Infective Endocarditis after Transcatheter Aortic Valve Replacement - New insights into incidence, clinical characteristics, management, and outcomes

Thèse

David Del Val Martin

Doctorat en sciences cliniques et biomédicales
Philosophiæ doctor (Ph. D.)

Québec, Canada

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David del Val Martin

Sous la direction de :

Josep Rodés-Cabau, directeur de recherche
Philippe Gervais, codirecteur de recherche

RÉSUMÉ

L’endocardite infectieuse (EI) est une complication rare mais potentiellement mortelle du remplacement valvulaire aortique percutané (TAVR). Le TAVR a révolutionné le traitement de la sténose aortique sévère et est récemment devenu une option thérapeutique pour les patients plus jeunes avec un risque chirurgical faible. Par conséquent, le nombre de patients à risque de développer cette complication grave augmente de façon exponentielle. Il existe peu de données sur l'EI après le TAVR et plusieurs questions restent sans réponse.

Tout d’abord, au cours des dernières années, il y a eu un intérêt croissant pour limiter les gestes invasifs péri-procéduraux au cours des TAVR. De plus, la simplification des procédures a permis un rétablissement plus rapide des patients, de réduire la durée d'hospitalisation et de réduire le risque d’infection nosocomiale. Cependant, l’impact de la combinaison de ces améliorations et du profil clinique contemporain des patients bénéficiant d’un TAVR sur l’incidence et les conséquences des EI post-TAVR reste à ce jour incertain. Deuxièmement, une EI causée par un *Staphylococcus aureus* ainsi que la survenue d'une accident vasculaire cérébral pendant l'hospitalisation pour EI sont classiquement associées à un pronostic sombre chez les patients présentant une EI sur valve native ou prothétique. Cependant, il existe peu de données sur l’incidence, la prise en charge et l'évolution de ces deux situations particulières dans le cadre des IE-TAVR. Ensuite, de nouvelles techniques d'imagerie sont apparues comme étant un outil prometteur en vue d’un diagnostic plus précis de l’IE post-TAVR. Au sein des valves prothétiques chirurgicales, une légère absorption des radio-traceurs dans la zone péri-valvulaire peut se produire en l'absence d'infection. Cependant, les preuves de l’existence d’un tel phénomène au sein des prothèses TAVR font défaut, et les normes permettant de distinguer une répartition normale d’une répartition anormale du traceur radioactif n'ont pas encore été établies. Enfin, bien que la chirurgie soit un traitement efficace et bien établi chez les patients présentant une EI sur valve prothétique, le traitement optimal de l'EI après le TAVR reste indéterminé.

Les principaux objectifs de ce projet de doctorat sont: (i) de déterminer les tendances temporelles de l'incidence, des caractéristiques cliniques, de la prise en charge et des résultats de l'EI post-TAVR, (ii) d'évaluer l'incidence et les résultats de l'EI post-

TAVR dans certains sous-groupes spécifiques de patients, (iii) de déterminer le rôle des nouvelles techniques d'imagerie pour le diagnostic de l'EI après le TAVR et (iv) d'évaluer les caractéristiques et les résultats des patients non sélectionnés atteints d'EI après le TAVR traités par chirurgie cardiaque comparés aux patients traités uniquement par antibiotiques.

ABSTRACT

Infective endocarditis (IE) is a rare but life-threatening complication following transcatheter aortic valve replacement (TAVR). TAVR has revolutionized the treatment of severe aortic stenosis and is currently expanding toward the treatment of younger patients with lower surgical risks. Consequently, the number of patients at risk of developing this serious complication is growing exponentially.

