012 with a follow-up of up to 18 years.[49] Among the 26 580 patients who underwent SAVR, there were 940 cases of hospitalization for PVE (3.53%). The highest incidence was in early PVE (HR, 1.65; 95% CI, 1.16–2.37) and in those who received tissue prostheses. The hypothesis is that bioprostheses have more opportunity for bacterial colonization on damaged biologic leaflets. This type of degeneration does not occur with the pyrolytic carbon of mechanical valve leaflets. Glaser's study concurs with Society of Thoracic Surgeons' finding of increased PVE seen with biologic versus mechanical aortic valve replacements in the 1990s (HR, 1.60; 95% CI, 1.31–1.94).[49,50] Of note, in the Swedish study, patients were age matched, but mechanical valve recipients were on average over 13 years younger. However, in the same age cohort (50–70 years old), Kyto et al found that mechanical valves conferred a lower rate of PVE in 10-year follow-up (HR, 0.46; 95%, CI 0.24–0.88; P=0.018).[51] This difference did not hold true in patients >70 years of age.[52]

Andrade and associates reported PVE in 32 of 1557 SAVR patients (2.0%) from 2009 to 2015.[53] PVE included occurred within 12 months of surgery, and 40.6% was in the aortic position. Offending agents were *Staph. epidermidis* and *Staph. aureus* in >20%, and interestingly, culture negative in 62.5%. Polymerase chain reaction was subsequently used on harvested valves. The high rate of culture-negative PVE in Brazil, where the study took place, was attributed to poor culture techniques, possibly after the start of antibiotics. This group was somewhat aggressive about operative intervention. At a median length of 2 weeks from diagnosis, 81.3% of patients had reoperative surgery with a 15.4% in-hospital mortality rate; the clinical treatment group had a 50% mortality rate.[53]

A common theme among institutions studying PVE (whether it be SAVR or TAVR) is that the endocarditis

team makes treatment decisions. The team may include a core cardiologist, a surgeon, and an infectious disease specialist. In Italy, a weekly review of cases with this multidisciplinary approach led to a statistically significant reduction in in-hospital and 3-year mortality (28% versus 13%, *P*=0.02; and 34% versus 16%, *P*=0.0007).[14] By standardizing protocol, a French endocarditis team reduced 1-year mortality from 18.5% to 8.2%.[14]

Recent data on PVE after SAVR are listed in Table 2.[4,46,47,49,51–63]

TAVR PVE Data

Regueiro et al published a study from 47 centers worldwide from 2005 to 2015 looking at 20 006 TAVR patients, 250 (1.24%) of whom developed PVE at a median time of 5.3 months. Offending organisms were Enterococci in 24.6%, which is different from surgery because of groin access, and *Staph. aureus* in 23.3%. Risk factors included younger age (could be secondary to increased co-morbidities to meet risk criteria), male sex, diabetes mellitus, and residual regurgitation.[64] Fever (80.4%) and acute heart failure (40.0%) were the most common presenting symptoms. Vegetations were present in 67.6% of patients, and self-expanding valves versus balloon-expandable valves exhibited a higher percentage of vegetations on the stent frame (26.2% versus 10.6%, *P*=0.01). Balloon-expandable valves exhibited a higher percentage of vegetations on the valve leaflet compared with self-expanding valves (58.8% versus 36.2%, *P*=0.02). This is not surprising considering the ratio of stent frame to valve leaflet in the composition of these 2 devices. Eighteen percent of patients developed either periannular abscess, fistulas, or pseudoaneurysms, but only 14.8% of patients underwent surgery, which did not reduce in-hospital mortality (29.7% versus 37.1%, *P*=0.39).[64] In-hospital mortality in the Global Study Cohort was associated with elevated logistic EuroSCORE (*P*=0.02) and heart (*P*<0.001)/renal (*P*=0.002) failure.[64]

