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Infective Endocarditis in the Transcatheter Era

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Destitutus ventis, remos adhibe.

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List of Abbreviations

18-FDG-PET	18 Fluorodeoxyglucose Positron Emission Tomography
AHA	American Heart Association
BCNIE	Blood Culture Negative Infective Endocarditis
CAMPAIGN	Clinical, Multicenter Project of Analysis of Infective Endocarditis in Germany
CDRIE	Cardiac device-related infective endocarditis
CoNS	Coagulase-negative staphylococci
CT	Computer Tomography
ECLS	Extracorporeal Life Support
EQ-SD-HRQoL	European Quality of Life 5 Dimensions Health-related quality of life
ESC	European Society of Cardiology
EuroSCORE	European System for Cardiac Operative Risk Evaluation
HRQOL	Health Related Quality of Life
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IE	Infective Endocarditis
IQR	Interquartile Range
KCCQ	Kansas City Cardiomyopathy Questionnaire
MHS	Mental Health Summary Score
MRSA	Methicillin-resistant Staphylococcus aureus
NICE	National Institute for Health and Care Excellence
NVE	Native Valve Endocarditis
NYHA	New York Heart Association
OPAT	Outpatient parenteral antibiotic therapy
OPS	Operation and procedure codes
PARTNER trial	Placement of Aortic Transcatheter Valves
PCI	Percutaneous coronary intervention
PHS	Physical health summary score
PPM	Patient Prosthesis Mismatch
PVE	Prosthetic Valve Endocarditis
PVL	Paravalvular Leakage
PVM	Prosthetic Valve Migration
SAVR	Surgical Aortic Valve Replacement
SD	Standard Deviation
SPECT	Single-photon emission computed tomography
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
SVD	Structural Valve Deterioration
TAVR	Transcatheter aortic valve replacement
THV	Transcatheter Heart Valve
TIE	Infective Endocarditis following Transcatheter aortic valve implantation
TOE	Transesophageal echocardiography
TTE	Transthoracic Echocardiography

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1. Introduction

1.1 Background

Transcatheter aortic valve replacement (TAVR) has come a long way since the first described case in 2002 by Cribier et al. [1] in a multimorbid patient in cardiogenic shock, with a high surgical risk profile. Although the patient died after 17 weeks, this set into motion a change in the treatment paradigm of aortic valve disease. Since then TAVR have now been performed in over 400,000 patients worldwide [2]. The number of TAVR procedures has been on the rise in Germany with a simultaneous decline in the number of isolated surgical aortic valve replacement (SAVR) procedures. In 2010, the number of isolated SAVR cases reported was 11,582 as compared to 3,629 TAVR cases. This declined to 9,233 isolated SAVR cases in 2019, whereas the number of TAVR cases rose to 15,304, with TAVR procedures accounting for 62.4% of the isolated aortic valve procedures [3].

The development of the TAVR procedure was aimed to be a minimally invasive surgical alternative for high-risk patients to treat aortic stenosis and improve quality of life. The initial trials carried out by Leon et al.[4] (PARTNER trial) reported significantly reduced all-cause mortality rates, repeat hospitalization, and cardiac symptoms, at the cost of higher incidence of major strokes and major vascular events [4,5]. Although a survival advantage has been established in comparison to medical treatment, the mortality rate has been described to be as high as 25-30% in the initial high risk cohorts [4,6]. A meta-analysis by Gonnah et al. [7], reported that the Kansas City Cardiomyopathy Questionnaire (KCCQ) and European Quality of Life 5 Dimensions Health-related quality of life (EQ-5D HRQoL) scores showed superiority for TAVI at 1 month but no significant difference compared with SAVR at 12 months. This was also the case for the improvement in Ney York Heart association (NYHA) classification [7].

The PARTNER 3 and the EVOLUT trials evaluated the benefit of TAVR in comparison to SAVR in low risk patients [8,9]. The trials demonstrated improved rates of survival and lower rates of disabling stroke in patients undergoing TAVR. However, longer follow-up of these patients showed that TAVR was non-superior to SAVR with respect to composite endpoints [8–11]. These trials led to a drastic increase in the number of TAVR procedures worldwide, due to fact that most patients following TAVR have shorter hospital stays and quicker return to daily activities [12].

With the percolation of the indication for TAVR in low-risk patients with a longer life expectancy and the increase in the number of TAVR procedures performed worldwide, it is also important to take a look at the long-term outcomes of this procedure in comparison to SAVR. The dysfunction of bioprosthetic valves has been divided into structural valve deterioration (SVD) and non-structural valve deterioration (non-SVD) [13–15].

Structural valve deterioration refers to intrinsic degeneration or dysfunction of the prosthetic valve materials whereas non-structural valve deterioration refers to secondary patient related processes such as intra-prosthetic or para- valvular regurgitation, prosthesis malposition, patient- prosthesis mismatch and late embolization [13,14]. Structural valve deterioration may also be caused due to pathological states such as thrombosis and endocarditis. With regard to structural valve deterioration, current literature compares the durability of SAVR and TAVR prostheses up to 5 years, with conflicting results [12,13]. While some studies report reduced valve durability due to moderate or severe aortic regurgitation, paravalvular regurgitation and reintervention, others reports suggest better durability in cases of TAVR prostheses [14,16]. Although long term TAVR data is lacking, long-term durability of SAVR prostheses has been reported to be excellent with a re-operation rate was 1.9% and 15% at 10 and 20 years, respectively [13,17]. Non-SVD refers to any abnormality which is not intrinsic to the valve prosthesis which leads to valve dysfunction, this includes residual intra-/para-prosthetic aortic regurgitation, pannus/suture entrapping of valve leaflets, inappropriate positioning/sizing of the valve prosthesis, aortic root dilatation, patient prosthesis mismatch and valve embolization [13,18]. Non-SVD can lead to valve-related death, reintervention, and haemodynamic dysfunction [13].

Of particular interest among the causes of structural valve deterioration of TAVR prostheses, is infective endocarditis (IE) following TAVR. Data regarding IE following TAVR is scarce, given the limited follow-up of first generation transcatheter heart valves (THV) and relatively small patient cohorts in comparison to available SAVR cohorts [19–21]. Even though IE following TAVR is recognized as a subtype of prosthetic valve endocarditis (PVE) and has been reported to have the same incidence as that of IE following SAVR, it is particularly challenging due to multimorbidity of the patients, raised rates of IE-related complications, the unknown role of cardiac surgery, and the bleak prognosis in most patients with IE following TAVR [22,23]. The majority of described cases occur early, usually within the first year following TAVR in intermediate- and high-risk patients [23,24]. Up to 90% of patients suffering from IE following TAVR undergo conservative treatment, and this has been

associated with high in-hospital mortality and poor short-term survival [25,26]. Furthermore, due to the multimorbidity of these patients and hight surgical risk, the current literature reports a general reluctance toward the surgical treatment of IE following TAVR, with some patients entering palliative care upon diagnosis [25–27]. Due to the lack of current evidence and possible profound impact on the outcomes of the TAVR procedure especially in young patients, this warrants further investigation.

1.2 Pathogenesis, incidence and risk factors of infective endocarditis following transcatheter aortic valve replacement

Infective endocarditis refers to the infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling cardiac device [23,28–30]. The development of IE occurs in 3 stages, the first of which is bacteraemia which involves bacteria or other pathogens entering the bloodstream via the mouth, gastrointestinal and urinary tracts, or the skin, through venous catheters or after invasive procedures. This is followed by adhesion, wherein pathogens adhere to abnormal or damaged endothelium. The final stage in the progression of the disease is colonization, in which the pathogens proliferate and additionally cause thrombosis, monocyte recruitment, and inflammation, leading to formation of a mature vegetation [28,29,31].

A significant difference between SAVR and TAVR for aortic valve stenosis is not only the access to the heart valve, but also the handling of the paravalvular tissue structures. While SAVR aims to remove the calcified native aortic valve as completely as possible, in cases of TAVR the calcifications of the native valve are used as a support for anchoring the valve prosthesis. This is of particular interest, as it has been shown that certain bacteria may be present dormant intramurally in the calcifications and that the TAVR procedure may rupture calcified valve tissue and might lead to reproliferation of intramurally localized bacteria [32,33].

Another major factor which may accelerate valve deterioration and may cause TIE is the process of crimping itself during the TAVR procedure as opposed to the “no-touch” technique applied by most operators performing SAVR [27,34]. Furthermore, it has been reported that the frame of the THV can also play a role in the development of IE following TAVR. Vegetations have been reported to be found more frequently anchored to the frame of self-expandable THVs, whereas balloon expandable THVs have been reported to be more prone to leaflet vegetations [35]. However the overall incidence of IE following TAVR is independent of the type of THV [23].

In 2019, the estimated incidence of IE was 13.8 cases per 100 000 subjects per year,and IE accounted for 66,300 deaths worldwide [23]. A review of the Destatis database, reveals an increasing number of patients being diagnosed with acute and sub-acute IE (International Classification of Diseases (ICD) code I33.0). In German hospitals, a total of 7,104 patients were hospitalised due to IE in 2015, this rose to 7,586 patients in 2016 and 8,017 patients in 2017.Right-sided IE accounts for 5–10% of IE cases. Although it may occur in patients with a

pacemaker, defibrillators, central venous catheter or congenital heart disease, this situation is most frequently observed in intravenous drug abusers, especially in patients with concomitant human immunodeficiency virus seropositivity or in immunosuppressed patients [23,36–38].

PVE is a serious form of IE and occurs in 1–6% of patients with valve prostheses and accounts for or 20–30% of all cases of IE. PVE may be further classified based on its onset. Early PVE refers to IE of prosthetic heart valves within 12 months of implantation, while late PVE refers to IE after 12 months [23,37,39]. Early PVE is most often caused by microorganisms indicating nosocomial infection, such as S. aureus, coagulase negative Staphylococci (CoNS), gram-negative bacteria, and fungi, whereas cases of late PVE are usually due to bacteria such as α-hemolytic streptococci and CoNS colonizing various human body surfaces [39]. There has been an increasing incidence of Enterococcus related TIE [19,20].

Despite substantial improvements in the TAVR procedure and its expansion to younger and healthier patients, the incidence of IE after TAVR remains stable, with incidence rates similar to those reported after surgical aortic valve replacement [19–21,40]. Current literature reports the incidence rate of IE following TAVR to lie between 2.3-3.4%, with the 5 year incidence of TIE following being 5.8% [41,42]. Autopsy case series have reported the incidence rate of IE to be as high as 12.5% in patients following TAVR [42]. It is quite possible that IE following TAVR is an underdiagnosed clinical entity, and only a small proportion of these patients are referred for surgical treatment.

There are several TAVR-specific factors which may lead to the development of IE. These include the non-sterile environment in the majority of cardiac catheterization laboratories and the high-risk profile of TAVR patients such as diabetes, immunosuppression (i.e., steroids, myelodysplastic syndromes), coincident infections, orotracheal intubation and renal failure [22,27]. Furthermore, leaflet compression during transcatheter valve preparation and loading resulting in a degree of leaflet damage which may act as a nidus for pathogen accumulation during transient bacteraemia [27,43]. The crimping of the valve leaflets and post dilatation may cause microscopic damage to the valve prosthesis, which may predispose it to infective endocarditis [27,43]. TAVR specific predisposing factors, such as younger age, male gender, renal dysfunction, significant residual aortic regurgitation,higher body mass index, severe pulmonary disease, pulmonary hypertension, cirrhosis, and prior cancer or chest radiation have been all associated with the development of IE following TAVR [19,23,44].

Identification of the specific underlying microbial etiology is essential for optimal patient management; delays in microbial diagnosis may contribute to late initiation of effective antimicrobial therapy, influencing morbidity and mortality [45]. Today, staphylococci and streptococci combined cause ca. 80% of cases. Staphylococcus aureus remains the dominant pathogen, associated with 25% to 30% of cases, while CoNS account for 11% of cases. Streptococci, primarily viridans group streptococci, cause ca. 30% of cases, with Streptococcus gallolyticus being involved in ca.20% to 50% of streptococcal cases [38,45]. Enterococci, especially Enterococcus faecalis, account for ca. 10% of cases. Gram-negative bacilli account for ca. 5% of cases and include the HACEK group (Haemophilus species, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae) organisms, less commonly, non-HACEK Gram-negative bacilli, such as the Enterobacteriaceae and nonfermenting Gram-negative bacilli. Fungi are rare endocarditis causes, with Candida species being the most common. A number of uncultivable or challenging to cultivate organisms cause endocarditis, the most common of which are Coxiella burnetii, Bartonella species, and Tropheryma whipplei [45,46].

The most (81.8%) frequently encountered agents in post-TAVR IE are coagulase-negative staphylococci (24.5%), Staphylococcus aureus (21%), enterococci (21%), and oral (formerly viridans) streptococci [27]. Less common causal agents include gram negative bacteria. The use of transfemoral access in TAVR and the proximity of the groin with genitourinary/intestinal system constitute a strong predisposing factor for the frequent isolation of enterococci. Staphylococci are dominant (29.4%) post transapical TAVR while enterococci represent the most common microorganisms (34.4%) post transfemoral TAVR [20,21,27].

1.3 Diagnostic challenges in infective endocarditis following transcather aortic valve replacement

Infective endocarditis is typically a syndrome diagnosis that is determined on the basis of the presence of multiple findings rather than a single definitive test result [47]. In cases of IE following TAVR, the predominant presenting symptoms include fever, clinical heart failure, conduction disorders, embolisms and general sepsis [47,48]. These generalized symptoms along with the multimorbid profile of these patients may skew diagnostic accuracy. Correct and timely diagnosis requires a high level of clinical suspicion and a multidisciplinary Endocarditis-Team Approach.

Duke Criteria

Diagnosis of infective endocarditis necessitates integration of clinical findings, microbiological analysis, and imaging results. The modified Duke clinical diagnostic criteria [29,47] incorporate these three domains and weigh findings as either major or minor criteria. A definite diagnosis requires two major, one major with three minor, or five minor criteria. Diagnosis of infective endocarditis is possible in the presence of one major and one minor criteria, or three minor criteria [29,47]. However, its diagnostic value is limited. For the diagnosis of IE, the Duke's criteria have been reported to be the gold standard. They have undergone several adjustments over the years including the St. Thomas modifications [31]. In the setting of native valve endocarditis (NVE) the Duke criteria have been shown to exhibit a sensitivity of 70–80%, but are less useful in the setting of PVE because of their lower sensitivity in this setting [37]. Furthermore, it has been reported that upto 15% of patients requiring surgery for IE do not meet the Duke criteria [36]. The current guidelines have further modified these guidelines to improve the sensitivity of diagnosis especially in cases of PVE [23]. This includes a multimodal diagnostic approach and identification of endocarditis typical microorganisms such as Enterococcus faecalis [23].

Echocardiography

Echocardiography is central to diagnosis and detection of IE. Three echocardiographic findings are major criteria in the diagnosis of IE: vegetation, abscess or pseudoaneurysm and new dehiscence of a prosthetic valve [23,30]. It is a matter of common knowledge that echocardiography may be normal or inconclusive in up to 30% of PVE patients and that the low sensitivity of the Duke criteria frequently leads to false negative diagnoses [30]. Although

trasnthoracic echocardiography (TTE) is the first applied imaging modality in cases of IE following TAVR, its diagnostic yield may be limited due to the metal struts which may cause acoustic shadowing. A transoseophageal echocardiography (TOE) can be used to better view of the prosthetic leaflets, and identification of perforations, abscesses, and fistulae [28,35]

Furthermore, data on echocardiographic interpretation of post-TAVR endocarditis is limited. This may be due to the unique characteristics with respect to variable valve locations, abscess formation, and obstructive patterns with leaflet thickening and fluctuating transvalvular gradients [49]. In the literature, it has been demonstrated that the diagnostic yield of echocardiography in IE following TAVR ranges between 55–86% [50]. Leaflet thickening and increased mean gradients (≥ 5 mm Hg) have been observed in up to 80% of confirmed TAVR endocarditis, respectively [51]. The presence of abscesses, prosthesis dehiscence, and new valvular regurgitation in the setting of IE following TAVR often complicate the diagnosis.

Computer Tomography

The current guidelines on IE have acknowledged the usefulness of modern imaging techniques such as computer tomography (CT) scans, 18-fluorodeoxyglucose positron emission tomography, (18-FDG-PET) or leukocyte scintigraphy (radiolabeled leukocyte single-photon emission computed tomography [SPECT]) in cases where the diagnosis is difficult by means of standard methods [28,30,52]. However, these imaging procedures are not universally available. Thus, it may be postulated, that a substantial number of cases remain undiagnosed due to lack of data and clinical experience [19,21].

Combining CT imaging with metabolic imaging by 18-FDG-PET or SPECT to show regions of metabolic activity or inflammation, respectively, is a hugely promising approach in patients who, according to the Duke criteria, have “possible” IE or suspected Cardiac device-related infective endocarditis (CDRIE) [28,52]. 18FDG-PET is a useful technique for detecting infection due to the high metabolic activity of inflammatory leukocytes. 18FDG-PET has been reported to have a sensitivity of 80.5% in detecting cases of PVE [52].

Coronary angiography

Coronary artery disease has a reported prevalence of 41% to 75% in patients with severe aortic stenosis undergoing TAVR [53]. Coronary angiography is recommended for the assessment of coronary artery disease when valvular surgery or intervention is planned, to determine if concomitant coronary revascularization is recommended [12]. Exceptions arise when there are

aortic vegetations that may be dislodged during catheterization or when emergency surgery is necessary. Furthermore, in cases of patients following TAVR, coronary access may be further challenging. This could be influenced by the height of the coronary ostia and the placement of the TAVR prostheses with respect to the commissures of the native aortic valve [53]. In these situations, high-resolution CT may be used to rule out significant coronary artery disease in haemodynamically stable patients [23,30].

1.4 Treatment of Infective Endocarditis

1.4.1 Endocarditis Team

Caring for patients with IE requires a team of physicians with expertise in various aspects of the disease. Because the clinical scenarios presented by patients with IE are most often complex, their successful management requires a multispecialty team approach. An Endocarditis-team should consist of cardiologists, cardiac surgeons, microbiologists, anaesthesiologists as well as radiologists, neurologists, and neurosurgeons. Additionally, general, and vascular surgeons and interventionalists are required to manage other embolic complications of IE [22,54]. Furthermore, the function of Endocarditis-teams entails close clinical follow up and cardiac rehabilitation [55]. The Endocarditis-team approach has been reported to result in early diagnosis, better management strategies as well as compliance in antimicrobial therapy and fewer cases of renal failure and deaths by embolic events and multiple organ failure [54,56].