Despite this, there is a paucity of data on IE following TAVR, and several questions remain unanswered. Firstly, there has recently been an increase in interest in simplifying the TAVR procedure. This would allow for more rapid patient recovery, a shorter length of hospital stay, and a lower risk of nosocomial infections. However, it is unknown whether this minimalist approach, combined with the contemporary clinical profile of TAVR patients, has influenced the incidence and outcomes of IE. Secondly, two specific subgroups of patients (those with IE caused by *Staphylococcus aureus,* and those with TAVR-IE complicated by stroke during the index hospitalization) have typically been associated with a worse prognosis in native and prosthetic valve IE. However, there is a scarcity of data on the incidence, management, and outcomes of these patients in the TAVR-IE population. Thirdly, novel imaging techniques have emerged as promising tools for improving diagnostic accuracy in patients with TAVR-IE. In surgical prosthetic valves, mild radiotracer uptake may be identified in the perivalvular area in the absence of infection. However, there is no evidence of this phenomenon in TAVR devices, and the standards for distinguishing normal and abnormal uptake patterns have not yet been described. Finally, although surgery is an effective and well-established treatment for prosthetic valve endocarditis in some clinical scenarios, the optimal management of TAVR-IE remains uncertain.

The main objectives of this Ph.D. research project are to: (i) determine temporal trends in the incidence, clinical characteristics, management, and outcomes of IE post-TAVR; (ii) assess the incidence and outcomes of TAVR-IE in specific patient subgroups; (iii) determine the role of novel imaging techniques for the diagnosis of TAVR-IE; and (iv) evaluate the characteristics and outcomes of patients with IE following TAVR who were treated with cardiac surgery, compared with those treated with antibiotics alone.

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LIST OF ABBREVIATIONS

AC: attenuation-corrected

AR: aortic regurgitation

AS: aortic stenosis

BEV: balloon-expandable valve

CC: contemporary cohort

CI: confidence interval

CMR: cardiac magnetic resonance

CoNS: coagulase-negative staphylococci

COPD: chronic obstructive pulmonary disease

CRF: chronic renal failure

CS: cardiac surgery

CT: computed tomography

EI: endocardite infectieuse

FDG: fluorodeoxyglucose

HC: historical cohort

HR: hazard ratio

IE-AB: infective endocarditis treated with antibiotics only

IE-CS: infective endocarditis treated with cardiac surgery (and antibiotics)

IE: infective endocarditis

IPTW: inverse probability treatment weighting

IQR: interquartile range

NAC: nonattenuation-corrected

non-SA IE: non- Staphylococcus aureus infective endocarditis

NS-IE: no stroke in patients with infective endocarditis

NVE: native valve endocarditis

OR: odds ratio

PET: positron emission tomography

PVE: prosthetic valve endocarditis

RF: risk factor

S-IE: stroke in patients with infective endocarditis

SA IE: Staphylococcus aureus infective endocarditis

SA: Staphylococcus aureus

SAVR: surgical aortic valve replacement

SD: standard deviation

SEV: self-expanding valve

SPECT: single-photon emission computed tomography

STS: society of thoracic surgeons

TAVI: transcatheter aortic valve intervention

TAVR: transcatheter aortic valve replacement

TEE: transesophageal echocardiography

TF: transfemoral

TTE: transthoracic echocardiography

VARC: valve academic research consensus

VHD: valvular heart disease

« Permettez-moi de vous révéler le secret qui m'a conduit à atteindre mon but. Ma force repose uniquement sur ma ténacité »

Louis Pasteur (1822-1895)

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I am grateful to the members of the research team—Emilie, Karine, Mélaine, Marie-Josée, Claire, Shirley, and Caroline—and particularly to Dominique and Melanie. I thank them for their welcome, hospitality, and extraordinary attention. Working side by side with them has been a pleasant and enjoyable experience. They are all part of our little *famille québécoise.*

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FOREWORD

This thesis is comprised of six original research articles, which have been peer-reviewed and published in high-impact medical journals.

The first article, entitled **"Temporal Trends, Characteristics, and Outcomes of Infective Endocarditis After Transcatheter Aortic Valve Replacement"**, was published in **Clinical Infectious Disease.** The study analyzed the temporal trend regarding the incidence, clinical characteristics, management, and outcomes of IE episodes after TAVR, using data from the Infectious Endocarditis After TAVR International Registry. Under the supervision of the director, the student participated in the conception and design of the study, the acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript. The student was listed as first author of this original research article, and Prof. Josep Rodés-Cabau as senior author. The other authors contributed with the acquisition and interpretation of data in different centers. All co-authors approved and revised the manuscript and contributed with their critical review.