Amat-Santos et al collected TAVR data from 21 centers with a total of 7891 patients and found the incidence of PVE to be 0.67% (53 cases) with an average initiation of symptoms at 6 months.[2] Fever (71.7%) and heart failure (58.5%) were the most common presenting factors, *coagulase-negative Staph*. (24.5%)/*Staph. aureus* (21%)/Enterococci (21%) were culprit organisms, 77.4% had vegetations on the stent frame in self-expanding valves (31.6% versus 8.8%), and 15.1% had paravalvular extension in the form of an abscess. Younger age and higher EuroSCORE were risk factors. Management in this study was conservative, with only 11.3% undergoing valve intervention (7.5% with surgical explantation and 3.8% with valve-in-valve treatment); in-hospital mortality was higher at 47.2%.[2]

Data from Mangner et al were consistent with Regueiro's and Amat-Santos's data when studying 1820 patients who underwent transfemoral TAVR from 2006 to 2014. The cumulative incidence of PVE was 3.0% with fever (94.5%) and heart failure (37%) being the most common presenting symptoms.[65] Prevalent organisms were Staphylococci (38.3% coagulase-positive) and Enterococci (30.9%). Risk factors of younger age (*P*=0.012) and postprocedural aortic regurgitation ≥ grade 2 (*P*=0.024) were consistent with other studies, and mortality was high at 1 year (74.5%).[65]

Like Glaser et al in the investigation of SAVR PVE, Bjursten et al used the national Swedish registry to analyze all TAVR procedures (4336) from 2008 to 2018. They found PVE incidence to be 2.4%, half with the TAVR valve affected.[66] *Staph. aureus* was present in 22.3% of cases, Alpha streptococci in 34.0%, and *E. faecalis* in 20.4%. Definite diagnosis was hindered by difficult echocardiogram interpretation with the stent frame of the TAVR valve obscuring views, and 32 (32%) of PVE patients had no documented vegetations. Consistent with other TAVR PVE studies, in univariate analysis, male sex was a risk factor (female sex HR, 0.62; 95% CI, 0.42–0.92), and in multivariate analysis, elevated mean gradient (*P*<0.009) and severe renal insufficiency (*P*<0.001) were independent predictors. This study also found higher body surface area (*P*<0.001), transapical access (*P*=0.008), critical preoperative state (*P*=0.033), amount of contrast used (*P*=0.016), and atrial fibrillation (*P*=0.047) to be risk factors. Surgical treatment with SAVR was used in only 2 patients, and in-hospital mortality was 17% with a 58% survival at 1 year after PVE diagnosis.[66]

From the US data, Yeo at al. found a 0.3% incidence of in-hospital TAVR PVE in a 41 025 patient study and Latib et al reported a 1.13% incidence in a 2572 multicenter patient study with a median follow-up of 393 days.[5,67] Most popular organisms were again *Staph. aureus* (16.7%), Enterococci (8.3%), and Viridans group streptococci (20.8%) in Yeo's study and Staphylococcus (31%), Enterococci (21%), and Streptococcus (14%) in Latib's study. Latib et al's patients presented with fever (76%) and heart failure (33%) at a median time of 158 days.[67] Younger age, drug abuse, and HIV were risk factors in Yeo's patients.[5] In-hospital mortality occurred in 45% of PVE patients in Latib's series and in 20.8% in Yeo's series, respectively.

Recent data on PVE after TAVR are listed in Table 3.[1]

Limitations

In August 2019, the US Food and Drug Administration approved TAVR for patients at low risk of morbidity/

Table 2. Recent Studies on Prosthetic Valve Endocarditis After Surgical Aortic Valve Replacement