1.4.2 Antibiotic prophylaxis and therapy

According to the current guidelines the use of antibiotic prophylaxis for IE has been restricted because of changes in pathophysiological conceptions [37,57–59]. On the one hand, the benefit from antibiotic prophylaxis for dental procedures remains unclear and prospective randomized controlled trials are lacking; on the other hand, there is a factual risk of the development of multi-resistant organisms and anaphylactic reactions [37]. These observations have been reflected in the guidelines of the American Heart Association (AHA) from 2007, those of the National Institute for Health and Clinical Excellence (NICE) from 2008, and of the European Society of Cardiology (ESC) from 2009 and 2015 [37,58,60,61]. High risk populations for IE which have been identified, include patients after prosthetic valve implantation or after cardiac valve repair using prosthetic material as well as patients after previous IE or untreated cyanotic congenital heart disease [37]. As a result of this de-escalation of antibiotic prophylaxis, a significant decrease of prescription of antibiotic prophylaxis has been observed [62]. At the same time, a significant increase in the incidence of IE was observed especially among high-risk individuals as well as, to a lesser degree, in moderate-risk individuals. An increasing trend

in the incidence of IE has also been reported in children [63]. Similarly, in Europe a 4% per year rise in the incidence of IE has been observed [64].

Due to the recent emergence of IE following TAVR, there are no randomized trials comparing different antibiotic regimens or treatment strategies. As a result, there are still no specific treatment recommendations, and antibiotic therapy recommendations are based on available guidelines for PVE [22,23]. Drug treatment of PVE should last longer (at least 6 weeks) than that of native valve endocarditis (NVE) (2–6 weeks). In NVE needing valve replacement by a prosthesis during antibiotic therapy, the postoperative antibiotic regimen should be that recommended for NVE, not for PVE [37]. Empirical therapy should cover should cover Staphylococci, Streptococci, Enterococci, and Gram-negative pathogens [43]. In cases of blood culture-negative infective endocarditis (BCNIE), treatment protocols with doxycycline and levofloxacin have been recommended. [43]. In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy (negative blood culture in the case of initial positive blood culture), not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, with the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate [37]. After careful selection, parenteral antibiotic therapy may also be administered in an outpatient setting (OPAT). This may be associated with shorter hospital stays, lower rates of nosocomial infections and lower cost [65]. OPAT is generally feasible following 2 weeks of in-hospital parenteral antibiotic therapy, when adequate infection control is achieved, and no adverse events have occurred.

Furthermore, there evidence for the use of oral antibiotics in IE as a step-down treatment after an initial period of parenteral therapy [66,67]. In cases of left sided IE caused by streptococcus, E. faecalis, S. aureus, or coagulase-negative staphylococci, in clinically stable condition and with an adequate response to initial treatment, a shift from initial intravenous to oral antibiotic treatment has been reported to be noninferior to continued intravenous antibiotic treatment [67]. It avoids the need for long hospital stays and the requirement for prolonged intravenous (IV) access, with its concurrent risks of infection and other complications. Administration of oral therapy would, however, come with the caveat of assuming reliable oral absorption and excellent patient compliance [66].

1.4.3 Surgical considerations

The two primary objectives of surgery for infective endocarditis are the total excision of infected tissues and reconstruction of cardiac morphology, which includes the repair or replacement of the affected valve(s) [37].

Infective endocarditis following TAVR

Surgery for infective endocarditis is the main cause of surgery following transcatheter aortic valve replacement [68]. Current literature reports that surgical explantation of the infected TAVR-prosthesis was performed in only 2–14% of IE following TAVR cases despite clear indications for surgical intervention in more than 80% of patients [25]. Early surgical treatment of complicated endocarditis improves outcome when compared to medical therapy alone, and can result in the reduction of 6-month mortality from 33 to 16% [69]. Open surgical intervention following TAVR should not be categorically excluded, because the number of younger and low-risk patients will continue to increase. The operative outcome is reasonable and predominantly driven by the complexity of the upcoming procedure itself rather than the fact of a former TAVR procedure. However, the indications for surgery should still be scrutinized critically [68].

Timing and Indications for surgery

As compared with conventional treatment, early surgery in patients with infective endocarditis and large vegetations significantly reduced the composite end point of death from any cause and embolic events by effectively decreasing the risk of systemic embolism [70]. Surgery is indicated when fever and positive blood cultures persist for several days (7–10 days) despite an appropriate antibiotic regimen and when extracardiac abscesses (splenic, vertebral, cerebral or renal) and other causes of fever have been excluded. However, the best timing for surgery in this difficult situation is unclear [37]. Delaying surgery could potentially increase the risk of developing local and systemic complications such as septic embolism, valve tissue destruction and invasion of paravalvular structures. The three main indications for early surgery in IE are heart failure, uncontrolled infection and prevention of embolic events [37].

Surgery is indicated in patients with heart failure caused by severe aortic or mitral regurgitation, intracardiac fistulae or valve obstruction caused by vegetations. Surgery is also indicated in patients with severe acute aortic or mitral regurgitation without clinical HF but with

echocardiographic signs of elevated left ventricular end-diastolic pressure, high left atrial pressure or moderate to severe pulmonary hypertension.

To achieve infection-control early surgery is indicated in fungal IE, in cases of multiresistant organisms (e.g., Methicillin resistant Staphylococcus aureus (MRSA) or vancomycin-resistant enterococci) or in the rare infections caused by Gram-negative bacteria. Surgery should also be considered in PVE caused by staphylococci or non-HACEK Gram-negative bacteria. Furthermore, S. aureus infection in the setting of NVE and PVE warrants surgery [37].

Surgery is indicated in patients with persisting vegetations >10 mm after one or more clinical or silent embolic events despite appropriate antibiotic treatment. Surgery undertaken for the prevention of embolism must be performed very early, during the first few days following initiation of antibiotic therapy, as the risk of embolism is highest at this time [37,71] .

Valve repair

Valve repair is favoured whenever possible, particularly when IE affects the mitral or tricuspid valve without significant destruction. Perforations in a single valve cusp or leaflet may be repaired with pericardial patches whereas ruptured chordae may be replaced by polytetrafluoroethylene neo-chordae. Following debridement, it is important to evaluate whether the remaining tissue is of sufficient quality to achieve a durable repair. Successful mitral valve repair in the setting of IE can be achieved by in up to 80% by experienced surgeons. Mitral subannular, annular or supraannular tissue defects are preferably repaired with pericardial patches, valve prostheses could be implanted in the reconstructed annulus if necessary. The choice of technique depends on the vertical extension of the lesion/tissue defect. In aortic valve IE, replacement of the aortic valve using a mechanical or biological prosthesis is the technique of choice [37].

Type of prostheses

Current guidelines do not distinguish between the use of mechanical and biological prostheses in the setting of IE. Homografts has been suggested to reduce the risk of persistent or recurrent infection, especially in the presence of annular abscesses. Homografts or stentless xenografts may be preferred in PVE or in cases where there is extensive aortic root destruction with aorto-ventricular discontinuity [37].

2. Aims and Objectives

It has been observed that the number of TAVR prostheses being implanted worldwide is increasing by leaps and bound, along with that the incidence of infective endocarditis is on the rise too. As with conventional SAVR prostheses, TAVR prostheses too are disposed to IE. Infective endocarditis following TAVR is a challenging disease and with the given paucity of clinical data it warrants further systematic investigation.

The aims of this work are the following:

- To analyse the causes of failure of transcatheter aortic valves.
- To explore the impact of the changes in the guidelines and pathogens causing infective endocarditis in the era of transcatheter valve replacement.
- To investigate the operative aspects and outcomes of surgery for infective endocarditis in patients following transcatheter aortic valve implantation.

3. Summary of Original Works

3.1 Failure of transcatheter aortic valves

3.1.1 Cardiac surgery following transcatheter aortic valve replacement

Saha S, Peterss S, Mueller C, Deseive S, Sadoni S, Hausleiter J, Massberg S, Hagl C, Joskowiak D.

Eur J Cardiothorac Surg. 2021 Nov 2;60(5):1149-1155. doi: 10.1093/ejcts/ezab217. PMID: 34021322.

Background:

Over half a million transcatheter aortic valve replacements (TAVR) have been performed worldwide with a case volume growing by 40% annually [72]. Intended for patients with high surgical risk, TAVR procedures further expanded into intermediate- and low-risk cohorts, based on the findings of recent multi-center trials like PARTNER 3 and Evolut LR [8,9]. However, even if comparable in periprocedural results, long term data regarding durability and integrity are limited [17]. The aim of the study was to review our institutional experience in patients undergoing such conventional cardiac surgery following a primary TAVR implantation and analyze the underlying causes and the operative results of such regimen.

Methods:

Between December 2012 and February 2020, 41 consecutive patients underwent cardiac surgery after TAVR procedure at our institution. Patients who underwent emergent operations due to periprocedural complications such as ventricular rupture and TAVR dislocation, were excluded from this study (n=12). Thus, 29 patients were included in the analysis. The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) were used to predict the risk of perioperative mortality at the time of the TAVR and at the time of surgical revision. Reoperations were defined as one or more previous major cardiac operations that involved opening the pericardium [73]. Degeneration of the TAVR prostheses was determined as recommended by Capodanno et al. [13]. Prosthetic valve endocarditis was diagnosed according to the modified Duke criteria and the 2015 European Society of Cardiology guidelines on infective endocarditis [37]. Data are presented as medians (25th-75th quartiles) or as absolute numbers (percentages).

Results:

Median age was 76 years (68-80), 58.6% male. The median time to secondary conventional procedure was 23 months (8-40), with 8 patients requiring surgical intervention within the first-year post TAVR. Indication for secondary conventional procedures were prosthesis endocarditis (n=15), prosthesis degeneration or dysfunction (n=7) and progress of valvular, aortic or coronary artery disease (n=7). Demographic characteristics are listed in **Table 1**.

	Total (n= 29)
Baseline characteristics	
Age (years)	76 (68-80)
Male (%)	17 (58.6)
Body mass index (kg/m^2)	26.6 (24.8-29.7)
EuroSCORE II (%)	13 (7.6-26.9)
STS PROM (%)	2.7 (1.4-3.5)
Comorbidities	
Arterial hypertension (%)	27 (93.1)
Atrial fibrillation (%)	8 (27.6)
Insulin-dependent diabetes (%)	11 (37.9)
Chronic kidney disease (%)	12 (41.4)
Hyerlipidemia (%)	16 (55.2)
COPD (%)	13 (44.8)
Coronary artery disease (%)	15 (51.7)
Peripheral artery disease (%)	6 (20.7)

Table 1: Demographics of patients undergoing cardiac surgery following TAVR.

Data are presented as medians (25th–75th percentiles) or absolute numbers (percentages).COPD: chronic obstructive pulmonary disease; EuroSCORE II: European System for Cardiac Operative Risk Evaluation II; STS PROM: Society of Thoracic Surgeons Predicted Risk of Mortality.

The details of surgical procedures performed is listed in **Table 2**. Surgical redo aortic valve replacement was performed in 24 patients (82.8%). No complications involving the aortic root, or the aorto-mitral continuity were observed. The operative mortality was 10.3%. Extracorporeal life support (ECLS) support was required in 3 patients (10.3%) for a median duration of 3 days (3-3 days) No adverse cerebrovascular events were observed postoperatively.

Postoperatively, 4 patients (13.8%) required a pacemaker and 7 patients (24.1%) required renal replacement therapy. Survival at 6-months and 1-year was 94.0% respectively.

	Total (n= 29)
Details of Surgery	
Cardiopulmonary bypass time (min)	121 (83-180)
Aortic cross-clamp time (min)	86 (59-112)
Primary Indication for surgery	
Surgical aortic valve replacement (%)	24 (82.8)
CABG (%)	3 (10.3)
Mitral valve surgery (%)	2 (6.9)
Concomitant procedures	
Mitral valve surgery (%)	5 (17.2)
Tricuspid valve surgery (%)	2 (6.9)
CABG (%)	1 (3.4)

Table 2: Details of surgery and concomitant procedures

Data are presented as medians (25th–75th percentiles) or absolute numbers (percentages). CABG: Coronary artery bypass grafting.

Main findings:

In this study, we analyzed our institutional experience of patients requiring cardiac surgery following TAVR. The goal of this study was to analyse the outcome of patients undergoing a potpourri of procedures following index TAVR. In this study we found that the main indications for cardiac surgery following TAVR were prosthetic valve endocarditis, prosthesis degeneration or dysfunction and progress of valvular, aortic or coronary artery disease. With prosthetic valve endocarditis being the main indication for surgery following TAVR (51.7%). As seen above this cohort is a multimorbid one, with a high rate of comorbidities. TAVR explantation is deemed surgically challenging and was performed in 24 patients in this cohort. The rate of post operative morbidities was low, with no adverse cerebrovascular events being observed. This study found good operative results and an operative mortality of 10.3%, which

was lower than estimated by the EuroSCORE II. In patients with TAVR, IE and the progress of other cardiac pathologies may warrant surgery.

Conclusions:

Open surgical intervention following TAVR should not be categorically excluded, as the number of younger and low-risk patients will further increase. The operative outcome is reasonable and predominantly driven by the complexity of the upcoming procedure itself rather than the fact of a former TAVR procedure. However, the indication for surgery should still be scrutinized critically. Conventional cardiac surgical procedures following TAVR are feasible with reasonable results and low complication rate.

3.1.2 Surgical Explantation After TAVR Failure: Mid-Term Outcomes From the EXPLANT-TAVR International Registry.

Bapat VN, Zaid S, Fukuhara S, **Saha S**, Vitanova K, Kiefer P, Squiers JJ, Voisine P, Pirelli L, von Ballmoos MW, Chu MWA, Rodés-Cabau J, DiMaio JM, Borger MA, Lange R, Hagl C, Denti P, Modine T, Kaneko T, Tang GHL; EXPLANT-TAVR Investigators.

JACC Cardiovasc Interv. 2021 Sep 27;14(18):1978-1991. doi: 10.1016/j.jcin.2021.07.015. PMID: 34556271.

Background:

Transcatheter aortic valve replacement (TAVR) was initially introduced to treat inoperable and high-risk patients with symptomatic severe aortic stenosis. Two options exist to address TAVR failure: redo TAVR (tricuspid aortic valve–in–tricuspid aortic valve) or surgical explantation of the TAVR device (TAVR explantation). Surgical explantation following TAVR may be required for structural valve degeneration, paravalvular leak, infection, or other reasons. However, in-depth data on indications and outcomes are lacking. The goal of this study was to report acute and mid-term results from the international EXPLANT-TAVR registry, including the timing of THV failure and its mechanism, the type of surgery performed, and clinical outcomes.

Methods:

Data from a multicenter, international registry (EXPLANT-TAVR) of patients who underwent TAVR explantation were reviewed retrospectively. Explantations performed during the same admission as initial TAVR were excluded. Clinical and echocardiographic outcomes were evaluated. Median follow-up duration was 6.7 months (interquartile range [IQR]: 1.0-18.8 months) after TAVR explantation and was 97.7% complete at 30 days and 86.1% complete at 1 year. All patients who required emergency surgical conversion immediately after TAVR or surgical intervention within the same hospitalization were excluded from the study.

Results:

From November 2009 to September 2020, 269 patients across 42 centers with a mean age of 72.7±10.4 years underwent TAVR explantation. About one quarter (25.9%) were deemed low surgical risk at index TAVR, and median Society of Thoracic Surgeons risk at TAVR explantation was 5.6% (Intraquatile Range (IQR): 3.2%-9.6%). Comorbidities at the time of

index TAVR are presented in **Table 3**. The median time to explantation was 11.5 months (IQR: 4.0-32.4 months). Balloon-expandable and self-expanding or mechanically expandable valves accounted for 50.9% and 49.1%, respectively.

Indications for explantation included endocarditis (43.1%), structural valve degeneration (20.1%), paravalvular leak (18.2%), and prosthesis-patient mismatch (10.8%). Redo TAVR was not feasible because of unfavorable anatomy in 26.8% of patients. Urgent or emergency cases were performed in 53.1% of patients, aortic root replacement in 13.4%, and 54.6% had concomitant cardiac procedures. The mean duration of cardiopulmonary bypass was 150.9±72.4 mins and the mean aortic cross-clamp time was 109.4±57 mins. Operative mortality was 0.7%. The most common postoperative complications included atrial fibrillation (9.0%), acute renal failure (8.2%) and multisystem organ failure (7.4%).

Characteristics at the Time of Index TAVR	
	(n=269)
Age (y)	72.7 ±10.4
Female	94 (34.9)
Frailty	85 (32.3)
Coronary artery disease	146 (54.3)
Stroke	41 (15.4)
Cerebrovascular disease	74 (27.7)
Peripheral vascular disease	55 (20.6)
Diabetes	93 (34.8)
Atrial fibrillation	105 (39.3)
Pulmonary hypertension	81 (31)
Chronic kidney disease	101 (38.8)
Dialysis dependent	11 (4.1)
Chronic obstructive pulmonary disease	66 (24.7)
Hostile chest or chest deformity	20 (7.5)
Porcelain aorta	17 (6.4)
Left ventricular ejection fraction (%)	51.2 ±12.2
Prior permanent pacemaker/ICD	57 (21.2)
Prior PCI	79 (29.4)
BSA, m2	2±0.3
NYHA functional class at original TAVR	
I	17 (6.9)
II	59 (24)
III	133 (54.1)
IV	37 (15)
Previous cardiac surgery	103 (38.3)
STS-PROM at original TAVR (%)	5.0±5.0
EuroSCORE II at original TAVR (%)	7.3 ±8.9
Risk stratification at original TAVR	
Low	51 (25.9)
Intermediate	65 (33)
High	63 (32)
Extreme	18 (9.1)

Table 3: Patient characteristics at index TAVR.

Values are mean±SD or n (%), n=269. EuroSCORE: European System for Cardiac Operative Risk Evaluation; ICD: implantable cardioverter-defibrillator; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR: transcatheter aortic valve replacement.