The second article, entitled **"Stroke Complicating Infective Endocarditis After Transcatheter Aortic Valve Replacement"**, was published in the **Journal of the American College of Cardiology (JACC)**. This study assessed the incidence, associated risk factors, clinical characteristics, management, and outcomes of patients with definite IE following TAVR complicated by stroke during the index IE hospitalization. Data from the Infectious Endocarditis After TAVR International Registry were used for this study. The student participated in the conception and design of the study, the acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript under the supervision of the director. In this original investigation, the student was listed as first author, and Prof. Josep Rodés-Cabau as senior author. The other authors contributed with the acquisition and interpretation of data in different centers. All co-authors approved and revised the manuscript, and provided valuable and constructive comments.

The third article, entitled **"Infective Endocarditis Caused by Staphylococcus aureus After Transcatheter Aortic Valve Replacement"**, was published in the **Canadian Journal of Cardiology.** This study evaluated the clinical characteristics, management, and in-hospital and late outcomes of patients with IE caused by *Staphylococcus aureus* after TAVR, using data from the Infectious Endocarditis After TAVR International Registry. Under the supervision of the director, the student participated in the conception and design of the study, the acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript. The student was listed as first author of this original research article, and Prof. Josep Rodés-Cabau as senior author. The other authors contributed with the acquisition and interpretation of data in different centers. All co-authors revised and approved the manuscript, providing salient suggestions and improving the final version.

The fourth article, entitled **"^{18}F-Fluorodeoxyglucose Uptake Pattern in Noninfected Transcatheter Aortic Valves"**, was published in **Circulation: Cardiovascular Imaging**. This study aimed to characterize the uptake pattern of ^{18}F-FDG in noninfected transcatheter aortic valves at three months following TAVR, and assessed the differences in uptake pattern between the two most widespread prostheses. This study was performed in collaboration with the Department of Nuclear Medicine at the Institute de Cardiologie et Pneumologie de Québec (IUCPQ, Laval University, Québec, City, Québec). The student participated in the conception and design of the study, the acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript, under the supervision of the director and Dr. Mikaël Trottier. In this research letter, the student was listed as first author, and Prof. Josep Rodés-Cabau as senior author. Drs. Trottier and Tessier participated in the design of the study, as well as in the interpretation of the data. All co-authors from the Institute de Cardiologie et Pneumologie de Québec contributed with comments and constructive suggestions that improved the final version of the manuscript.

The fifth article, entitled **"Surgical Treatment of Patients With Infective Endocarditis After Transcatheter Aortic Valve Implantation"**, was published in the **Journal of the American College of Cardiology (JACC).** This study evaluated the

characteristics and outcomes of patients with TAVR-IE treated with cardiac surgery and antibiotics, compared to patients treated with antibiotics alone, and applied an appropriate propensity score-based method to provide adjusted estimates of the treatment effect for in-hospital and 1-year all-cause mortality. Data from the Infectious Endocarditis After TAVR International Registry were used for this study. The student participated in the conception and design of the study, the acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript, in close collaboration with Dr. Norman Mangner from Herzzentrum Dresden, Technische Universität Dresden, Germany. In this original investigation, the student was listed as joint first author (with Dr. Norman Mangner), and Prof. Josep Rodés-Cabau as senior author. The other authors contributed with the acquisition and interpretation of data in different centers. All co-authors approved and revised the manuscript, providing valuable and constructive comments.

Finally, the sixth article included in this thesis is entitled **"Long-Term Outcomes After Infective Endocarditis After Transcatheter Aortic Valve Replacement"**, and was published in **Circulation.** This study evaluated the long-term outcomes and prognostic factors in patients who developed definite IE after TAVR and survived the index hospitalization, using data from the Infectious Endocarditis After TAVR International Registry. Under the supervision of the director, the student participated in the conception and design of the study, the acquisition, analysis and interpretation of the data, and the drafting and revision of the manuscript. The student was listed as first author of this research letter, and Prof. Josep Rodés-Cabau as senior author. The other authors contributed with the acquisition and interpretation of data in different centers. All co-authors approved the manuscript and contributed with their critical review.