Study	Study Period	Study Population	SAVR Aortic PVE	Mean/Median Follow-Up	Mortality in SAVR PVE	Predictors of PVE
van Valen et al[54]	2008–2015	2466	91 (3.7%) in PVE composite population	Mean since redo surgery 35 mo in *P. acnes* patients (1–81 mo)	4 (4.4%) 30-d mortality in composite population	Male sex
Glaser et al[49]	1995–2012	26 580 (16 426 bioprostheses; 10 154 mechanical)	940/164 168 (0.57% per patient-year)	Mean 6.2 y (maximum 18 y)	Undefined	Bioprostheses
Grubitzsch et al[55]	2000–2014	116 with PVE (86 bioprostheses; 30 mechanical)	116 (100%-only patients undergoing surgery for PVE were studied)	Median 3.8 y (0–13.9 y)	16 (13.8%) at 30-d; 30 (25.9%) at 1 y	Mortality/morbidity determined by delayed diagnosis, advanced age, preoperative state, need for mechanical circulatory support, concomitant procedures
Leon et al[56]	2011–2013	2032 intermediate-risk patients (1021 with SAVR)	6 (0.7%)	2 y	Undefined	Undefined
Deeb et al[57] Gleason et al[58]	2011–2013	797 (359 with attempted SAVR)	5 (1.7%) at 3 y 5 (1.7%) at 5 y	Median 34.6 mo Median 41.0 mo	Undefined	Undefined
Kolte et al[4]	2013–2014	66 077	811 (1.2%)	Unmatched cohort median 183 d (interquartile range 91–275 d)	Undefined	Undefined
Kyto et al[51]	2004–2014	2982 patients 50 to 70 y old with SAVR±CABG (576 matched mechanical and biologic prostheses)	2% for mechanical and 3.4% for biologic at 1 y	Mean 4.9±3.0 y, median 1702 d	Undefined	Bioprostheses
Kyto et al[52]	2004–2014	4227 patients >70 y old with SAVR±CABG (296 matched mechanical to 888 biologic prostheses)	2.3% for mechanical and 1.0% for biologic at 1 y	Mean 8.3 y	Undefined	No statistically significant difference between valve types
Myllykangas et al[59]	2004–2014	7.616 patients with SAVR±CABG	2.1% in men and 1.0% in women at 1 y	Mean 6.5±2.6 y	Undefined	Men with biologic prostheses
Andrade et al[53]	2009–2015	1557	32 (2.1%) for all valves (18 bioprostheses, 13 mechanical); 13 (40.6% in aortic position)	12-mo after index surgery	7 (22%) for all valves in-hospital	No statistically significant independent risk factors
Butt et al[47]	2008–2016	3777	186 (4.9%)	Mean 4.3 y	43 (23%) 1-y mortality	Male sex, history of diabetes mellitus
Ando et al[60]	2002–2018	1866 (meta-analysis)	24 (1.3%)	Mean 3.4 y	Undefined	Undefined
Moriyama et al[46]	2008–2017	4333 (all bioprostheses)	53 (1.2%)	Mean 4.2±2.6 y	17 (32%) in-hospital	Male sex, Deep sternal wound infection
Fauchier et al[61]	2010–2018	16 291	594 with IE (3.6%)	Mean 731 d, Median 424 d (interquartile range 15–1239 d)	8.08 deaths per year	Younger age, Charlson comorbidity index, frailty index, male sex, previous myocardial infarction, pacemaker/defibrillator, obesity, alcohol-related disorders
Mack et al[62]	2016–2017	1000 low-risk patients (454 with biologic SAVR)	2 (0.5%) at 1-y	1 y	Undefined	Undefined
Popma et al[63]	2016–2018	678	0.4% at 12 mo	Median 12.2 mo	Not distinguished in overall 3% 1-y mortality	Undefined

CABG indicates coronary artery bypass grafting; PVE, prosthetic valve endocarditis; and SAVR, surgical aortic valve replacement.

Table 3. Recent Studies on Prosthetic Valve Endocarditis After Transcatheter Aortic Valve Replacement