Overall survival at last follow-up was 76.1%. In-hospital, 30-day, and 1-year mortality rates were 11.9%, 13.1%, and 28.5%, respectively, and stroke rates were 5.9%, 8.6%, and 18.7%, respectively.

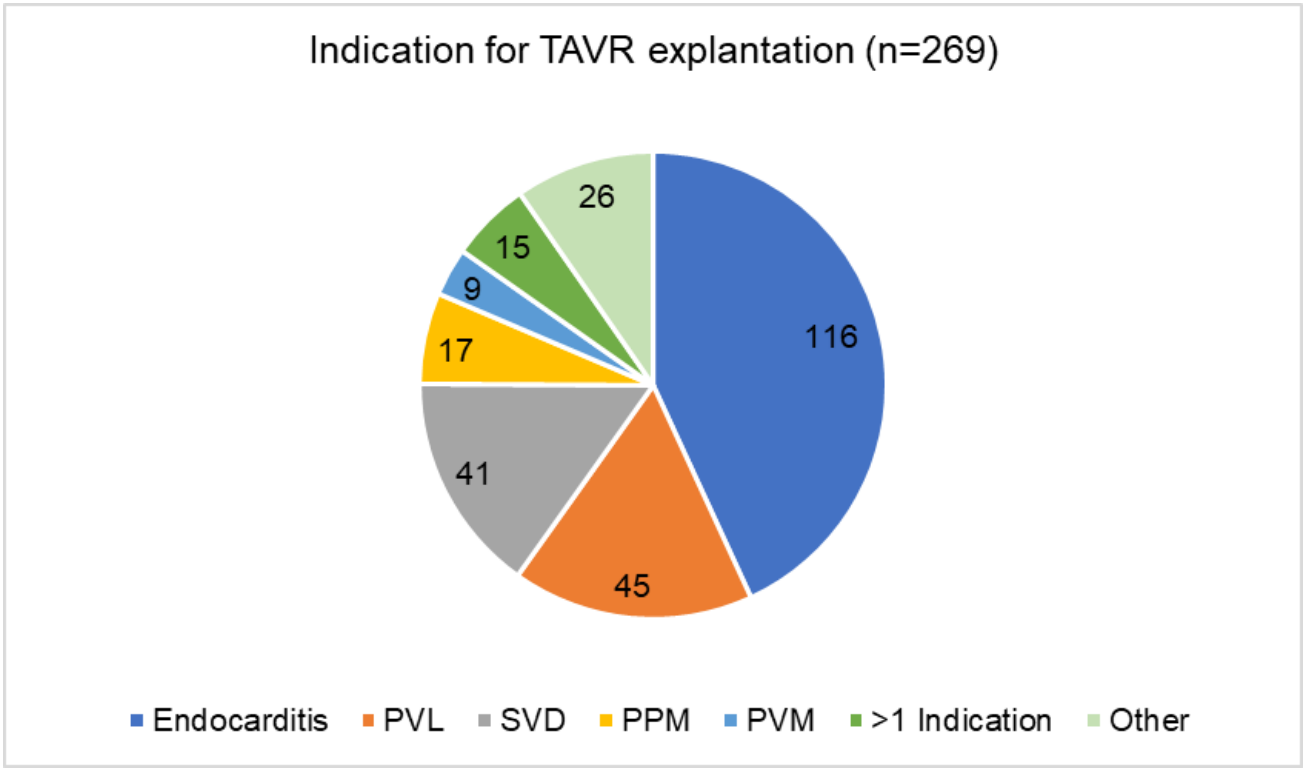

Figure 1: Indications for TAVR explantation.

PPM: Patient prosthesis mismatch; PVL: Paravalvular leakage; PVM: Prosthetic valve migration, SVD: Structural valve degeneration.

Main findings:

Following this we investigated further in a multicenter analysis. In this study data was collected across 42 centres worldwide. A total of 269 patients underwent TAVR explantation per our inclusion criteria. All adult patients who underwent surgical aortic valve intervention requiring TAVR explantation due to the following conditions: infective endocarditis, structural valve disease, paravalvular leak, severe prosthesis-patient mismatch, delayed coronary obstruction requiring valve explantation, or inability to perform redo TAVR after initial TAVR. High risk patients made up more than a third of the cohort. Even in this cohort IE was by far the most common indication for the explantation of TAVR prostheses. In this cohort, IE accounted for 43% of the cases which required TAVR explantation followed by structural valve deterioration

(20.1%) and paravalvular leakage (18.2%). Concomitant cardiac procedures were performed in 54.6% of the patients. The operative mortality was as low as 0.7% in this cohort.

Conclusions:

Infective endocarditis was an important indication for the TAVR explantation. The EXPLANT-TAVR registry reveals that surgical risks associated with TAVR explantation are not negligible and should be taken into consideration in the lifetime management of aortic stenosis.

3.1.3 Explant vs Redo-TAVR After Transcatheter Valve Failure Mid-Term Outcomes From the EXPLANTORREDO-TAVR International Registry

Tang GHL, Zaid S, Kleiman NS, Goel SS, Fukuhara S, Marin-Cuartas M, Kiefer P, Abdel-Wahab M, De Backer O, Søndergaard L, **Saha S**, Hagl C, Wyler von Ballmoos M, Bhadra O, Conradi L, Grubb KJ, Shih E, DiMaio JM, Szerlip M, Vitanova K, Ruge H, Unbehaun A, Kempfert J, Pirelli L, Kliger CA, Van Mieghem N, Hokken TW, Adrichem R, Modine T, Corona S, Wang L, Petrossian G, Robinson N, Meier D, Webb JG, Cheung A, Ramlawi B, Herrmann HC, Desai ND, Andreas M, Mach M, Waksman R, Schults CC, Ahmad H, Goldberg JB, Geirsson A, Forrest JK, Denti P, Belluschi I, Ben-Ali W, Asgar AW, Taramasso M, Rovin JD, Di Eusanio M, Colli A, Kaneko T, Nazif TN, Leon MB, Bapat VN, Mack MJ, Reardon MJ, Sathananthan J.

JACC Cardiovasc Interv. 2023 Apr 24;16(8):927-941. doi: 10.1016/j.jcin.2023.01.376. PMID: 37100556.

Background:

Transcatheter aortic valve replacement (TAVR) is now approved across all surgical risk profiles. As TAVR expands to younger, lower-risk patients with longer life expectancies, reintervention is likely to become more common. Given that long-term data on THV durability are limited, lifetime management of aortic stenosis and THV failure is becoming more important. There are currently 2 treatment strategies for THV failure: redo-TAVR or surgical explantation of TAVR (TAVR-explant), with redo-TAVR having more favourable 30-day outcomes compared with TAVR-explant. Other registry studies have reported the incidence, characteristics, and outcomes from each group independently, but none have compared the 2 groups across the same centers and included detailed procedural and imaging data. It also remains unclear which treatment option is preferred, as each may have certain inherent limitations. For example, redo-TAVR (TAVR-in-TAVR) may not be feasible in a subgroup of patients who have unfavourable anatomy or may not be appropriate due to a prior valve-in-valve procedure. We therefore sought to evaluate the incidence, characteristics, and outcomes of patients who had TAVR-explant or redo-TAVR, specifically in patients with THV failure, that were not acute or due to endocarditis, in a multicentre international registry.

Methods:

From May 2009 to February 2022, 396 patients in the international EXPLANTORREDO-TAVR registry underwent TAVR-explant (181, 46.4%) or redo-TAVR (215, 54.3%) for THV failure during a separate admission from the initial TAVR. Outcomes were reported at 30 days and 1 year.

Results:

The incidence of reintervention after THV failure was 0.59% with increasing volume during the study period. Median time from index-TAVR to reintervention was shorter in TAVR-explant vs redo-TAVR (17.6 months [IQR: 5.0-40.7 months] vs 45.7 months [IQR: 10.6-75.6 months]; p< 0.001], respectively.

	Redo-TAVR	TAVR-Explant	p-value
Structural valve deterioration	63.7	51.9	0.023
Paravalvular leakage	32.8	28.7	0.44
Patient prosthesis mismatch	0.5	17.1	<0.001
THV Thrombosis	3.9	1.7	0.23
THV migration	0.5	3.9	0.055

Table 4: Mechanisms of TAVR Failure.

Data is presented as percentages. THV: Transcatheter Heart Valve

TAVR explant had more prosthesis–patient mismatch (17.1% vs 0.5%; p< 0.001) as the indication for reintervention, whereas redo-TAVR had more structural valve degeneration (63.7% vs 51.9%; p=0.023), with a similar incidence of moderate paravalvular leak between groups (28.7% vs 32.8% in redo-TAVR; p=0.44). There was a similar proportion of balloon-expandable THV failures (39.8% TAVR-explant vs 40.5% redo-TAVR; p=0.92). Median follow-up was 11.3 (IQR: 1.6-27.1 months) after reintervention. Stroke rates were similar between the 2 groups at 30 days (4.2% redo-TAVR vs 2.4% TAVR-explant; p=0.40) and 1 year (5.8% vs 4.6%; p=0.78). Compared with redo-TAVR, TAVR-explant had higher mortality at 30 days (13.6% vs 3.4%; p< 0.001) and 1 year (32.4% vs 15.4%;p<0.001), with similar stroke rates between groups. On landmark analysis, mortality was similar between groups after 30 days (p=0.91). On univariate analysis, 1-year mortality after redo-TAVR was associated with STS PROM at index-TAVR, heart team–determined risk at index-TAVR, diabetes, stroke, dialysis, STS PROM at redo-TAVR, and new permanent pacemaker implantation.

Main findings:

We investigated the outcomes of patients who had underwent explantation of the TAVR prosthesis or redo-TAVR, specifically in patients with failure of transcatheter aortic valves, that were not acute or due to endocarditis. This multicenter, international EXPLANTORREDO-TAVR registry is the first study to report the incidence, characteristics, and mid-term outcomes of TAVR-explant and redo-TAVR across the same centers. This registry included 29 centres performing both surgical and transcatheter reintervention for THV failure. A total of 553 patients were identified. In this study, all patients suffering from IE following TAVR excluded (28.4%). Redo TAVR was performed in 215 patients and the TAVR prosthesis was explanted in 181 patients. This study shows similar mortality and stroke rates following the interventional or surgical management of TAVR failure. It is important to note that all patients who suffered from IE following TAVR, underwent surgery in this cohort.

Conclusions:

In this first report of the EXPLANTORREDO-TAVR global registry, TAVR-explant had a shorter median time to reintervention, with less structural valve degeneration, more prosthesis–patient mismatch, and similar paravalvular leak rates compared with redo-TAVR. TAVR-explant had higher mortality at 30 days and 1 year, but similar rates on landmark analysis after 30 days.

3.2 Changes in the guidelines and pathogens causing infective endocarditis.

3.2.1 Bacterial Spectrum and Infective Foci in Patients Operated for Infective Endocarditis: Time to Rethink Strategies?

Saha S, Dudakova A, Danner BC, Kutschka I, Schulze MH*, Niehaus H*.

Thorac Cardiovasc Surg. 2023 Jan;71(1):2-11. doi: 10.1055/s-0041-1740540. Epub 2022 Feb 8. PMID: 35135025.

Background:

As a result of the de-escalation of antibiotic prophylaxis, a significant decrease of prescription of antibiotic prophylaxis has been observed [62]. At the same time, a significant increase in the incidence of IE was observed especially among high-risk individuals as well as, to a lesser degree, in moderate-risk individuals. An increasing trend in the incidence of IE has also been reported in children [63]. It has been reported that the annual incidence of IE is 3-10 in 100,000 citizens with a mortality of up to 30% at 30 days [74].

Objective:

The rising incidence of IE along with changes to the antibiotic prophylaxis in the guidelines along with multimorbidity makes the management of IE challenging. We reviewed all patients who underwent cardiac surgery for IE at our institution with a focus on causative organisms and infective foci.

Methods:

Between January 2013 and December 2017, a total of 3952 patients underwent cardiac surgery at our center, this included 160 patients (4.0%) who were operated due to I.E. Patients with pacemaker infection, without indication for heart valve surgery were excluded from the study. Postoperative treatment and data acquisition were performed as part of routine patient care. All procedures described in this study were in accordance with the institutional research committee, national data safety regulations, and the 1964 Helsinki declaration and its last amendment by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Data acquisition was based on our institutional database and has been de-identified. The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was used to predict the risk of perioperative mortality.

Results:

In German hospitals, a total of 7,104 patients were hospitalized due to IE in 2015; this rose to 7,586 patients in 2016 and 8,017 patients in 2017, as reported by the Destatis database [75].The predominantly affected valves were the aortic (30.0%) and mitral valve (26.9%) as well as a combination of both (8.8%). A total of 28.8% of patients suffered from prosthetic valve endocarditis (PVE).

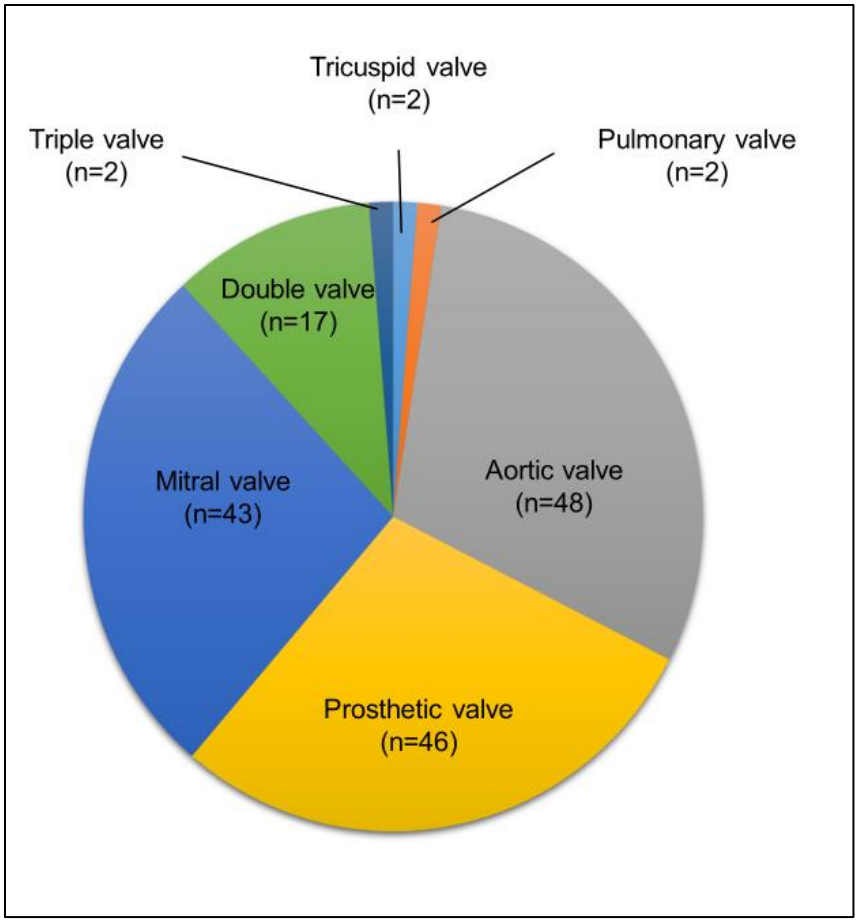

Figure 2: Valves affected.by infective endocarditis.

The evaluation of the Duke criteria revealed a total of 115 patients (71.8%) presenting with two major criteria and a total of 21 patients (13.1%) presenting with one major criterion and three minor criteria, whereas 24 patients (15%) did not meet the Duke criteria. A positive blood culture was available in 121 patients (75.6%). Echocardiographic evidence of vegetations was present in 148 patients (93%), whereas echocardiographic findings were consistent with respect to IE in 11 patients (6.9%).

The most frequently identified causative organisms were Staphylococcus (45.6%), Streptococcus (27.5%) and Enterococcus species (16.7%), which was predominantly associated

with PVE (p=0.050). In 13.1% of patients a causative organism has not been detected. The most frequent infective foci were dental (15.0%), soft tissue infections (15.0%), spondylodiscitis (10.0%) and infected intravascular implants (8.8%). Relevant predisposing factors were immunosuppression (9.4%) and intravenous drug abuse (4.4%). Septic cerebral infarctions were diagnosed in 28.8% of patients, the majority of whom were patients with MRSA infections (p=0.039). A total of 124 patients (77.5%) survived to discharge. The most frequently observed adverse events were cardiogenic shock in 67 patients (41.9%), acute kidney injury in 64 patients (40%), and nosocomial pneumonia in 61 patients (38.1%). Extracorporeal life support (ECLS) was required in a total of seven patients (4.4%), whereas an intra-aortic balloon pump was applied in five patients (3.1%). Median time on ECLS was 6 days (1–8). Median time on mechanical ventilation was 26 hours (9–119), with a median stay on intensive care unit of 5 days (2–12).

Main findings:

In this study, we reviewed our institutional experience of infective endocarditis. We observed a steady increase in the number of cases of infective endocarditis, as seen in the Destatis database. Furthermore, we found that 15% of the patients did not meet the Duke criteria. The most frequent infective foci were dental (15.0%), soft tissue infections (15.0%), spondylodiscitis (10.0%) and infected intravascular implants (8.8%). Septic cerebral infarctions were diagnosed more often in patients with MRSA infections. In-hospital mortality was 22.5% and was comparable to the mortality reported in the literature.

Conclusions:

Infective endocarditis remains a life-threatening disease associated with a substantial morbidity and mortality in cardiac surgery patients. As the predominant infective foci as well as the most frequent pathogens are still the "old acquaintances" for which standardized effective and low-risk protocols for antibiotic prophylaxis are available and with regard to the continuously increasing incidence of IE, current risk-benefit evaluations may need to be re-visited.

3.2.2 *Impact of the 2009 ESC Guideline Change on Surgically Treated Infective Endocarditis*

Weber C, Luehr M, Petrov G, Misfeld M, Akhyari P, Tugtekin SM, Diab M, **Saha S**, Elderia A, Lichtenberg A, Hagl C, Doenst T, Matschke K, Borger MA, Wahlers T.

Ann Thorac Surg. 2022 Oct;114(4):1349-1356. doi: 10.1016/j.athoracsur.2022.01.054. Epub 2022 Feb 22. PMID: 35216990.

Background:

In 2009, updated European Society of Cardiology guidelines on the prevention, diagnosis, and treatment of infective endocarditis (IE) were released and restricted the use of antibiotic prophylaxis to high-risk patients only. The aim of this study was to analyze the effect of the restrictive antibiotic regimen on the incidence and manifestations of surgically treated IE before and after the guideline change.

Methods:

This national multicenter retrospective analysis of the CAMPAIGN working group (Clinical, Multicenter Project of Analysis of Infective Endocarditis in Germany) included the relevant clinical data of all consecutive 4917 patients who underwent operations for IE in 6 German cardiac surgery centers between 1994 and 2018. There were no formal exclusion criteria. Each participating center used the International Classification of Diseases, 10th Revision with German Modification (ICD-10-GM) codes and operation and procedure codes (OPS codes) to identify patients who underwent surgical therapy for IE. The information collected included demographic data and comorbidities, the manifestations of IE according to the modified Duke criteria (echocardiographic and microbiologic data), perioperative data (cardiopulmonary bypass time, cross-clamp time, and concomitant procedures) and relevant postoperative outcomes. Potential risk factors for 30-day mortality were assessed using logistic regression. IE-relevant complications were reported for the hospital stay. Interrupted time series regression was used to evaluate the effect of the guideline change on the manifestation of IE.

Results:

A total of 2014 patients (41%) underwent surgical procedures before the guideline change, and 2903 patients (59%) underwent surgical procedures after the change. After 2009, patients were older (67.0 years IQR,56.0-74.0 years] vs 64.0 years [IQR, 52.0-71.0 years]; p< .001), and they

presented with more comorbidities, such as hypertension (56.9% vs 41.7%; p< .001), diabetes (27.4% vs 24.4%; p=.020), peripheral artery disease (8.5% vs 6.5%;p=.011), and preoperative acute kidney injury (42.8% vs 31.9%;p< .001). Patients had worse clinical outcomes with respect to 30-day mortality (18.1% vs 14.3%; p=.001) and 1-year mortality (37.1% vs 29.1%; p< .001). An increase in Streptococcus-related IE (p=.002) and an increase in mitral valve IE (p<.035) were observed after the guideline change.

Main findings:

Our study explored the effects of the changes in the antibiotic regimes on the presentation of patients with IE. We found that the number of patients with mitral valve endocarditis increased. We found an increase in the number of patients presenting prosthetic valve endocarditis following the changes in the prophylaxis regimes. Although we observed an increased incidence of pacemaker-associated IE, the incidence of right-sided IE was substantially lower after the 2009 changes in the guidelines. Although we could not determine a causal relationship, we were able to describe an increase in Streptococcal mediated IE. However, Streptococci did not remain an independent risk factor in the multivariable analysis, the increase in streptococcal IE seems not to be responsible for the worse outcomes of IE following changes in the guidelines.

Conclusions:

Since 2009, there has been a significant increase in the incidence of mitral valve IE and Streptococcus related IE. Patients undergoing surgical procedures for IE present with more comorbidities, which contribute to high mortality rates.

3.2.3 *Four decades of experience of prosthetic valve endocarditis reflect a high variety of diverse pathogens*

Oberbach A, Schlichting N, Hagl C, Lehmann S, Kullnick Y, Friedrich M, Köhl U, Horn F, Kumbhari V, Löffler B, Schmidt F, Joskowiak D, Born F, **Saha S**, Bagaev E.

Cardiovasc Res. 2023 Mar 31;119(2):410-428. doi: 10.1093/cvr/cvac055.

Background:

Prosthetic valve endocarditis (PVE) remains a serious condition with a high mortality rate. Precise identification of the PVE-associated pathogen/s and their virulence is essential for successful therapy and patient survival. The commonly described PVE-associated pathogens are staphylococci, streptococci, and enterococci, with Staphylococcus aureus being the most frequently diagnosed species. Furthermore, multi-drug resistance pathogens are increasing in prevalence and continue to pose new challenges mandating a personalized approach. Blood cultures in combination with echocardiography are the most common methods to diagnose PVE, often being the only indication, it exists. In many cases, the diagnostic strategy recommended in the clinical guidelines does not identify the precise microbial agent, and frequently, false-negative blood cultures are reported. Despite the fact that blood culture findings are not always a good indicator of the actual PVE agent in the valve tissue, only a minority of re-operated prostheses are subjected to microbiological diagnostic evaluation. In this review, we focus on the diversity and the complete spectrum of PVE-associated bacterial, fungal, and viral pathogens in blood and prosthetic heart valve, their possible virulence potential, and their challenges in making a microbial diagnosis. We are curious to understand if the unacceptable high mortality of PVE is associated with the high number of negative microbial findings in connection with a possible PVE. Herein, we discuss the possibilities and limits of the diagnostic methods conventionally used and make recommendations for enhanced pathogen identification. We also show possible virulence factors of the most common PVE-associated pathogens and their clinical effects. Based on blood culture, molecular biological diagnostics, and specific valve examination, better derivations for the antibiotic therapy as well as possible preventive intervention can be established in the future.

Methods:

To select articles for the Review, the PubMed database was searched using the terms ‘prosthetic’ AND ‘valve’ AND ‘endocarditis’. We considered papers published between July 2009 and October 2019. First, we filtered all abstracts of indexed clinical studies, case reports, and case series that reported bacterial, fungal, and viral microorganisms that caused PVE. Second, only full text papers in English, German, and French language were included. After strict filtering, 326 publications (59 clinical studies, 267 case reports/series) were finally analysed.

Main findings:

In the last decades, the diagnostic methods have been further developed to detect pathogens involved in IE. A high diversity of 136 different PVE-associated microbial species were identified in the literature. The review describes 114 different PVE-associated microbial species in blood as well as the direct detection of 77 different species in prosthetic heart valve material. At the fact, most clinical studies presented only the most common pathogen S. aureus or groups like coagulase-negative staphylococci, streptococci, and enterococci. Only a few investigations showed a more detailed overview of the specific pathogens and named species such as E. faecalis, C. acnes, C. albicans, or S. equinus. The clinical studies did not represent the entire microbial diversity of PVE-associated pathogens, which are the real challenges in diagnostics and therapy. In contrast, 59% of the microbial species detected in blood, as well as 51% of the pathogens detected in prosthetic valve material, were described only via case reports. The focus of the case reports was mainly on pathogens that were difficult to diagnose and treat and due to this often caused a severe course of disease. Thus, bacteria such as M. chimaera, C. burnetti, and B. henselae or fungi like Aspergillus became the focus of attention. The inclusion of the 293 case reports in the overall evaluation led to an added value regarding microbial diversity, and diagnostic strategies. The small number of case reports (5%) did not lead to a shift in the frequency of the most common pathogens described in the clinical studies. In addition, the literature research revealed a high potential of possible virulence factors that decisively influence the pathogenicity of the microorganisms and thus the course of the disease. Starting with the initial blood culture diagnosis, the high diversity of bacteria, fungi and viruses as possible PVE agents should be taken into account, and a cultivation time of at least 21 days (for mycobacteria 12 weeks), as well as different culture media and cell cultures should be used. During the surgical heart valve replacement, it must be urgently considered that cardioplegic

solutions exert an influence on the growth behaviour of microorganisms. The use of potassium- and/or sodium-free solutions should be preferred. Further research is needed here. In order to identify the actual PVE agent, each explanted heart valve should be subjected to microbial testing, especially in cases of BCNE and failed antibiotic therapy with resistant infections. The infected prosthetic material must be homogenized, mechanically, and enzymatically digested as well as subjected to subsequent sonication to access the intracellular hiding microorganisms, in biofilm embedded bacteria as well as persistent pathogens. However, challenges remain in the application of culture-dependent microbiological diagnostic approaches, especially when patients have been preconditioned with antibiotics, persistent cells exist, or intracellular living organisms make rapid diagnostics impossible. In these cases, molecular biological methods should be used. The methodological spectrum ranging from targeted genome analyses via PCR to untargeted analyses platforms that can represent the entire genome and its virulence profile. The importance of molecular-based diagnostic approaches in terms of clinical intervention and patient outcome is still under-investigated. The combination of blood culture, molecular biological diagnostic and heart valve examination will certainly raise the spectrum of possible pathogens and the knowledge about their pathogenicity. In the future, this is an opportunity for more targeted patient-oriented therapy based on state-of-the-art diagnostic techniques. Beside the overall bacterial pathogens, future treatment of PVE should also have a special view on fungal, and viral pathogens that severe the clinical outcome. The guidelines for the management of IE and PVE no longer reflect the current state of knowledge about the pathogen spectrum of PVE and the technical progress in microbial diagnostics. Further clinical studies based on molecular biological methods are necessary in order to deduce future therapeutic options and update the guidelines for the diagnostic and treatment of PVE.

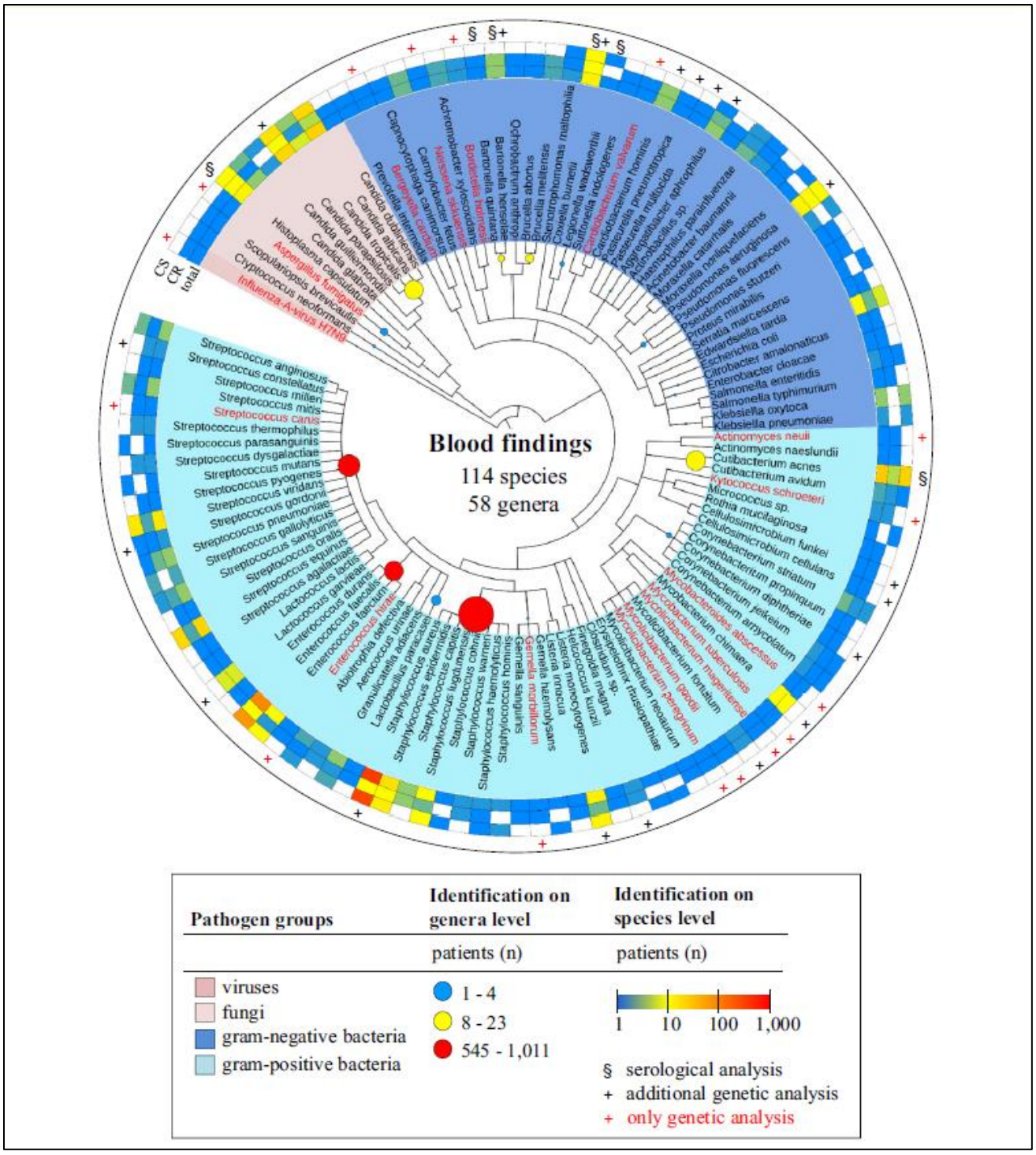

Figure 3: Pathogen spectrum in blood specimens of PVE patients [76]

Conclusions:

The combination of blood culture, molecular biological diagnostic and heart valve examination will certainly raise the spectrum of possible pathogens and the knowledge about their pathogenicity. In the future, this is an opportunity for more targeted patient-oriented therapy based on state-of-the-art diagnostic techniques. Beside the overall bacterial pathogens, future treatment of PVE should also have a special view on fungal, and viral pathogens that severe the clinical outcome.

Starting with the initial blood culture diagnosis, the high diversity of bacteria, fungi and viruses as possible PVE agents should be taken into account, and a cultivation time of at least 21 days (for mycobacteria 12 weeks), as well as different culture media and cell cultures should be used. During the surgical heart valve replacement, it must be urgently considered that cardioplegic solutions exert an influence on the growth behaviour of microorganisms. The use of potassium- and/or sodium-free solutions should be preferred. Further research is needed here. To identify the actual PVE agent, each explanted heart valve should be subjected to microbial testing, especially in cases of BCNE and failed antibiotic therapy with resistant infections. The infected prosthetic material must be homogenized, mechanically, and enzymatically digested as well as subjected to subsequent sonication to access the intracellular hiding microorganisms, in biofilm embedded bacteria as well as persistent pathogens. However, challenges remain in the application of culture-dependent microbiological diagnostic approaches, especially when patients have been preconditioned with antibiotics, persistent cells exist, or intracellular living organisms make rapid diagnostics impossible.

3.2.4 Virulence of Staphylococcus Infection in Surgically Treated Patients with Endocarditis – A Multi-center Analysis

Luehr M, Weber C, Misfeld M, Lichtenberg A, Tugtekin SM, Diab M, **Saha S**, Li Y, Matschke K, Doenst T, Borger MA, Wahlers T, Akhyari P, Hagl C.

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Background:

Infection of the heart valves by bacteria has always been recognized as a dreadful disease with mortality rates of up to 100% in the pre-antibiotic era [77]. However, the successful development of potent antibiotics in the early and mid 20th century made infective endocarditis (IE) a treatable disease, and ultimately, paved the way for surgical replacement with prosthetic heart valves in affected patients [78]. Infective endocarditis (IE) caused by Staphylococcus species is believed to be associated with higher morbidity and mortality rates. We hypothesize that Staphylococcus species are more virulent compared to other commonly causative bacteria of IE with regard to short- and long-term mortality. It remains unclear if patients suffering from IE due to Staphylococcus species should be referred for surgical treatment earlier than other IE patients to avoid septic embolism and to optimize perioperative outcome.

Methods:

The database of the CAMPAIGN registry, comprising 4917 consecutive patients undergoing heart valve surgery, was retrospectively analyzed. Patients were divided into two groups with regard to the identified microorganisms: Staphylococcus group and non-staphylococcus group. The non-staphylococcus group was sub-divided for further analyses: Streptococcus group, Enterococcus group and all other bacteria group.

Results:

On comparing the Staphylococcal group to the non-Staphylococcal group we found that Patients in the Staphylococcus group were more often female (32.3% vs 25.6%; $p< 0.001$) and suffered significantly more from preoperative comorbidities such as coronary artery disease (29.0% vs 25.6%; $P = 0.043$), previous myocardial infarction

(10.4% vs 7.5%; P = 0.004), diabetes mellitus (29.9% vs 25.1%;P = 0.003), renal insufficiency (47.5% vs 34.3%; p< 0.001), with need for dialysis (14.2% vs 6.3%; p< 0.001), peripheral artery disease (11.3% vs 9.0%; P = 0.041), and previous stroke (34.4% vs 24.0%; p< 0.001). Despite equally distributed valve vegetation size on admission, the incidence of preoperative cerebral (47.0% vs 28.7%) and peripheral (35.6% vs 18.3%) embolism were significantly increased in the Staphylococcus group (p< 0.001). Whereas, in comparison with the Streptococcus group, patients with Staphylococcus endocarditis were significantly older (62.5 vs 59.7; p< 0.001), more often female (32.3% vs 24.0%; p< 0.001) and more morbid (median EuroSCORE: 10.0 vs 8.2; p< 0.001). Whereas Enterococcus patients were found to be significantly older than Staphylococcus patients (67.7 vs 62.5%; p< 0.001) but were less frequently female (21.6% vs 32.3%; p< 0.001). Moreover, patients suffering from Enterococcus infection showed higher incidences of coronary artery disease (34.0% vs 29.0%; p= 0.038), aortic regurgitation (62.1% vs 45.7%; p< 0.001),arterial (69.9% vs 64.8%; p= 0.044), and pulmonary hypertension (24.4% vs 19.3%; p= 0.017), and previous cardiac surgery (37.7% vs 14.2%; p= 0.006).

The respective mortality rates at 30 days (18.7%vs.11.8%;p<0.001), 1 (24.7%vs.17.7%; p<0.001) and 5 years (32.2%vs.24.5%; p<0.001) were significantly higher in Staphylococcus patients (n=1260) compared to the Non-Staphylococcus group (n=1787). Multivariate regression identified LVEF<30% (p<0.001), COPD (p=0.045), renal insufficiency (p=0.002), Staphylococcus (p=0.032) and Streptococcus spp. (p=0.013) as independent risk factors for 30-day mortality. Independent risk factors for 1-year mortality were identified as: age (p<0.001), female gender (p=0.018), diabetes (p=0.018), preoperative stroke (p=0.039), COPD (p=0.001), preoperative dialysis (p<0.001) and valve vegetations (p=0.004).

Main findings:

Our study showed that IE due to Staphylococcus spp. is more virulent compared with other common causative microorganisms in a large consecutive surgical cohort. We found that patients with IE due to Staphylococcus spp. are more likely to be critically ill than those patients suffering from IE due to other bacterial infections. It seems that more of these patients were immunocompromised compared with the non-Staphylococcus group with regard to an almost 4-fold incidence of open wounds the portal of entry. Septic embolism occurred at an early stage of the disease process with more than one third suffering from preoperative stroke and almost one fifth requiring mechanical ventilation at the time of admission. More than one third of the patients suffering Staphylococcal IE were female. At 1 and 5 years, the mortality rates were

significantly higher in the Staphylococcus group. In comparison, the estimated survival was significantly inferior to the non-Staphylococcus group as well as to the 3 subgroups (i.e. Streptococci, Enterococci and Other bacterial group).