Study	Study Period	Study Population	Valve Type	TAVR Aortic PVE	Mean/Median Follow-Up	Mortality in TAVR PVE	Predictors of PVE
Latib et al[67]	2008–2013	2572	CoreValve (1343), SAPIEN (1191)	29 (1.1%)	393 d median follow-up (191–785 d)	18 (62%)	Systemic infections/diseases, healthcare-associated infections
Amat- Santos et al[2]	2007–2014	7944	CoreValve (1562), SAPIEN (6329)	53 (0.7%)	Mean 1.1±1.2 y	38 (72%)	Orotracheal intubation, CoreValve
Olsen et al[3]	2007–2014	509	CoreValve (509)	18 (3.5%)	Median 1.4 y (interquartile range 0.5–2 y)	4 (2.2%)	Male sex, low implantation, at least moderate PVL, >1 prosthesis implantation, vascular/bleeding complications
Martinez-Selles et al[68]	2008–2013	952	CoreValve (650), SAPIEN (302)	6 (0.6%)	Undefined, at least 1 y in PVE patients	3 (50%)	Nosocomial/healthcare-related infections
Regueiro et al[64]	2005–2015	20 006	Global Study Cohort with IE: CoreValve (119), SAPIEN (131)	250 (1.2%)	Median in Global Study Cohort after IE 10.5 mo (interquartile range 3.0–20.8 mo)	140 (56%)	Younger age, Diabetes mellitus, chronic renal failure, chronic pulmonary disease, orotracheal intubation, moderate or severe aortic regurgitation
Mangner et al[65]	2006–2014	1820	CoreValve (≈75%), SAPIEN (≈25%)	55 (3.0%)	Median 366 d (interquartile range 161–1033 d)	41 (74.5%) 1-y mortality	Younger age, chronic obstructive pulmonary disease, peripheral artery disease, chronic kidney stage ≥3b, chronic hemodialysis, stroke, residual aortic regurgitation ≥ grade 2 and mean pressure gradient
Leon et al[56]	2011–2013	2032 intermediate-risk patients	1011 SAPIEN XT	11 (1.2%) at 2 y	2 y	Undefined	Undefined
Deeb et al[57] Gleason et al[58]	2011–2013	797	391 with attempted CoreValve	3 (0.9%) at 3 y 5 (1.8%) at 5 y	Median 35.8 mo Median 49.9 mo	Undefined	Undefined
Gallouche et al[69]	2012–2016	326	CoreValve (83), SAPIEN (243)	6 (1.8%)	460 d (median interquartile range 189–852 d)	2 (33%)	Undefined
Kolte et al[4]	2013–2014	29 306	Undefined	224 (0.8%)	Unmatched cohort median 153 d (interquartile range 91–244 d)	35 (16%) in-hospital	Younger age, cardiac arrest, sepsis, need for permanent pacemaker, history of heart failure, major bleeding
Yeo et al[5]	2012–2014	41 025	Undefined	120 (0.3%) in-hospital	Index hospitalization	25 (21%)	Younger age, drug abuse, HIV infection, fluid/electrolyte disorder, dyslipidemia
Thourani et al[70]	2014–2014	1077 intermediate-risk patients	SAPIEN 3	8 (0.8%) at 1-y	1 y	Undefined	Undefined
Spartera et al[71]	2008–2015	621	CoreValve/Evolut R, SAPIEN/XT/3, Direct Flow, Lotus, Evolut, Engager, Portico, Symetis,	8 (1.3%)	Median 402 d	6 (75%)	Undefined

(*Continued*)