Conclusions:

Staphylococcus endocarditis is associated with an almost twice as high 30-day mortality and significantly inferior long-term outcome compared to IE by other commonly causative bacteria. Patients with Staphylococcus infection are more often female and critically ill, with more than 50% of these patients suffering from clinically relevant septic embolism. Early diagnosis and referral to a specialized center for surgical treatment is strongly recommended to reduce the incidence of preoperative deterioration and stroke due to septic embolism.

3.3 Operative aspects and outcomes of surgery for infective endocarditis in patients following transcatheter aortic valve implantation.

3.3.1 Surgery for Aortic Prosthetic Valve Endocarditis in the Transcatheter Era

Saha, S., Ali, A., Schnackenburg, P., Horke, K.M., Oberbach, A., Schlichting, N., Sadoni, S., Rizas, K., Braun, D. Luehr, M., Bagaev, E, Hagl, C, and Joskowiak, D.

J Clin Med. 2022 Jun 14;11(12):3418. doi: 10.3390/jcm11123418.

Background:

Although current guidelines consider surgery to be the best option in cases of prosthetic valve endocarditis (PVE), the current literature reports a general reluctance toward the surgical treatment of IE following transcatheter aortic valve implantation (TIE), with some patients entering palliative care upon diagnosis. Up to 90% of patients suffering from TIE undergo conservative treatment, and this has been associated with high in-hospital mortality and poor short-term survival. Along with clinical evaluation, risk scores play an important role in the decision-making process. Endocarditis-specific risk scores have been reported to have better prognostic performance than classical risk scores, as they take into consideration specific factors such as microbiological cultures, abscess formation, and sepsis. Although surgery for aortic PVE entails a high rate of early morbidity and mortality, survivors exhibit satisfactory long-term survival, with a low risk of recurrent endocarditis. With the rise in the number of transcatheter aortic valve replacements (TAVRs) and the indubitable rise in TIE, an indisposition to surgical therapy can be disastrous. As surgical experience with infective endocarditis following transcatheter aortic valve replacement is scarce, this study compared the perioperative and short-term outcomes of patients suffering from endocarditis following surgical aortic valve replacement and transcatheter aortic valve replacement.

Methods:

Between January 2013 and December 2020, 468 consecutive patients were admitted to our center for surgery for IE. Among them, 98 were operated on for endocarditis following surgical aortic valve replacement and 22 for endocarditis following transcatheter aortic valve replacement. Data acquisition was based on institutional databases, and the data were then de-identified. We analyzed the patient characteristics, individual risk scores, surgical details, and postoperative and early outcomes of these patients.

To predict the postoperative mortality, the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), as proposed by Nashef et al. [73], and the Society of Thoracic

Surgeons Predicted Risk of Mortality (STS PROM) score were calculated. Furthermore, endocarditis-specific scores such as the Endoscore, as proposed by Di Mauro et al. [79]; the Risk E score, as proposed by Olmos et al. [80]; and the De Feo Score [81] were calculated. The ICE Score, as proposed by Park et al. [82], was used to predict the 6-month mortality following surgery for IE.

Results:

The median EuroSCORE II (52.1 (40.6–62.0) v/s 45.4 (32.6–58.1), p = 0.207) and STS-PROM (1.8 (1.6–2.1) v/s 1.9 (1.4–2.2), p = 0.622) were comparable. The endocarditis specific risk scores have been presented below. The median Charlson Comorbidity Index was 5 (4–7) in the SAVR–PVE group and 7 (6–8) in the TIE group (p = 0.005). Endocarditis following transcatheter aortic valve replacement accounted for 13.7% of the aortic prosthetic valve endocarditis between 2013 and 2015; this increased to 26.9% in the years 2019 and 2020. The time to IE was significantly longer in patients who underwent SAVR as compared to those who underwent TAVR (3.7 years (0.8–9.5 years) v/s 1.2 years (0.4–2.8 years); p = 0.001). BCNIE accounted for 27 cases (27.8%) in the SAVR–PVE group and 1 case (4.5%) in the TIE group (p = 0.024). The causative organisms in our cohort were predominantly Gram-positive, with Gram-negative organisms accounting for 2.5% of the cases. Concomitant procedures were performed in 35 patients (29.2%). Bentall procedures were carried out in 34 patients (34.7%), in the SAVR–PVE group and in 1 patient (4.5%) in the TIE-group (p = 0.004). Stentless xenopericardial prostheses were used in 30 patients (30.6%) in the SAVR–PVE group and in 1 patient (4.5%) in the TIE group. The operative mortality was 26.5% in the endocarditis following surgical aortic valve replacement group and 9.1% in the endocarditis following transcatheter aortic valve replacement group (p = 0.098). Upon follow-up, survival at 6 months was found to be 98% in the group with endocarditis following surgical aortic valve replacement and 89% in the group with endocarditis following transcatheter aortic valve replacement (p = 0.081).

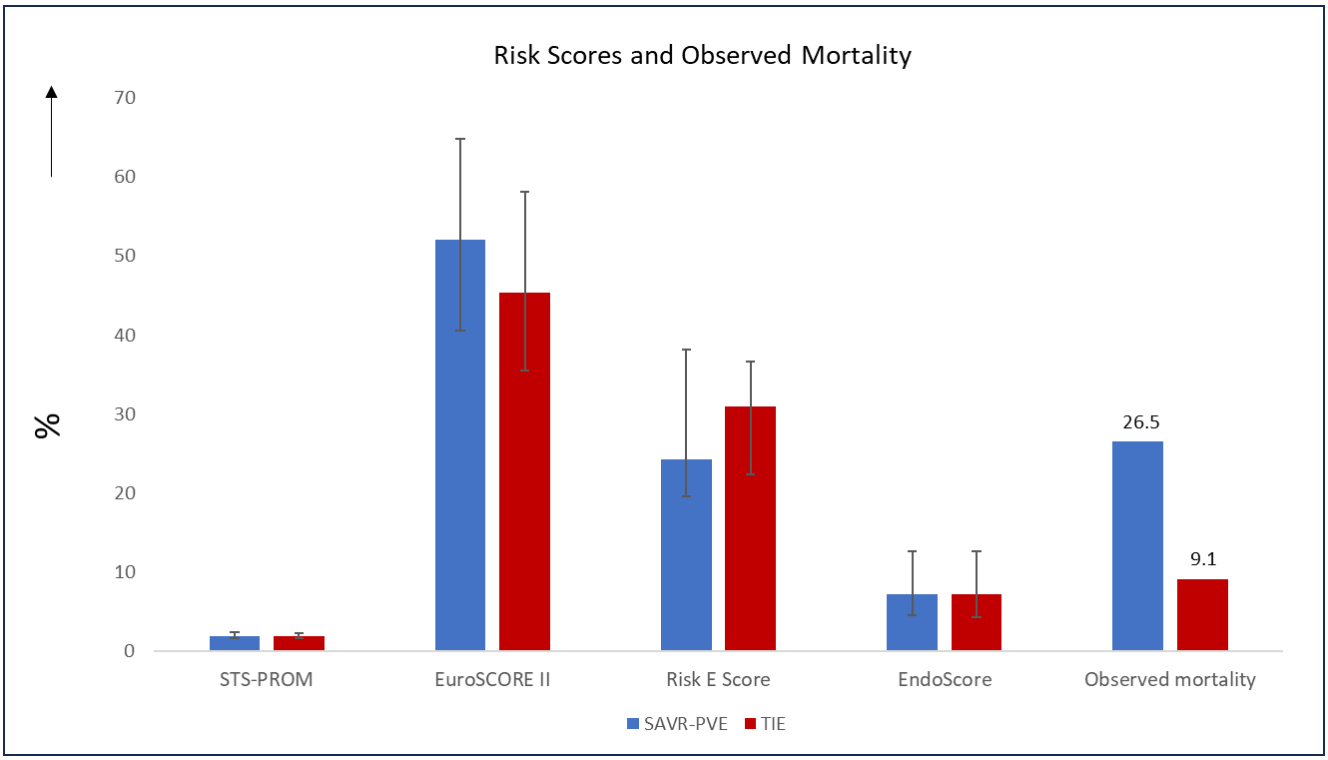

Figure 4: Risk Scores and observed mortality in cases of aortic PVE.

EuroSCORE II: European System for Cardiac Operative Risk Evaluation II [73], EndoScore proposed by Di Mauro et al. [79], Risk E Score proposed by Olmos et al. [80], STS-PROM : Society of Thoracic Surgeons Predicted Risk of Mortality.

Main findings:

Between 2019 and 2020, TIE accounted for more than one-fourth of the cases of aortic PVE at our center. The time to IE was significantly longer in patients who underwent SAVR as compared to those who underwent TAVR. The causative organisms in our cohort were predominantly Gram-positive organisms. Concomitant procedures were performed in 35 patients (29.2%), with no differences being observed between the groups. In our cohort, the operative mortality in the TIE group was under 10%, and the rates of in-hospital mortality and early survival were comparable to patients suffering from SAVR–PVE.

Conclusions:

To date, the current literature advises surgeons to err on the side of caution in cases of TIE; our results, however, indicate that patients suffering from SAVR–PVE and TIE present with comparable risk profiles and can be surgically treated with comparable results. The high rates of postoperative complications may be attributed to the disease and its severity. Endocarditis-specific risk scores should be included more frequently in the decision-making process, as they

may predict the operative risk with more precision as compared to the classical scores. The endocarditis-team approach and a patient-centered approach should always be considered.

3.3.2 Surgery for infective endocarditis following low-intermediate risk transcatheter aortic valve replacement—a multicentre experience.

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Eur J Cardiothorac Surg 2022; doi:10.1093/ejcts/ezac075.

Background:

With the expansion of transcatheter aortic valve replacement (TAVR) into intermediate and low risk, the number of TAVR procedures is bound to rise and along with it the number of cases of infective endocarditis following TAVR (TIE). The incidence of TIE within the first year has been reported to be between 0.1% and 3.4%, with a 5-year incidence of up to 5.8%, which is comparable to that of PVE following surgical aortic valve replacement [42,83]. The aim of this study was to review a multicentre experience of patients undergoing surgical intervention for TIE and to analyse the underlying indications and operative results.

Methods:

We retrospectively identified and analysed 69 patients who underwent cardiac surgery due to infective endocarditis following TAVR at 9 cardiac surgical departments across Germany. The primary outcome was operative mortality, 6-month and 1-year survival.

Results:

Median age was 78 years (72–81) and 48(69.6%) were male. The median time to surgical aortic valve replacement was 14 months (5–24) after TAVR, with 32 patients (46.4%) being diagnosed with early TIE. Cardiac reoperations were performed in 17% of patients and 33% underwent concomitant mitral valve surgery. The main causative organisms were: Enterococcus faecalis (31.9%), coagulase-negative Staphylococcus spp. (26.1%), Methicillin-sensitive Staphylococcus aureus (15.9%) and viridians group streptococci (14.5%). Extracorporeal life support was required in 2 patients (2.9%) for a median duration of 3 days. Postoperative adverse cerebrovascular events were observed in 13 patients (18.9%). Postoperatively, 9 patients (13.0%) required a pacemaker and 33 patients (47.8%) needed

temporary renal replacement therapy. Survival to discharge was 88.4% and survival at 6 months and 1 year was found to be 68% and 53%,respectively.

Details of Surgery	**(n= 69)**
Cardiac reoperations (%)	12 (17.4)
Duration of surgery (min)	196 (158–261)
Duration of cardiopulmonary bypass (min)	108 (84–152)
Duration of aortic cross-clamping (min)	77 (58–101)
Concomitant procedures	
Mitral valve surgery	
• Mitral valve repair (%)	13 (18.9)
• Mitral valve replacement (%)	10 (14.5)
Tricuspid valve repair (%)	6 (8.7)
CABG (%)	6 (8.7)
Aortic root enlargement (%)	6 (8.7)
Aortic root replacement (%)	4 (5.8)
Supracoronary ascending aortic replacement (%)	2 (2.9)
Abscess debridement (%)	10 (14.5)
Repair of the aortomitral continuity (%)	3 (4.3)
Repair of the LVOT (%)	1 (1.4)
Repair of the aortic wall due to strut penetration (%)	1 (1.4)
Prostheses implanted	
Biological (%)	58 (84.1)
Rapid Deployment (%)	6 (8.7)
Mechanical (%)	5 (7.2)

Table 5: Procedural details of patients undergoing surgery for infective endocarditis following TAVR.

Data are presented as medians (25th–75th percentiles) or absolute numbers (percentages). CABG: coronary artery bypass grafting.

Main findings:

About half the patients in this cohort suffered from early PVE. In our cohort, preoperative cerebral emboli were diagnosed in more than one-fourth of the patients, additionally another 18.4% of the patients suffered from postoperative adverse cerebrovascular events. In this cohort, 12 patients had undergone previous cardiac surgery prior to the index TAVR procedure The TAVR prostheses were successfully explanted in all cases with aortic root surgery being required in 14.5% of the cases.

Conclusions:

The simultaneous rise in TAVR procedures and TIE warrants a more liberal consideration of surgery as a curative option in especially low- and intermediate-risk patients. Our results suggest that TIE can be treated according to the guidelines for PVE, namely with early surgery. Which according to our findings is associated with acceptable morbidity and mortality rates. Lack of clinical experience and limited diagnostic imaging techniques, reduced indications of antibiotic prophylaxis and surgical complexity, in addition to predisposing factors make TIE a challenging disease. Surgery should be discussed liberally as a treatment option in patients with TIE by the ‘endocarditis team’ in referral centres.

3.3.3 Health-Related Quality of Life following Surgery for Native and Prosthetic Valve Infective Endocarditis.

Saha, S., Ali, A., Schnackenburg, P., Horke, K.M., Oberbach, A., Schlichting, N., Sadoni, S., Rizas, K., Braun, D. Luehr, M., Bagaev, E, Hagl, C, and Joskowiak, D.

J Clin Med. 2022 Jun 22;11(13):3599. doi: 10.3390/jcm11133599.

Background:

The incidence of IE in Germany has been on the rise, with a case fatality rate of 17% [1]. The rising incidence of IE over the last decade may be attributed to several factors, which include an aging population, rise in the use of implantable cardiac devices, increase in the number of patients undergoing hemodialysis, and changes in antibiotic prophylaxis for the prevention of IE The objective of this study was to compare the long-term outcomes and health-related quality of life (HRQOL) of patients following surgery for infective native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE).

Methods:

We retrospectively identified 633 consecutive patients who had undergone surgery for infective endocarditis at our center between January 2005 and October 2018. The patients were interviewed, and the SF-36 survey was used to assess the HRQOL of survivors. Propensity score matching (2:1) was performed with data from a German reference population. Multivariable analysis incorporated binary logistic regression using a forward stepwise (conditional) model.

Results:

The median age of the cohort was 67 (55–74) years, and 75.6% were male. Operative mortality was 13.7% in the NVE group and 21.6% in the PVE group ($p = 0.010$). The overall survival at 1 year was 88.0% and was comparable between the groups. The physical health summary scores were 49 (40–55) for the NVE patients and 45 (37–52) for the PVE patients ($p = 0.043$). The median mental health summary scores were 52 (35–57) and 49 (41–56), respectively ($p = 0.961$). On comparison of the HRQOL to the reference population, the physical health summary scores were comparable. However, significant differences were observed with regard to the mental health summary scores ($p = 0.005$).

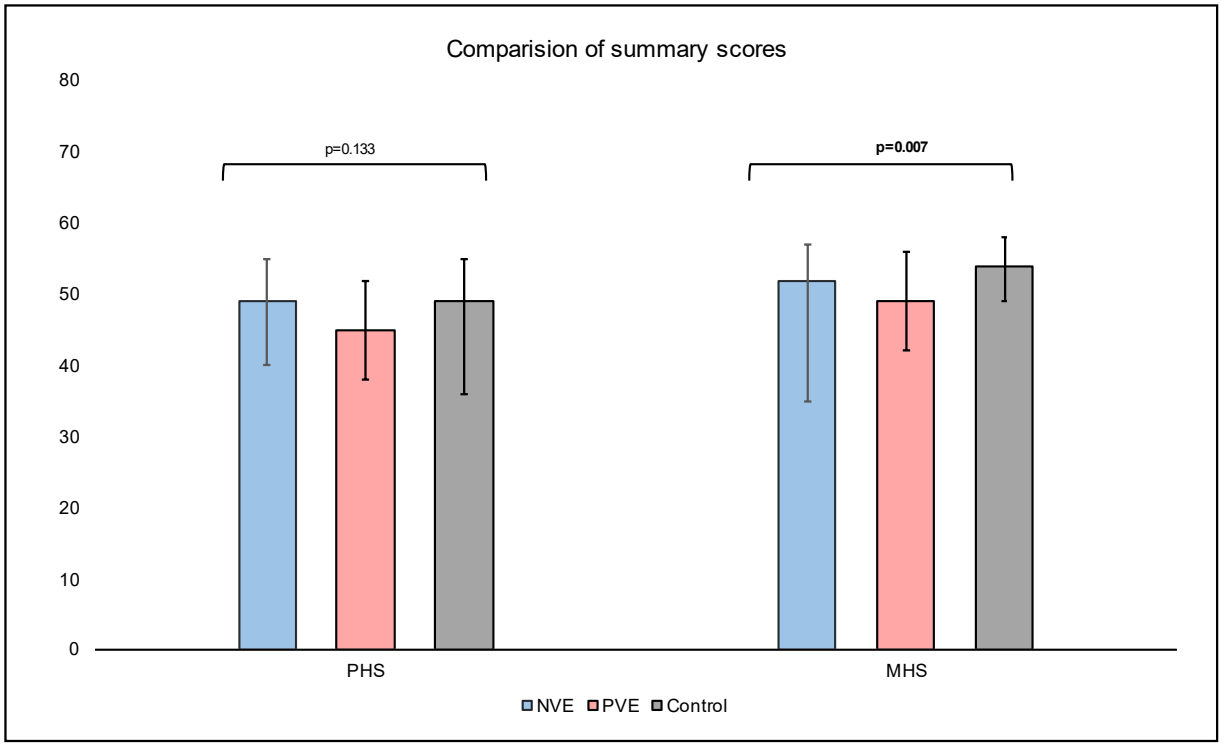

Figure 5: Comparison of Health Related Quality of Life summary scores.