Table 3. Continued

Study	Study Period	Study Population	Valve Type	TAVR Aortic PVE	Mean/Median Follow-Up	Mortality in TAVR PVE	Predictors of PVE
Cahill et al[72]	2007–2016	16 014	Undefined	157 with IE (1.0%)	Median 23.8 mo (interquartile range 7.8–52.4 mo)	1-y survival of 54.4%	Male sex, mechanically expandable/ balloon-expandable valves, elevated postdeployment aortic valve gradient
Butt et al[47]	2008–2016	2680	Undefined	115 (4.4%) patients without history of endocarditis and alive at discharge	Mean 2.8 y	46 (40%) 1-y mortality	Male sex, history of chronic kidney disease
Brennan et al[73]	2008–2017	661	Undefined	13 (2.0%)	Mean 40.4 mo	6 (46%) in-hospital	Undefined
Ali et al[38]	2008–2018	1337	Undefined	13 (1.0%)	Median 2.3 y (interquartile range 1.3–4.0 y)	5 (39%) in-hospital, 7 (54%) during study	Undefined
Bjursten et al[66]	2008–2018	4336	Undefined	103 (2.4%) with PVE, 50% with TAVR valve affected	Median 25.1 mo (interquartile range 11.7–43.7 mo)	17 (17%) in-hospital, 31 (30%) within 6 mo of PVE	Male sex, larger patients, decreased renal function, critical preoperative state, atrial fibrillation, history of malignancy, high mean aortic gradient, transapical access, amount of contrast used
Servoz et al[74]	2008–2018	996	Undefined	11 (1.1%)	1 y	4 (36%)	Chronic kidney disease, diabetes mellitus prevalent
Ando et al[60]	2002–2018	1895 overall IE (meta-analysis)	Undefined	75 (2.0%)	Mean 3.4 y	Undefined	Intermediate surgical risk cohort
Moriyama et al[46]	2008–2017	2130	Undefined	15 (0.7%)	Mean 3.1±1.7 y	3 (20%) in-hospital	Male sex, Vascular access-site infection
Mack et al[62]	2016–2017	1000 low-risk patients	496 with SAPIEN 3	1 (0.2%) at 1-y	1 y	Undefined	Undefined
Scislo et al[75]	2010–2018	311	Undefined	4 (1.3%)	Undefined	3 (75%)	Self-expandable valve system, increase in aortic regurgitation, urinary tract/lung infections
Fauchier et al[61]	2010–2018	16 291	All transfemoral, 8539 (52%) balloon-expandable	476 with IE (2.9%)	Mean 731 d, Median 424 d (interquartile range 15–1239 d)	12.60 deaths per year	Younger age, Charlson comorbidity/ frailty index, male sex, tricuspid regurgitation, atrial fibrillation, anemia
Popma et al[63]	2016–2018	725	Self-expandable	0.2% at 12 mo	Median 12.2 mo	Not distinguished in overall 2.4% mortality	Undefined

IE indicates infective endocarditis; PVE, prosthetic valve endocarditis; PVL, paravalvular leak; and TAVR, transcatheter aortic valve replacement.