NVE: native valve endocarditis; PVE: prosthetic valve endocarditis.

	NVE (n=160)	PVE (n=69)	Standard (n=458)	p-value
Physical functioning	80 (63-95)	75 (50-90)	90 (60-95)	0.005
Role Physical	100 (25-100)	63 (0-100)	100 (50-100)	<0.001
Bodily pain	100 (62-100)	84 (62-100)	74 (51-100)	0.001
General health	62 (46-72)	59 (39-77)	62 (45-77)	0.600
Vitality	60 (40-75)	55 (40-70)	60 (45-75)	0.135
Social functioning	88 (63-100)	88 (63-100)	100 (75-100)	<0.001
Role Emotional	100 (33-100)	100 (33-100)	100 (100-100)	<0.001
Mental Health	76 (64-88)	76 (64-84)	76 (64-88)	0.678
Physical summary score	49 (40-55)	45 (37-52)	49 (36-55)	0.315
Mental summary score	52 (35-57)	49 (41-56)	54 (49-58)	0.005

Table 6: Individual domains of the SF-36 Questionnaire

Data are presented as medians (25th–75th percentiles).

Main Findings:

We found several differences in the individual domians of HRQOL among these patients and also significant differences in the mental health summary scores. This shows that the patients with PVE could benefit from psychological counselling following surgery. This may be since patients in the PVE group had longer ICU stays, longer duration of ventilation and more complicated postoperative courses as compared to the patients suffering from NVE. Furthermore, patients suffering from PVE had a significantly higher rate of in-hospital mortality. However, this did not have any effect on the long-term survival of these patients.

Conclusions:

Our study shows that there are significant differences in the various domains of HRQOL, not only between NVE and PVE groups, but also in comparison to healthy individuals. Despite adequate surgical therapy, prosthetic endocarditis remains one of the most serious complications in the treatment of valvular heart disease, decisively affecting both somatic health and quality of life. In addition to preoperative health status, it is important to consider the patient's expectations regarding surgery. Further prospective studies on the prevention of prosthetic endocarditis are needed.

3.4 Summary

The main findings of this work are as follows:

- Infective endocarditis is one of the main reasons for the failure of transcatheter aortic valves.
- With changes in the guidelines for the prophylaxis and management of IE, there's has been a steady increase in the number of cases of IE.
- The spectrum of pathogens causing infective endocarditis is wide and some organisms such as Staphylococcus aureus are more virulent than others.
- Surgery for infective endocarditis following transcatheter aortic valve replacement is possible with good results.

Infective endocarditis following TAVR

Infective endocarditis following TAVR is a serious complication and has been reported to have dismal outcomes [22,84]. In some cases patients have been treated with palliation following diagnosis [26]. Along with endocarditis related conditions such as extensive tissue destruction, sepsis, multiorgan failure, cerebral embolization and cardiac decompensation, infective endocarditis following TAVR may be further complicated by TAVR specific factors such as high rate of comorbidities, frailty and advanced age [23,30,85,86]. The incidence of IE following TAVR has been reported to be 0.3 to 2.0 per 100 person-years [22,27]. Several studies have found no differences in the incidence of IE following SAVR and TAVR [19,20,41,43,87]. The indications for TAVR have been expanded to younger and healthier patients and the number of TAVR procedures being carried out worldwide has been increasing. As per our results, infective endocarditis is by far the most common cause of failure of TAVR prostheses and often demands surgery [68,85]. Lack of clinical experience and limited diagnostic imaging techniques, reduced indications of antibiotic prophylaxis and surgical complexity, in addition to predisposing factors make IE following TAVR a challenging disease [49].

In our studies we found that infective endocarditis was the most prominent indication for valve explantation [68,85]. This was further reflected in our finding that in recent times the proportion

of patients suffering from IE following TAVR has been increasing and about more than one fourth of the patients suffering from PVE had undergone TAVR [86].

The degeneration of TAVR prostheses underlies the same pathomechanisms that occur with conventional surgical prostheses such as structural valve deterioration and non-structural dysfunction like paravalvular leakage, valve thrombosis, endocarditis, and others [22,27,49]. The diagnosis of IE following TAVR can be challenging. The modified Duke criteria have a lower diagnostic accuracy for TAVR-IE than for native valve IE, with upto 15% of patients with IE not fulfilling the Duke criteria [22,36]. Computed tomography, magnetic resonance imaging, and metabolic imaging can be useful as part of a multi-imaging approach for the diagnosis of IE following TAVR [22,23,49].

Furthermore, the simultaneous rise in TAVR procedures and IE warrants a more liberal consideration of surgery as a curative option in especially low- and intermediate-risk patients suffering from IE. Our results suggest that IE following TAVR can be treated according to the guidelines for PVE, namely with early surgery. According to our findings surgery is associated with acceptable morbidity and mortality rates [68,85,86,88].

Guideline change and pathogen spectrum

Our study has shown that, following changes in the guidelines for the prevention and management of IE, there has been a significant increase in the incidence of mitral valve IE and Streptococcus related IE [89]. Nowadays Staphylococcus spp. have been reported to be the most predominant microorganism causing IE in industrialized countries, followed by Streptococcus spp. and Enterococcus spp [90,91].

A similar study by Keller et al.[92] showed an increase in the annual prevalence of infective endocarditis in Germany between 2005 and 2014, i.e. before the 2015 changes in the ESC guidelines for the management of infective endocarditis [37]. They found the mean prevalence of infective endocarditis in Germany in the study period to be 11.6 per 100,000 citizens and thus lower compared to the United States of America but higher compared to England [92]. However, it must be noted that although the prevalence of infective endocarditis has increased , the rate of valve replacement and mortality has remained constant [92].

Prosthetic valve endocarditis has been reported to account for upto 30% of the cases of IE and IE following TAVR is considered a sub type of PVE [22,37]. We identified a high diversity of 136 different PVE-associated microbial species in the literature. Due to this diverse spectrum

of pathogens capable of causing PVE, reliable identification of the pathogen is central to the treatment of PVE [45,46,76]. The combination of blood culture, molecular biological diagnostic and heart valve examination will certainly raise the spectrum of possible pathogens and the knowledge about their pathogenicity. In the future, this is an opportunity for more targeted patient-oriented therapy based on state-of-the-art diagnostic techniques. Beside the overall bacterial pathogens, future treatment of PVE should also have a special view on fungal, and viral pathogens that severe the clinical outcome [76].

Over the years, several microorganisms have developed resistance of antibiotics, which are the cornerstone for the treatment of IE. An ideal example of a virulent microorganism developing antibiotic resistance is the Staphylococcus aureus and the sub-group of methicillin-resistant Staphylococcus aureus (MRSA). Our study showed that Staphylococcus endocarditis is associated with an almost twice as high 30-day mortality and significantly inferior long-term outcome compared to IE by other commonly causative bacteria [91]. With regard to IE following TAVR, more than half of cases have been reported to be health-care associated, which is more than twice the rate observed with IE following SAVR and often is caused due to a multidrug-resistant pathogen [22]. In patients undergoing SAVR, Staphylococcus sp. was more commonly the responsible organism whereas higher rates of Streptococcal endocarditis in TAVR have been reported. With the most common pathogen causing IE following TAVR being enterococci, S. aureus, and coagulase-negative staphylococci [19,20,22,88]. The involvement of multidrug resistant organisms and multimorbidity of the patients, makes the treatment of IE following TAVR challenging. With the rise in the number of cases of IE following TAVR, there have been suggestions to improve the antibiotic prophylaxis of patients undergoing TAVR. These include the switch from cephalosporin to amoxicillin/clavulanic acid due to its efficacy against enterococci or adding a glycopeptide (teicoplanin or vancomycin) to cephalosporins to also cover methicillin-resistant staphylococci [22,44].

Surgical treatment of infective endocarditis following TAVR

The treatment of IE following TAVR ideally begins with the Endocarditis-Team approach. Endocarditis teams use a multidisciplinary approach to treat infective endocarditis and have been reported to significantly reduce mortality rates [54,93]. This is of utmost importance in patients suffering from IE following TAVR, as they tend to be multimorbid requiring specialist treatment. Furthermore, Endocarditis-specific risk scores should be included more frequently in the decision-making process, as they may predict the operative risk with more precision as

compared to the classical scores. Between 2019 and 2020, TIE accounted for more than one-fourth of the cases of aortic PVE at our center. Furthermore we found that the time to IE was significantly longer in patients who underwent SAVR as compared to those who underwent TAVR[86].

Surgery as a curative option should not be blatantly rejected, even in high-risk cohorts. The endocarditis-team approach and a patient-centered approach should always be considered [36,86,88].

In cases of TIE, there are several factors to be taken into consideration. Early surgical explantation of TAVR prosthesis is relatively uncomplicated, due to the lack of extensive endothelialization, whereas late surgical explantations are more challenging due to endothelialization of the TAVR prosthesis as well as calcifications and thrombus formation at the aortic root. The type of TAVR prosthesis may also play a critical role at the time of explantation. Balloon-expandable prostheses may be easier to remove due to the ability to crush the valve and facilitate its mobilization, whereas elf-expanding prosthesis has multiple points of apposition in the ascending aorta, the anterior leaflet of the mitral valve and left ventricular outflow tract, which makes their explantation more challenging [94]. There are have been several reports detailing the surgical explantation of TAVR prostheses. Tully et al. [95] describe the effectively resheathing the valve by using a portion of 3/8-inch pump tubing in an 80-year old patient following a type A aortic dissection following TAVR. Another novel technique has been described by Kim et al. [96] using ligatures and careful endarterectomy for the careful removal of TAVR prosthesis, a so called lass-technique. However in cases where, the TAVR prosthesis has been in situ for a longer period of time, the explantation can be challenging. This is is described by Nakazato et al. [97], where they describe the careful explantation of a TAVR prosthesis which was endothelialised into the aortic annulus and subvalvular tissue. Furthermore, early PVE rarely remains restricted to leaflets alone; since it frequently involves the stent frame and annulus, leading to valve dehiscence and paravalvular abscesses. Possible destruction of the aortic root, stent ingrowth in the ascending aorta or weakness of the aorto-mitral continuity are feared complications since they can be associated with a dismal outcome. The explantation of the TAVR prosthesis in the setting of TIE might be further complicated due to the presence of abscesses and fragility of the tissue, especially in patients on chronic steroid therapy. Periannular abscesses have been reported in up to 12–25% of patients with TIE, and there is a similar rate of periannular complications in cases of SAVR–PVE, with 50–60% of patients presenting with an annular abscesses, fistulae, or false aneurysms [25,26]. Infection

of adjacent heart valves and the progress of other cardiovascular diseases following index TAVR procedure often warrant additional surgery [86,88]. In our studies , we too observed a relatively high rate of concomitant procedures being required for patients undergoing TAVR explantation [68,85,86,88].

Furthermore, another important aspect to the surgical treatment of IE following TAVR, is the postoperative course. In cases of IE following TAVR, a high rate of serious complications, including acute heart failure, acute renal failure, septic shock, acute myocardial infarction, and systemic embolization have been reported [22]. Another important consideration is the incidence of adverse cerebrovascular events and strokes. About 20-40% of patients with IE suffer from strokes [23,37,98]. This can be further complicated by postoperative adverse cerebrovascular events. We found that preoperative cerebral emboli were diagnosed in more than one-fourth of the patients suffering IE following TAVR, additionally another 18.4% of the patients suffered from postoperative adverse cerebrovascular events [88]. This further underscores the need for a specialised multidisciplinary approach while treating IE following TAVR.

Surgical treatment of IE is associated with increased in-hospital mortality of 10% to 20% in native IE and may increase up to 40% in cases of PVE [37,91]. Malvindi et al. [25] report that the overall postoperative in-hospital mortality for patients undergoing surgery for TIE is 28%, whereas other studies report mortality rates as high as 50% [19,20,22,99]. Our studies have shown that surgery for IE following can be performed with acceptable rates of morbidity and mortality [86,88]. This may be partly due to the high case volume setting and treatment by an interdisciplinary endocarditis team. We found no differences in survival rates among patients suffering from IE following TAVR and SAVR on long term follow up [86]

Due to the serious nature of the disease patients suffering from IE have long hospital stays, invasive procedures and often undergo surgery and intensive care treatment. This could lead to the development of post-traumatic stress and reduced quality of life in these patients [100]. Despite adequate surgical therapy, prosthetic valve endocarditis remains one of the most serious complications in the treatment of valvular heart disease, decisively affecting both somatic health and quality of life. there are significant differences in the various domains of HRQOL, not only between NVE and PVE groups, but also in comparison to healthy individuals [101]. Our study [101] showed that although there was no difference in the long term survival following surgery for IE, patients suffering from PVE had significant differences in HRQOL

following surgery, especially in the mental health summary scores. This should be taken into consideration while treating patients with PVE to achieve optimal patient-centric results.

3.5 Outlook

The introduction of TAVR has forever changed the treatment of aortic valve disease. TAVR failure is a growing concern, as they are being implanted in younger and low-risk patients. We found that infective endocarditis was the most common cause of failure of transcatheter heart valves and required complex surgery entailing valve explantation. Although our results show that surgery can be carried out with good results, further investigation is required to cfully understand the problem, as a lot of patients remain undiagnosed and untreated. Changes in the treatment and prophylaxis guidelines pose new challenges to the treatment of infective endocarditis. This has led to an increase in the incidence of infective endocarditis especially mitral valve and Streptococcal endocarditis. Further research is required in the field of infective endocarditis, so that risk-factors may be identified and outcomes improved. Further multicenter prospective studies are required to better understand this challenge disease and optimise outcomes of the patients suffering from it. Furthermore, with advances in surgical techniques, it is important not to lose sight of the patients' wellbeing.

4.References

[1] Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: First human case description. Circulation 2002;106:3006–8. https://doi.org/10.1161/01.CIR.0000047200.36165.B8.

[2] Spears J, Al-Saiegh Y, Goldberg D, Manthey S, Goldberg S. TAVR: A Review of Current Practices and Considerations in Low-Risk Patients. J Interv Cardiol 2020;2020:2582938. https://doi.org/10.1155/2020/2582938.

[3] Beckmann A, Meyer R, Lewandowski J, Markewitz A, Gummert J. German Heart Surgery Report 2019: The Annual Updated Registry of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg 2020;68:263–76. https://doi.org/10.1055/s-0040-1710569.

[4] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. N Engl J Med 2010;363:1597–607. https://doi.org/10.1056/NEJMoa1008232.

[5] Swift SL, Puehler T, Misso K, Lang SH, Forbes C, Kleijnen J, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis: A systematic review and meta-Analysis. BMJ Open 2021;11. https://doi.org/10.1136/bmjopen-2021-054222.

[6] Lindman BR, Alexander KP, O'Gara PT, Afilalo J. Futility, benefit, and transcatheter aortic valve replacement. JACC Cardiovasc Interv 2014;7:707–16. https://doi.org/10.1016/j.jcin.2014.01.167.

[7] Gonnah AR, Abdelwahab M, Taylor R, Labib A, Masoud O, Debski M, et al. Health-related quality of life following TAVI or cardiac surgery in patients at intermediate and low risk: a systematic review and meta-analysis. Clin Med 2023;23:594–605. https://doi.org/10.7861/clinmed.2023-0258.

[8] Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med 2019;380:1695–705. https://doi.org/10.1056/NEJMoa1814052.

[9] Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med 2019;380:1706–15. https://doi.org/10.1056/NEJMoa1816885.

[10] Muller Moran HR, Eikelboom R, Lodewyks C, Yan W, Zelentsov I, Arora RC, et al. Two-year outcomes from the PARTNER 3 trial: where do we stand? Curr Opin Cardiol 2021;36:141–7. https://doi.org/10.1097/HCO.0000000000000813.

[11] Braghiroli J, Kapoor K, Thielhelm TP, Ferreira T, Cohen MG. Transcatheter aortic valve replacement in low risk patients: A review of PARTNER 3 and Evolut low risk trials. Cardiovasc Diagn Ther 2020;10:59–71. https://doi.org/10.21037/cdt.2019.09.12.

[12] Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by

the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Rev Esp Cardiol (Engl Ed) 2022;75:524. https://doi.org/10.1016/j.rec.2022.05.006.

[13] Capodanno D, Petronio AS, Prendergast B, Eltchaninoff H, Vahanian A, Modine T, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interve. Eur Heart J 2017;38:3382–90. https://doi.org/10.1093/eurheartj/ehx303.

[14] Montarello NJ, Willemen Y, Tirado-Conte G, Travieso A, Bieliauskas G, Sondergaard L, et al. Transcatheter aortic valve durability: a contemporary clinical review. Front Cardiovasc Med 2023;10:1–6. https://doi.org/10.3389/fcvm.2023.1195397.

[15] Dvir D, Bourguignon T, Otto CM, Hahn RT, Rosenhek R, Webb JG, et al. Standardized Definition of Structural Valve Degeneration for Surgical and Transcatheter Bioprosthetic Aortic Valves. Circulation 2018;137:388–99. https://doi.org/10.1161/CIRCULATIONAHA.117.030729.

[16] Ler A, Ler A, Ying YJ, Ying YJ, Sazzad F, Sazzad F, et al. Structural durability of early-generation Transcatheter aortic valve replacement valves compared with surgical aortic valve replacement valves in heart valve surgery: A systematic review and meta-analysis. J Cardiothorac Surg 2020;15:1–13. https://doi.org/10.1186/s13019-020-01170-7.

[17] Kataruka A, Otto CM. Valve durability after transcatheter aortic valve implantation. J Thorac Dis 2018;10:S3629–36. https://doi.org/10.21037/jtd.2018.07.38.

[18] Patel SP, Garcia S, Sathananthan J, Tang GHL, Albaghdadi MS, Pibarot P, et al. Structural Valve Deterioration in Transcatheter Aortic Bioprostheses: Diagnosis, Pathogenesis, and Treatment. Struct Hear J Hear Team 2023;7:100155. https://doi.org/10.1016/j.shj.2022.100155.

[19] Summers MR, Leon MB, Smith CR, Kodali SK, Thourani VH, Herrmann HC, et al. Prosthetic Valve Endocarditis after TAVR and SAVR: Insights from the PARTNER Trials. Circulation 2019. https://doi.org/10.1161/CIRCULATIONAHA.119.041399.

[20] Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, Kapadia S, Lerakis S, Cheema AN, et al. Infective endocarditis after transcatheter aortic valve implantation: results from a large multicenter registry. Circulation 2015;131:1566–74. https://doi.org/10.1161/CIRCULATIONAHA.114.014089.

[21] Regueiro A, Linke A, Latib A, Ihlemann N, Urena M, Walther T, et al. Infective Endocarditis following Transcatheter Aortic Valve Replacement: Comparison of Balloon-Versus Self-Expandable Valves. Circ Cardiovasc Interv 2019;12:1–8. https://doi.org/10.1161/CIRCINTERVENTIONS.119.007938.

[22] David del V, Vassili P, A. MC, M. MJ, Josep R-C. Infective Endocarditis After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2023;81:394–412. https://doi.org/10.1016/j.jacc.2022.11.028.

[23] Delgado V, Ajmone Marsan N, De Waha S, Bonaros N, Brida M, Burri H, et al. 2023 ESC Guidelines for the management of endocarditis. Eur Heart J 2023;44:3948–4042. https://doi.org/10.1093/eurheartj/ehad193.

[24] Medranda GA, Rogers T, Ali SW, Zhang C, Shea C, Sciandra KA, et al. Prosthetic valve endocarditis after transcatheter aortic valve replacement in low-risk patients. Catheter Cardiovasc Interv 2022;99:896–903. https://doi.org/10.1002/ccd.29943.

[25] Malvindi PG, Luthra S, Sarvananthan S, Zingale A, Olevano C, Ohri S. Surgical treatment of transcatheter aortic valve infective endocarditis. Netherlands Hear J 2021;29:71–7. https://doi.org/10.1007/s12471-020-01494-y.

[26] Brouwer J, van den Brink FS, Nijenhuis VJ, Vossenberg TN, Delewi R, van Mourik MS, et al. Incidence and outcome of prosthetic valve endocarditis after transcatheter aortic valve replacement in the Netherlands. Neth Heart J 2020;28:520–5. https://doi.org/10.1007/s12471-020-01420-2.

[27] Chourdakis E, Koniari I, Hahalis G, Kounis NG, Hauptmann KE. Endocarditis after transcatheter aortic valve implantation : a current assessment. J Geriatr Cardiol 2018 Jan; 15(1) 61–65 2018:61–5. https://doi.org/10.11909/j.issn.1671-5411.2018.01.003.

[28] Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, et al. Challenges in Infective Endocarditis. J Am Coll Cardiol 2017;69:325–44. https://doi.org/10.1016/j.jacc.2016.10.066.

[29] Cahill TJ, Prendergast BD. Infective endocarditis. Lancet (London, England) 2016;387:882–93. https://doi.org/10.1016/S0140-6736(15)00067-7.

[30] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J 2015;36:3075–123. https://doi.org/10.1093/eurheartj/ehv319.

[31] Prendergast BD. Diagnostic criteria and problems in infective endocarditis. Heart 2004;90:611–3. https://doi.org/10.1136/hrt.2003.029850.

[32] Oberbach A, Friedrich M, Lehmann S, Schlichting N, Kullnick Y, Graber S, et al. Bacterial infiltration in structural heart valve disease. J Thorac Cardiovasc Surg 2019. https://doi.org/10.1016/j.jtcvs.2019.02.019.

[33] Oberbach A, Schlichting N, Friedrich M, Lehmann S, Kullnick Y, Pichlmaier M, et al. Quantification of Multiple Bacteria in Calcified Structural Valvular Heart Disease. Semin Thorac Cardiovasc Surg 2019. https://doi.org/10.1053/j.semtcvs.2019.10.003.

[34] Webb JG, Blanke P, Meier D, Sathananthan J, Lauck S, Chatfield AG, et al. TAVI in 2022: Remaining issues and future direction. Arch Cardiovasc Dis 2022;115:235–42. https://doi.org/10.1016/j.acvd.2022.04.001.

[35] Kaur S, Misbah Rameez R, Jaber W, Griffin BP, Xu B. Transcatheter Aortic Valve Replacement Associated Infective Endocarditis: A Clinical Update. Struct Hear 2020;4:152–8. https://doi.org/10.1080/24748706.2020.1733718.

[36] Saha S, Dudakova A, Danner BC, Kutschka I, Schulze MH, Niehaus H. Bacterial Spectrum and Infective Foci in Patients Operated for Infective Endocarditis: Time to Rethink Strategies? Thorac Cardiovasc Surg 2022;71:2–11. https://doi.org/10.1055/s-0041-1740540.

[37] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology

(ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European . Eur Heart J 2015;36:3075–128. https://doi.org/10.1093/eurheartj/ehv319.

[38] Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, et al. Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. Eur Heart J 2019;40:3222–32. https://doi.org/10.1093/eurheartj/ehz620.

[39] Berisha B, Ragnarsson S, Olaison L, Rasmussen M. Microbiological etiology in prosthetic valve endocarditis: A nationwide registry study. J Intern Med 2022;292:428–37. https://doi.org/10.1111/joim.13491.

[40] Stortecky S, Heg D, Tueller D, Pilgrim T, Muller O, Noble S, et al. Infective Endocarditis After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2020;75:3020–30. https://doi.org/10.1016/j.jacc.2020.04.044.

[41] Butt JH, Ihlemann N, De Backer O, Søndergaard L, Havers-Borgersen E, Gislason GH, et al. Long-Term Risk of Infective Endocarditis After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2019;73:1646–55. https://doi.org/10.1016/j.jacc.2018.12.078.

[42] Kuttamperoor F, Yandrapalli S, Siddhamsetti S, Frishman WH, Tang GHL. Infectious Endocarditis after Transcatheter Aortic Valve Replacement: Epidemiology and Outcomes. Cardiol Rev 2019;27:236–41. https://doi.org/10.1097/CRD.0000000000000244.

[43] Alexis SL, Malik AH, George I, Hahn RT, Khalique OK, Seetharam K, et al. Infective endocarditis after surgical and transcatheter aortic valve replacement: A state of the art review. J Am Heart Assoc 2020;9. https://doi.org/10.1161/JAHA.120.017347.

[44] Conen A, Stortecky S, Moreillon P, Hannan MM, Franzeck FC, Jeger R, et al. A review of recommendations for infective endocarditis prevention in patients undergoing transcatheter aortic valve implantation. EuroIntervention 2021;16:1135–40. https://doi.org/10.4244/EIJ-D-19-00993.

[45] Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory Diagnosis of Infective Endocarditis. J Clin Microbiol 2017;55:2599–608. https://doi.org/10.1128/JCM.00635-17.

[46] Cuervo G, Escrihuela-Vidal F, Gudiol C, Carratalà J. Current Challenges in the Management of Infective Endocarditis. Front Med 2021;8:1–15. https://doi.org/10.3389/fmed.2021.641243.

[47] Li JS, Sexton DJ, Mick N, Nettles R, Fowler VGJ, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis an Off Publ Infect Dis Soc Am 2000;30:633–8. https://doi.org/10.1086/313753.

[48] Lnu K, Ansari S, Mahto S, Gada H, Mumtaz M, Loran D, et al. Transcatheter aortic valve replacement associated infective endocarditis case series: broadening the criteria for diagnosis is the need of the hour. BMC Cardiovasc Disord 2021;21:1–9. https://doi.org/10.1186/s12872-021-02364-0.

[49] Puls M, Eiffert H, Hünlich M, Schöndube F, Hasenfuß G, Seipelt R, et al. Prosthetic valve endocarditis after transcatheter aortic valve implantation: the incidence in a

single-centre cohort and reflections on clinical, echocardiographic and prognostic features. EuroIntervention J Eur Collab with Work Gr Interv Cardiol Eur Soc Cardiol 2013;8:1407–18. https://doi.org/10.4244/EIJV8I12A214.

[50] Miranda WR, Connolly HM, Baddour LM, Goel K, Wilson WR, Greason KL, et al. Infective endocarditis following transcatheter aortic valve replacement: Diagnostic yield of echocardiography and associated echo-Doppler findings. Int J Cardiol 2018;271:392–5. https://doi.org/10.1016/j.ijcard.2018.03.124.

[51] Salaun E, Sportouch L, Barral P-A, Hubert S, Lavoute C, Casalta A-C, et al. Diagnosis of Infective Endocarditis After TAVR: Value of a Multimodality Imaging Approach. JACC Cardiovasc Imaging 2018;11:143–6. https://doi.org/10.1016/j.jcmg.2017.05.016.

[52] Pizzi MN, Roque A, Fernandez-Hidalgo N, Cuellar-Calabria H, Ferreira-Gonzalez I, Gonzalez-Alujas MT, et al. Improving the Diagnosis of Infective Endocarditis in Prosthetic Valves and Intracardiac Devices With 18F-Fluordeoxyglucose Positron Emission Tomography/Computed Tomography Angiography: Initial Results at an Infective Endocarditis Referral Center. Circulation 2015;132:1113–26. https://doi.org/10.1161/CIRCULATIONAHA.115.015316.

[53] Ochiai T, Chakravarty T, Yoon S-H, Kaewkes D, Flint N, Patel V, et al. Coronary Access After TAVR. JACC Cardiovasc Interv 2020;13:693–705. https://doi.org/10.1016/j.jcin.2020.01.216.

[54] Davierwala PM, Marin-Cuartas M, Misfeld M, Borger MA. The value of an "Endocarditis Team". Ann Cardiothorac Surg 2019;8:621–9. https://doi.org/10.21037/acs.2019.09.03.

[55] Pettersson GB, Hussain ST. Current AATS guidelines on surgical treatment of infective endocarditis. Ann Cardiothorac Surg 2019;8:630–44. https://doi.org/10.21037/acs.2019.10.05.

[56] Prendki V. Management of elderly patients with infective endocarditis. Clin Microbiol Infect 2019;25:1169–70. https://doi.org/10.1016/j.cmi.2019.06.023.

[57] Naber CK. [S2 Guideline for diagnosis and therapy of infectious endocarditis]. Z Kardiol 2004;93:1005–21. https://doi.org/10.1007/s00392-004-0183-0.

[58] Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European. Eur Heart J 2009;30:2369–413. https://doi.org/10.1093/eurheartj/ehp285.

[59] Danchin N, Duval X, Leport C. Prophylaxis of infective endocarditis: French recommendations 2002. Heart 2005;91:715–8. https://doi.org/10.1136/hrt.2003.033183.

[60] Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Co. Circulation 2007;116:1736–54. https://doi.org/10.1161/CIRCULATIONAHA.106.183095.

[61] Richey R, Wray D, Stokes T. Prophylaxis against infective endocarditis: summary of NICE guidance. BMJ 2008;336:770–1. https://doi.org/10.1136/bmj.39510.423148.AD.

[62] Thornhill MH, Gibson TB, Cutler E, Dayer MJ, Chu VH, Lockhart PB, et al. Antibiotic Prophylaxis and Incidence of Endocarditis Before and After the 2007 AHA Recommendations. J Am Coll Cardiol 2018;72:2443–54. https://doi.org/10.1016/j.jacc.2018.08.2178.

[63] Sakai Bizmark R, Chang R-KR, Tsugawa Y, Zangwill KM, Kawachi I. Impact of AHA's 2007 guideline change on incidence of infective endocarditis in infants and children. Am Heart J 2017;189:110–9. https://doi.org/10.1016/j.ahj.2017.04.006.

[64] Talha KM, Baddour LM, Thornhill MH, Arshad V, Tariq W, Tleyjeh IM, et al. Escalating incidence of infective endocarditis in Europe in the 21st century. Open Hear 2021;8. https://doi.org/10.1136/openhrt-2021-001846.

[65] Pericà S JM, Llopis J, González-Ramallo V, Goenaga MÁ, Muñoz P, García-Leoni ME, et al. Outpatient Parenteral Antibiotic Treatment for Infective Endocarditis: A Prospective Cohort Study From the GAMES Cohort. Clin Infect Dis 2019;69:1690–700. https://doi.org/10.1093/cid/ciz030.

[66] Brown E, Gould FK. Oral antibiotics for infective endocarditis: a clinical review. J Antimicrob Chemother 2020;75:2021–7. https://doi.org/10.1093/jac/dkaa106.

[67] Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. N Engl J Med 2019;380:415–24. https://doi.org/10.1056/NEJMoa1808312.

[68] Saha S, Peterss S, Mueller C, Deseive S, Sadoni S, Hausleiter J, et al. Cardiac surgery following transcatheter aortic valve replacement. Eur J Cardio-Thoracic Surg 2021;00:1–7. https://doi.org/10.1093/ejcts/ezab217.

[69] Gomes A, Jainandunsing JS, van Assen S, van Geel PP, Sinha B, Gelsomino S, et al. A standardized approach to treat complex aortic valve endocarditis: A case series. J Cardiothorac Surg 2018;13:1–10. https://doi.org/10.1186/s13019-018-0715-8.

[70] Kang D-H, Kim Y-J, Kim S-H, Sun BJ, Kim D-H, Yun S-C, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012;366:2466–73. https://doi.org/10.1056/NEJMoa1112843.

[71] Dashkevich A, Bratkov G, Li Y, Joskowiak D, Peterss S, Juchem G, et al. Impact of Operative Timing in Infective Endocarditis with Cerebral Embolism-The Risk of Intermediate Deterioration. J Clin Med 2021;10. https://doi.org/10.3390/jcm10102136.

[72] Fukuhara S, Brescia AA, Shiomi S, Rosati CM, Yang B, Kim KM, et al. Surgical explantation of transcatheter aortic bioprostheses: Results and clinical implications. J Thorac Cardiovasc Surg 2020. https://doi.org/10.1016/j.jtcvs.2019.11.139.

[73] Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. Euroscore II. Eur J Cardio-Thoracic Surg 2012;41:734–45. https://doi.org/10.1093/ejcts/ezs043.

[74] Rajani R, Klein JL. Infective endocarditis: A contemporary update. Clin Med 2020;20:31–5. https://doi.org/10.7861/clinmed.cme.20.1.1.

[75] German Federal Statistical Office n.d. https://www.destatis.de.

[76] Oberbach A, Schlichting N, Hagl C, Lehmann S, Kullnick Y, Friedrich M, et al. Four decades of experience of prosthetic valve endocarditis reflect a high variety of diverse pathogens. Cardiovasc Res 2022. https://doi.org/10.1093/cvr/cvac055.

[77] Lynn DJ, Kane JG, Parker RH. Haemophilus parainfluenzae and influenzae endocarditis: a review of forty cases. Medicine (Baltimore) 1977;56:115–28. https://doi.org/10.1097/00005792-197703000-00003.

[78] Mattila S, Ketonen P, Kyllönen K, Tala P. Valve replacement for bacterial endocarditis. Scand J Thorac Cardiovasc Surg 1982;16:23–7. https://doi.org/10.3109/14017438209100604.

[79] Di Mauro M, Dato GMA, Barili F, Gelsomino S, Santè P, Corte A Della, et al. A predictive model for early mortality after surgical treatment of heart valve or prosthesis infective endocarditis. The EndoSCORE. Int J Cardiol 2017;241:97–102. https://doi.org/10.1016/j.ijcard.2017.03.148.

[80] Olmos C, Vilacosta I, Habib G, Maroto L, Fernández C, López J, et al. Risk score for cardiac surgery in active left-sided infective endocarditis. Heart 2017;103:1435–42. https://doi.org/10.1136/heartjnl-2016-311093.

[81] De Feo M, Cotrufo M, Carozza A, De Santo LS, Amendolara F, Giordano S, et al. The need for a specific risk prediction system in native valve infective endocarditis surgery. Sci World J 2012;2012. https://doi.org/10.1100/2012/307571.

[82] Park LP, Chu VH, Peterson G, Skoutelis A, Lejko-Zupa T, Bouza E, et al. Validated risk score for predicting 6-month mortality in infective endocarditis. J Am Heart Assoc 2016;5:1–13. https://doi.org/10.1161/JAHA.115.003016.

[83] Fauchier L, Bisson A, Herbert J, Lacour T, Bourguignon T, Etienne C Saint, et al. Incidence and outcomes of infective endocarditis after transcatheter aortic valve implantation versus surgical aortic valve replacement. Clin Microbiol Infect 2020;26:1368–74. https://doi.org/10.1016/j.cmi.2020.01.036.

[84] Habib G. Infective endocarditis after transcatheter aortic valve replacement: The worst that can happen. J Am Heart Assoc 2018;7:1–3. https://doi.org/10.1161/JAHA.118.010287.

[85] Bapat VN, Zaid S, Fukuhara S, Saha S, Vitanova K, Kiefer P, et al. Surgical Explantation After TAVR Failure: Mid-Term Outcomes From the EXPLANT-TAVR International Registry. JACC Cardiovasc Interv 2021;14:1978–91. https://doi.org/10.1016/j.jcin.2021.07.015.

[86] Saha S, Ali A, Schnackenburg P, Horke KM, Oberbach A, Schlichting N, et al. Surgery for Aortic Prosthetic Valve Endocarditis in the Transcatheter Era. J Clin Med 2022;11. https://doi.org/10.3390/jcm11123418.

[87] Kolte D, Goldsweig A, Kennedy KF, Abbott JD, Gordon PC, Sellke FW, et al. Comparison of Incidence, Predictors, and Outcomes of Early Infective Endocarditis after Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in the United States. Am J Cardiol 2018;122:2112–9. https://doi.org/10.1016/j.amjcard.2018.08.054.

[88] Saha S, Joskowiak D, Marin-Cuartas M, Diab M, Schwaiger BM, Sandoval-Boburg R, et al. Surgery for infective endocarditis following low-intermediate risk transcatheter

aortic valve replacement-a multicentre experience. Eur J Cardio-Thoracic Surg Off J Eur Assoc Cardio-Thoracic Surg 2022. https://doi.org/10.1093/ejcts/ezac075.

[89] Weber C, Luehr M, Petrov G, Misfeld M, Akhyari P, Tugtekin S-M, et al. Impact of the 2009 ESC Guideline Change on Surgically Treated Infective Endocarditis. Ann Thorac Surg 2022;114:1349–56. https://doi.org/10.1016/j.athoracsur.2022.01.054.