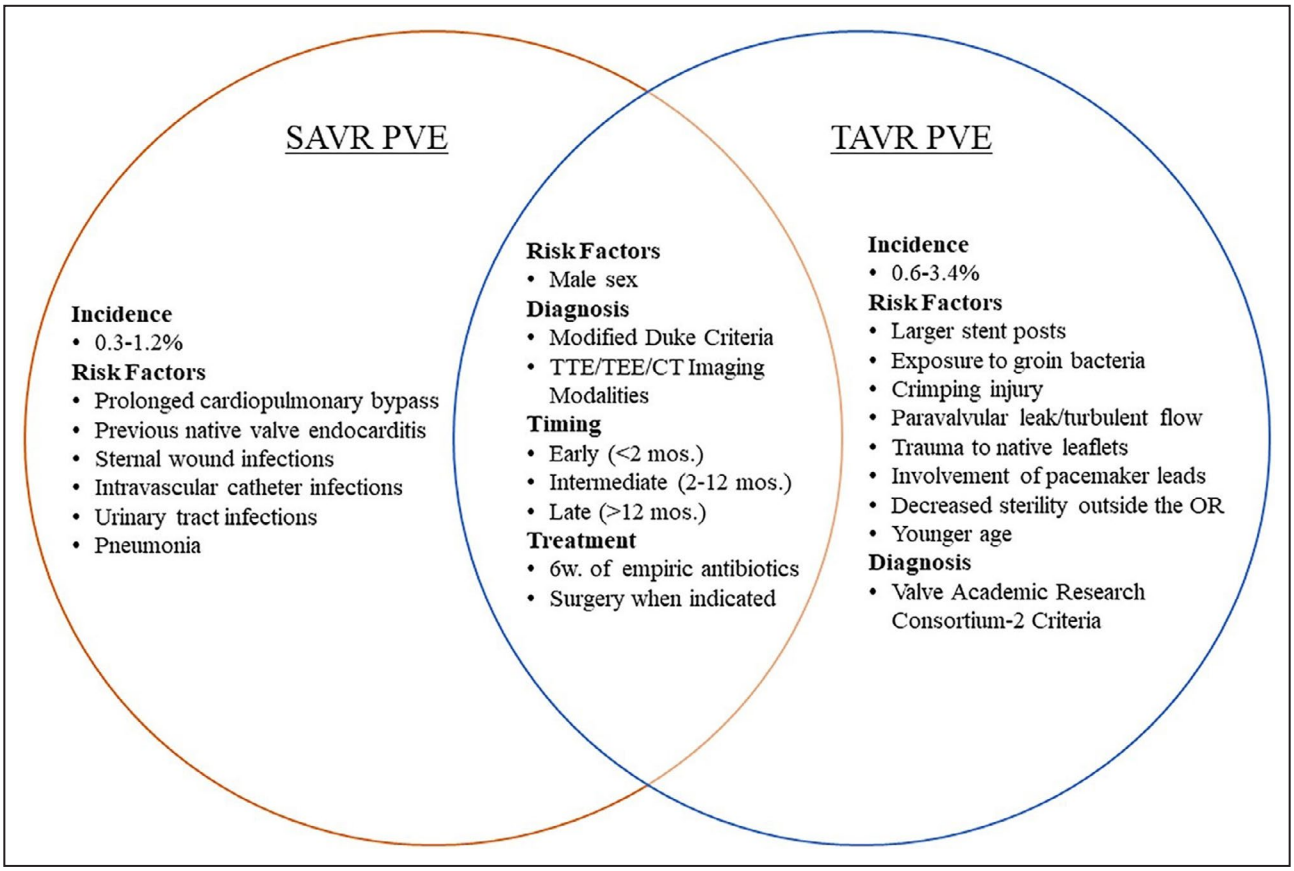

Figure 3. Summary of surgical and transcatheter aortic valve endocarditis.
CT indicates computed tomography; OR, operating room; PVE, prosthetic valve endocarditis; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TEE, transesophageal echography; and TTE, transthoracic echography.

mortality for SAVR. Therefore, longitudinal data on development of PVE in this population are limited. With <1 year of adverse event reporting and studies by Reguiero et al,[64] Mangner et al,[65] and Fauchier et al[61] that have shown younger age as a risk factor for TAVR PVE, we could see a shift in outcomes in the coming years.

Second, identifying vegetations in transcatheter patients with echocardiography can be challenging with the acoustic shadowing of the stented frame, contributing to lower diagnostic sensitivity by modified Duke criteria.[12,19,38] Distinguishing between postoperative paravalvular leak and prosthetic valve dehiscence is difficult, and adjunctive imaging such as ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography has only recently been used.[19,34,35]

In terms of study design, there is scant literature comparing SAVR and TAVR PVE and not all studies include predictors of the development of PVE. The heterogeneity among studies prevents pooling of key characteristics and outcomes for analysis. Further studies on factors influencing the high rate of TAVR PVE mortality are warranted.

CONCLUSIONS

PVE is a serious consequence of bacterial seeding in both SAVR and TAVR that comes with high risk of morbidity and mortality. Although culprit bacteria have typically been Streptococci and Staphylococci, Enterococci has become a predominant agent with transfemoral TAVR.[2] Young age has persistently been a risk factor in contracting PVE, which makes it a priority to understand the pathogenesis, patient presentation, and guideline-directed treatment of TAVR PVE, as it expands to younger and lower-risk patients (Figure 3). Utilization of an endocarditis team consisting of a surgeon, cardiologist, and infectious disease specialist can improve institutional results and provide bespoke care for these complex patients.