[90] Vogkou CT, Vlachogiannis NI, Palaiodimos L, Kousoulis AA. The causative agents in infective endocarditis: a systematic review comprising 33,214 cases. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 2016;35:1227–45. https://doi.org/10.1007/s10096-016-2660-6.

[91] Luehr M, Weber C, Misfeld M, Lichtenberg A, Tugtekin S-M, Diab M, et al. Virulence of Staphylococcus Infection in Surgically Treated Patients With Endocarditis : A Multicenter Analysis. Ann Surg 2022. https://doi.org/10.1097/SLA.0000000000005448.

[92] Keller K, von Bardeleben RS, Ostad MA, Hobohm L, Munzel T, Konstantinides S, et al. Temporal Trends in the Prevalence of Infective Endocarditis in Germany Between 2005 and 2014. Am J Cardiol 2017;119:317–22. https://doi.org/10.1016/j.amjcard.2016.09.035.

[93] El-Dalati S, Cronin D, Riddell J, Shea M, Weinberg RL, Washer L, et al. The Clinical Impact of Implementation of a Multidisciplinary Endocarditis Team. Ann Thorac Surg 2022;113:118–24. https://doi.org/10.1016/j.athoracsur.2021.02.027.

[94] Mangi AA, Ramchandani M, Reardon M. Surgical Removal and Replacement of Chronically Implanted Transcatheter Aortic Prostheses: How I Teach It. Ann Thorac Surg 2018;105:12–4. https://doi.org/10.1016/j.athoracsur.2017.08.015.

[95] Tully A, Lee ACH, Gruessner S, Massad M, Abdelhady K. Surgical Transcatheter Aortic Valve Replacement Explantation Technique. Ann Thorac Surg 2022;114:e471–3. https://doi.org/10.1016/j.athoracsur.2022.03.015.

[96] Kim YS, Yoo JS. Easy surgical explantation technique for self-expanding transcatheter aortic valve: "lasso technique." Interact Cardiovasc Thorac Surg 2022;34:691–3. https://doi.org/10.1093/icvts/ivab304.

[97] Nakazato T, Toda K, Kuratani T, Sawa Y. Redo surgery after transcatheter aortic valve replacement with a balloon-expandable valve. JTCVS Tech 2020;3:72–4. https://doi.org/10.1016/j.xjtc.2020.06.018.

[98] Chen CC, Wu VCC, Chang CH, Chen CT, Hsieh PC, Liu ZH, et al. Long-term Outcome of Neurological Complications after Infective Endocarditis. Sci Rep 2020;10:1–9. https://doi.org/10.1038/s41598-020-60995-3.

[99] Mangner N, Leontyev S, Woitek FJ, Kiefer P, Haussig S, Binner C, et al. Cardiac Surgery Compared With Antibiotics Only in Patients Developing Infective Endocarditis After Transcatheter Aortic Valve Replacement. J Am Heart Assoc 2018;7:e010027. https://doi.org/10.1161/JAHA.118.010027.

[100] Verhagen DWM, Hermanides J, Korevaar JC, Bossuyt PMM, Van Den Brink RBA, Speelman P, et al. Health-related quality of life and posttraumatic stress disorder among survivors of left-sided native valve endocarditis. Clin Infect Dis 2009;48:1559–65. https://doi.org/10.1086/598930.

[101] Saha S, Mladenova R, Radner C, Horke KM, Buech J, Schnackenburg P, et al. Health-Related Quality of Life following Surgery for Native and Prosthetic Valve Infective Endocarditis. J Clin Med 2022;11. https://doi.org/10.3390/jcm11133599.

5. List of Publications

- **Saha S**, Lang A, von der Linden J, Wassilowsky D, Peterss S, Pichlmaier M, Hagl C, Juchem G, Joskowiak D. Clinical Results and Quality of Life after Nonelective Cardiac Surgery in Octogenarians. Thorac Cardiovasc Surg. 2022 Aug;70(5):384-391. doi: 10.1055/s-0041-1730029. Epub 2021 Jul 16. PMID: 35948015.

- **Saha S**, Mladenova R, Radner C, Horke KM, Buech J, Schnackenburg P, Ali A, Peterss S, Juchem G, Luehr M, Hagl C, Joskowiak D. Health-Related Quality of Life following Surgery for Native and Prosthetic Valve Infective Endocarditis. J Clin Med. 2022 Jun 22;11(13):3599. doi: 10.3390/jcm11133599. PMID: 35806881; PMCID: PMC9267565.

- **Saha S**, Ali A, Schnackenburg P, Horke KM, Oberbach A, Schlichting N, Sadoni S, Rizas K, Braun D, Luehr M, Bagaev E, Hagl C, Joskowiak D. Surgery for Aortic Prosthetic Valve Endocarditis in the Transcatheter Era. J Clin Med. 2022 Jun 14;11(12):3418. doi: 10.3390/jcm11123418. PMID: 35743488; PMCID: PMC9225107.

- **Saha S***, Joskowiak D*, Marin-Cuartas M, Diab M, Schwaiger BM, Sandoval-Boburg R, Popov AF, Weber C, Varghese S, Martens A, Cebotari S, Scherner M, Eichinger W, Holzhey D, Dohle DS, Wahlers T, Doenst T, Misfeld M, Mehilli J, Massberg S, Hagl C. Surgery for infective endocarditis following low-intermediate risk transcatheter aortic valve replacement-a multicentre experience. Eur J Cardiothorac Surg. 2022 Jun 15;62(1):ezac075. doi: 10.1093/ejcts/ezac075. PMID: 35190828.

- **Saha S**, Dudakova A, Danner BC, Kutschka I, Schulze MH, Niehaus H. Bacterial Spectrum and Infective Foci in Patients Operated for Infective Endocarditis: Time to Rethink Strategies? Thorac Cardiovasc Surg. 2022 Feb 8. doi: 10.1055/s-0041-1740540. Epub ahead of print. PMID: 35135025.

- **Saha S**, Fabry TG, Buech J, Ali A, Joskowiak D, Tsilimparis N, Hagl C, Pichlmaier M, Peterss S. Time is of the essence: where can we improve care in acute aortic dissection?

Interact Cardiovasc Thorac Surg. 2021 Nov 22;33(6):941-948. doi: 10.1093/icvts/ivab190. PMID: 34255060; PMCID: PMC8632747.

- **Saha S**, Peterss S, Mueller C, Deseive S, Sadoni S, Hausleiter J, Massberg S, Hagl C, Joskowiak D. Cardiac surgery following transcatheter aortic valve replacement. Eur J Cardiothorac Surg. 2021 Nov 2;60(5):1149-1155. doi: 10.1093/ejcts/ezab217. PMID: 34021322.

- **Saha S**, Karaca K, Jebran AF, Waezi N, Ort K, Brandes I, Hagl C, Niehaus H. Diagnostic Value of Cholinesterase Activity for the Development of Postoperative Delirium after Cardiac Surgery. Thorac Cardiovasc Surg. 2021 Dec;69(8):693-699. doi: 10.1055/s-0040-1716897. Epub 2020 Nov 20. PMID: 33225437.

- **Saha S**, Hofmann S, Jebran AF, Waezi N, Kutschka I, Friedrich MG, Niehaus H. Safety and efficacy of digital chest drainage units compared to conventional chest drainage units in cardiac surgery. Interact Cardiovasc Thorac Surg. 2020 Jul 1;31(1):42-47. doi: 10.1093/icvts/ivaa049. PMID: 32249898.

- **Saha S***, Jebran AF*, Leistner M, Kutschka I, Niehaus H. Turning Things Around: The Role of Prone Positioning in the Management of Acute Respiratory Failure After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2020 Jun;34(6):1434-1438. doi: 10.1053/j.jvca.2019.10.055. Epub 2019 Nov 9. PMID: 31812562.

- **Saha S**, Varghese S, Herr M, Leistner M, Ulrich C, Niehaus H, Ahmad AA, Baraki H, Kutschka I. Minimally invasive versus conventional extracorporeal circulation circuits in patients undergoing coronary artery bypass surgery: a propensity-matched analysis. Perfusion. 2019 Oct;34(7):590-597. doi: 10.1177/0267659119842060. Epub 2019 Apr 12. PMID: 30977430.

- Waezi N*, **Saha S***, Bougioukas I, Emmert A, Danner BC, Baraki H, Kutschka I, Zenker D, Stojanovic T, Jebran AF. Viabahn stent graft compared with prosthetic

surgical above-knee bypass in treatment of superficial femoral artery disease: Long-term results of a retrospective analysis. Medicine (Baltimore). 2018 Oct;97(40):e12449. doi: 10.1097/MD.0000000000012449. PMID: 30290602; PMCID: PMC6200476.

- **Saha S**, Varghese S, Ahmad AA, Jebran AF, Waezi N, Niehaus H, Baraki H, Kutschka I. Complex Valve Surgery in Elderly Patients: Increasingly Necessary and Surprisingly Feasible. Thorac Cardiovasc Surg. 2020 Mar;68(2):107-113. doi: 10.1055/s-0038-1670663. Epub 2018 Sep 15. PMID: 30218992.

- **Saha S**, Baraki H, Kutschka I, Hadem J. Predictive value of ScvO2 monitoring for pericardial tamponade after cardiac surgery. Herz. 2019 Feb;44(1):76-81. English. doi: 10.1007/s00059-017-4629-3. Epub 2017 Oct 17. PMID: 29043406.

- Zaid S, Hirji SA, Bapat VN, Denti P, Modine T, Nguyen TC, Mack MJ, Reardon MJ, Kaneko T, Tang GHL; **EXPLANT-TAVR Investigators**. Surgical Explantation of Failed Transcatheter Aortic Valve Replacement. Ann Thorac Surg. 2023 Jun 22:S0003-4975(23)00612-4. doi: 10.1016/j.athoracsur.2023.05.036. Epub ahead of print. PMID: 37354965.

- Zaid S, Avvedimento M, Vitanova K, Akansel S, Bhadra OD, Ascione G, **Saha S**, Noack T, Tagliari AP, Pizano A, Donatelle M, Squiers JJ, Goel K, Leurent G, Asgar AW, Ruaengsri C, Wang L, Leroux L, Flagiello M, Algadheeb M, Werner P, Ghattas A, Bartorelli AL, Dumonteil N, Geirsson A, Van Belle E, Massi F, Wyler von Ballmoos M, Goel SS, Reardon MJ, Bapat VN, Nazif TM, Kaneko T, Modine T, Denti P, Tang GHL; CUTTING-EDGE Investigators. Impact of Mitral Regurgitation Etiology on Mitral Surgery After Transcatheter Edge-to-Edge Repair: From the CUTTING-EDGE Registry. JACC Cardiovasc Interv. 2023 May 22;16(10):1176-1188. doi: 10.1016/j.jcin.2023.02.029. PMID: 37225288.

- Tang GHL, Zaid S, Kleiman NS, Goel SS, Fukuhara S, Marin-Cuartas M, Kiefer P, Abdel-Wahab M, De Backer O, Søndergaard L, **Saha S**, Hagl C, Wyler von Ballmoos M, Bhadra O, Conradi L, Grubb KJ, Shih E, DiMaio JM, Szerlip M, Vitanova K, Ruge H, Unbehaun A, Kempfert J, Pirelli L, Kliger CA, Van Mieghem N, Hokken TW,

Adrichem R, Modine T, Corona S, Wang L, Petrossian G, Robinson N, Meier D, Webb JG, Cheung A, Ramlawi B, Herrmann HC, Desai ND, Andreas M, Mach M, Waksman R, Schults CC, Ahmad H, Goldberg JB, Geirsson A, Forrest JK, Denti P, Belluschi I, Ben-Ali W, Asgar AW, Taramasso M, Rovin JD, Di Eusanio M, Colli A, Kaneko T, Nazif TN, Leon MB, Bapat VN, Mack MJ, Reardon MJ, Sathananthan J. Explant vs Redo-TAVR After Transcatheter Valve Failure: Mid-Term Outcomes From the EXPLANTORREDO-TAVR International Registry. JACC Cardiovasc Interv. 2023 Apr 24;16(8):927-941. doi: 10.1016/j.jcin.2023.01.376. PMID: 37100556.

- Doldi PM, Stolz L, Buech J, **Saha S**, Weckbach L, Gmeiner J, Orban M, Braun D, Stocker TJ, Nabauer M, Lange CM, Massberg S, Hagl C, Hausleiter J. Indocyanine green clearance predicts outcome in patients undergoing transcatheter valve intervention for severe atrio-ventricular valve regurgitation. Interdiscip Cardiovasc Thorac Surg. 2023 Feb 6;36(2):ivad024. doi:10.1093/icvts/ivad024.

- Luehr M, Weber C, Misfeld M, Lichtenberg A, Tugtekin SM, Diab M, **Saha S**, Li Y, Matsche K, Doenst T, Borger MA, Wahlers T, Akhyari P, Hagl C. Virulence of Staphylococcus Infection in Surgically Treated Patients With Endocarditis : A Multicenter Analysis. Ann Surg. 2022 Jul 8. doi: 10.1097/SLA.0000000000005448. Epub ahead of print. PMID: 35801702.

- Vitanova K, Zaid S, Tang GHL, Kaneko T, Bapat VN, Modine T, Denti P; **EXPLANT-TAVR Investigators**. Aortic valve versus root surgery after failed transcatheter aortic valve replacement. J Thorac Cardiovasc Surg. 2022 Mar 26:S0022-5223(22)00348-8. doi: 10.1016/j.jtcvs.2021.12.060. Epub ahead of print. PMID: 35525801.

- Buech J, Radner C, Fabry TG, Horke KM, Ali A, **Saha S**, Hagl C, Pichlmaier MA, Peterss S. Visceral and renal malperfusion syndromes in acute aortic dissection type A: the fate of the branch vessel. J Cardiovasc Surg (Torino). 2022 Apr;63(2):117-123. doi: 10.23736/S0021-9509.22.12276-7. Epub 2022 Mar 3. PMID: 35238524.

- Weber C, Luehr M, Petrov G, Misfeld M, Akhyari P, Tugtekin SM, Diab M, **Saha S**, Elderia A, Lichtenberg A, Hagl C, Doenst T, Matschke K, Borger MA, Wahlers T;

Clinical, Multicenter Project of Analysis of Infective Endocarditis in Germany (CAMPAIGN) Study Group. Impact of the 2009 ESC Guideline Change on Surgically Treated Infective Endocarditis. Ann Thorac Surg. 2022 Oct;114(4):1349-1356. doi: 10.1016/j.athoracsur.2022.01.054. Epub 2022 Feb 22. PMID: 35216990.

- Kaneko T, Hirji S, Zaid S, Lange R, Kempfert J, Conradi L, Hagl C, Borger MA, Taramasso M, Nguyen TC, Ailawadi G, Shah AS, Smith RL, Anselmi A, Romano MA, Ben Ali W, Ramlawi B, Grubb KJ, Robinson NB, Pirelli L, Chu MWA, Andreas M, Obadia JF, Gennari M, Garatti A, Tchetche D, Nazif TM, Bapat VN, Modine T, Denti P, Tang GHL; **CUTTING-EDGE Investigators**. Mitral Valve Surgery After Transcatheter Edge-to-Edge Repair: Mid-Term Outcomes From the CUTTING-EDGE International Registry. JACC Cardiovasc Interv. 2021 Sep 27;14(18):2010-2021. doi: 10.1016/j.jcin.2021.07.029. PMID: 34556275.

- Bapat VN, Zaid S, Fukuhara S, **Saha S**, Vitanova K, Kiefer P, Squiers JJ, Voisine P, Pirelli L, von Ballmoos MW, Chu MWA, Rodés-Cabau J, DiMaio JM, Borger MA, Lange R, Hagl C, Denti P, Modine T, Kaneko T, Tang GHL; EXPLANT-TAVR Investigators. Surgical Explantation After TAVR Failure: Mid-Term Outcomes From the EXPLANT-TAVR International Registry. JACC Cardiovasc Interv. 2021 Sep 27;14(18):1978-1991. doi: 10.1016/j.jcin.2021.07.015. PMID: 34556271.

- Jebran AF, **Saha S**, Waezi N, Al-Ahmad A, Niehaus H, Danner BC, Baraki H, Kutschka I. Design and training effects of a physical reality simulator for minimally invasive mitral valve surgery. Interact Cardiovasc Thorac Surg. 2019 Sep 1;29(3):409-415. doi: 10.1093/icvts/ivz112. PMID: 3106567

- Varghese S, Slottosch I, **Saha S**, Wacker M, Awad G, Wippermann J, Scherner M. Surgical Management of Iatrogenic Left Ventricle Perforation by Chest Tube Insertion. Ann Thorac Surg. 2019 Dec;108(6):e405-e407. doi: 10.1016/j.athoracsur.2019.06.104. Epub 2019 Aug 27. PMID: 31470008.

- Oberbach A, Schlichting N, Hagl C, Lehmann S, Kullnick Y, Friedrich M, Köhl U, Horn F, Kumbhari V, Löffler B, Schmidt F, Joskowiak D, Born F, **Saha S**, Bagaev E.

Four decades of experience of prosthetic valve endocarditis reflect a high variety of diverse pathogens. Cardiovasc Res. 2022 Apr 14:cvac055. doi: 10.1093/cvr/cvac055. Epub ahead of print. PMID: 35420122.

- Bagaev E, Ali A, **Saha S**, Sadoni S, Orban M, Naebauer M, Mehilli J, Massberg S, Oberbach A, Hagl C. Hybrid Surgery for Severe Mitral Valve Calcification: Limitations and Caveats for an Open Transcatheter Approach. Medicina (Kaunas). 2022 Jan 7;58(1):93. doi: 10.3390/medicina58010093. PMID: 35056401; PMCID: PMC8777627.

- Buentzel J, Heinz J, Bleckmann A, Bauer C, Röver C, Bohnenberger H, **Saha S**, Hinterthaner M, Baraki H, Kutschka I, Emmert A. Sarcopenia as Prognostic Factor in Lung Cancer Patients: A Systematic Review and Meta-analysis. Anticancer Res. 2019 Sep;39(9):4603-4612. doi: 10.21873/anticanres.13640. PMID: 31519557.

- **Saha S**, Schnackenburg P, Sadoni S, Joskowiak D, Hagl C. Infektiöse Endokarditis. Zeitschrift für Herz-,Thorax- und Gefäßchirurgie 2022;36:298-308.

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