ARTICLE INFORMATION

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Supplementary Materials

Tables S1–S2
Figure S1
References 2–5, 38, 46, 47, 56–58, 60–75

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SUPPLEMENTAL MATERIAL

Table S1. The Newcastle-Ottawa Scale quality assessment of the included studies
Surgical Aortic Valve Replacement (SAVR) Studies

Study	**Selection of cohorts**			**Comparability of cohorts**			**Outcome**		**Total – GRADE**
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	*Note=Single arm studies were marked against a maximum of 6 points instead of 8 because of lack of a comparison*
Van Valen et al. [54]	1	X	1	1	X	1	1	1	6/6- A
Glaser et al. [49]	1	1	1	1	1	1	1	1	8/8- A
Grubitzsch et al. [55]	1	X	1	0	X	1	1	1	5/6- A
Leon et al. [56]	1	1	1	1	1	1	1	1	8/8- A
Deeb et al. [57]	1	1	1	1	1	1	1	1	8/8-A
Gleason et al. [58]	1	1	1	1	1	1	1	1	8/8-A
Kolte et al. [4]	1	X	1	1	X	1	0	1	5/6- A
Kyto et al. [51]	1	1	1	1	1	1	1	1	8/8- A

Kyto et al. [52]	1	1	1	1	1	1	1	1	8/8- A
Myllykangas et al. [59]	1	1	1	1	1	1	1	1	8/8- A
Andrade et al. [53]	1	X	1	1	X	1	1	1	6/6- A
Butt et al. [47]	1	1	1	1	1	1	1	1	8/8- A
Ando et al.* [60]	1	1	1	1	1	1	1	1	8/8-A
Moriyama et al. [46]	1	1	1	1	1	1	1	1	8/8-A
Fauchier et al. [61]	1	X	1	1	X	1	1	1	6/6-A
Mack et al. [62]	1	1	1	1	1	1	1	1	8/8-A
Popma et al. [63]	1	1	1	1	1	1	1	1	8/8-A

*Contains data from PARTNER, US CoreValve, NOTION, and PARTNER 2 Trials

Table S2. Transcatheter Aortic Valve Replacement (TAVR) Studies.

Study	Selection of cohorts			Comparability of cohorts		Outcome			Total – GRADE
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	*Note=Singl arm studies were marked against a maximum o 6 points instead of 8 because of lack of a comparison*
Latib et al. [67]	1	X	1	1	X	1	1	1	6/6- A
Amat-Santos et al. [2]	1	X	1	1	X	1	1	1	6/6- A
Olsen et al. [3]	1	X	1	1	X	1	1	1	6/6- A
Martinez-Selles et al. [68]	1	1	1	1	1	1	1	1	8/8- A
Regueiro et al. [64]	1	X	1	1	X	1	1	1	6/6- A
Mangner et al. [65]	1	X	1	1	X	1	1	1	6/6- A
Leon et al. [56]	1	1	1	1	1	1	1	1	8/8- A
Deeb et al. [57]	1	1	1	1	1	1	1	1	8/8-A

Gleason et al. [58]	1	1	1	1	1	1	1	1	8/8-A
Gallouche et al. [69]	1	X	1	1	X	1	1	1	6/6- A
Kolte et al. [4]	1	X	1	1	X	1	0	1	5/6- A
Yeo et al. [5]	1	X	1	0	X	1	0	0	3/6-B
Thourani et al. [70]	1	1	1	1	1	1	1	1	8/8-A
Spartera et al. [71]	1	X	1	1	X	1	1	1	6/6- A
Cahill et al. [72]	1	X	1	1	X	1	1	1	6/6-A
Butt et al. [47]	1	1	1	1	1	1	1	1	8/8-A
Brennan et al. [73]	1	X	1	1	X	1	1	1	6/6-A
Ali et al. [38]	1	X	1	1	X	1	1	1	6/6-A
Bjursten et al. [66]	1	X	1	1	X	1	1	1	6/6-A
Servoz et al. [74]	1	X	1	1	X	1	1	1	6/6- A
Ando et al.* [60]	1	1	1	1	1	1	1	1	8/8-A
Moriyama et al. [46]	1	1	1	1	1	1	1	1	8/8-A
Mack et al. [62]	1	1	1	1	1	1	1	1	8/8-A
Scislo et al. [75]	1	X	1	1	X	1	1	1	6/6-A

Fauchier et al. [61]	1	X	1	1	X	1	1	1	6/6-A
Popma et al. [63]	1	1	1	1	1	1	1	1	8/8-A

*Contains data from PARTNER, US CoreValve, NOTION, and PARTNER 2 Trials

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.