INTRODUCTION

1. INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) is a multisystem disease characterized by infection of the endothelial lining of intracardiac structures, including the heart valves, mural endocardium, and endocardial covering of intracardiac devices (prosthetic heart valves and indwelling devices).

1.1 Historical perspective

Jean François Fernel (1497-1558), a French physician considered one of the fathers of pathology, included in his *Medinici* what is likely to be the earliest mention of "endocarditis".[1] Years later, Lazare Rivière (1589-1655) treated a patient who complained of palpitations, swollen legs, and an irregular pulse. The patient's condition worsened progressively, and autopsy revealed in the left ventricle "small round outgrowths, the largest about the size of a hazelnut which blocked the aortic valve".[2] This observation was followed by Giovanni Maria Lancisi's (1654-1720) description of "rough structures on the valves and small nodules of flesh" in close relationship with the valvular tissue, and the introduction of the term "vegetation" by Jean Nicholas Corvisart (1755-1821) at the beginning of the 19th century.[3] Within a few years, Jean-Bastiste Bouillaud (1796-1881) identified the "endocardium" as an inner membrane of the heart that joins the inner lining of the vessels. Emmanuel Winge (1817-1894) first introduced the term *"mycosis endocardii"* and suggested an infectious origin of IE; shortly afterwards, Edwin Klebs (1834-1913) expressed his own conviction of this theory, and supported this with the results of twenty-seven autopsies, showing the presence of microorganisms in valvular vegetations.[2–4] One of the most prominent endocarditis clinicians was Sir William Osler (1849-1919), who made several fundamental advances in the understanding of this disease,[4,5] and outlined the major pathophysiological features in his famed *Gulstonian Lectures* in 1885.[6,7] The understanding of IE continued to evolve throughout the first half of the 20th century, and from the mid-1940s, penicillin provided the first effective treatment.[5].

1.2 Epidemiology

The overall disease burden of IE is unknown, and varies widely according to geographical features and multiple patient factors. Nevertheless, some population-based studies have estimated reliable incidence rates, ranging from 3 to 15 cases per 100,000

person-years.[8–16] These disparities reflect the complexity of identifying a representative cohort in epidemiologic studies of IE. Furthermore, these incidence rates may be underestimated, as high-quality data are derived mainly from high-income countries, and IE remains an underdiagnosed disease in low- and middle-income countries.

The epidemiology of IE has changed over the past few years. Despite the dramatic decline of rheumatic heart disease in high-income countries, the effects of an aging patient population with increasing medical complexity have resulted in a steady rise in global incidence. The Global Burden of Disease Study, which analyzed data sources from 204 countries from 1990 to 2019, reported 1,090,527 incident cases in 2019.[17] The study also found that the age-standardized incidence rate has increased from 9.91 to 13.80 per 100,000 person-year over the past 30 years **(Figure 1)**.[17]

The patient profile has also evolved over time. Currently, in high-income regions, the highest rates of IE are observed in elderly patients, with a peak between 70 and 80 years of age and a notably increased prevalence in males.[18,19] Importantly, more than one-third of the new cases are associated with health care exposure (nosocomial or non-nosocomial).[20] In contrast, IE in low- and middle-income countries remains linked to rheumatic heart disease, and typically affects young patients.

IE represents a health- and economic challenge. A population-based study revealed a 54% increase in hospitalizations due to IE in the United States over the past decade, with over 40,000 new cases each year and average hospital charges of more than $120,000 per patient.[21] The total number of disability-adjusted life-years (DALYs), years of life lost, and years lived with disability due to IE have also increased across all ages groups since 1990, accounting for 1.72 million DALYs in 2019.[22] According to the Global Burden of Disease Study, 83,400 deaths were attributed to IE in 2017, an increase of 32.2% over ten years, with an age-standardized death rate of 1.1 per 100,000 people.[23]

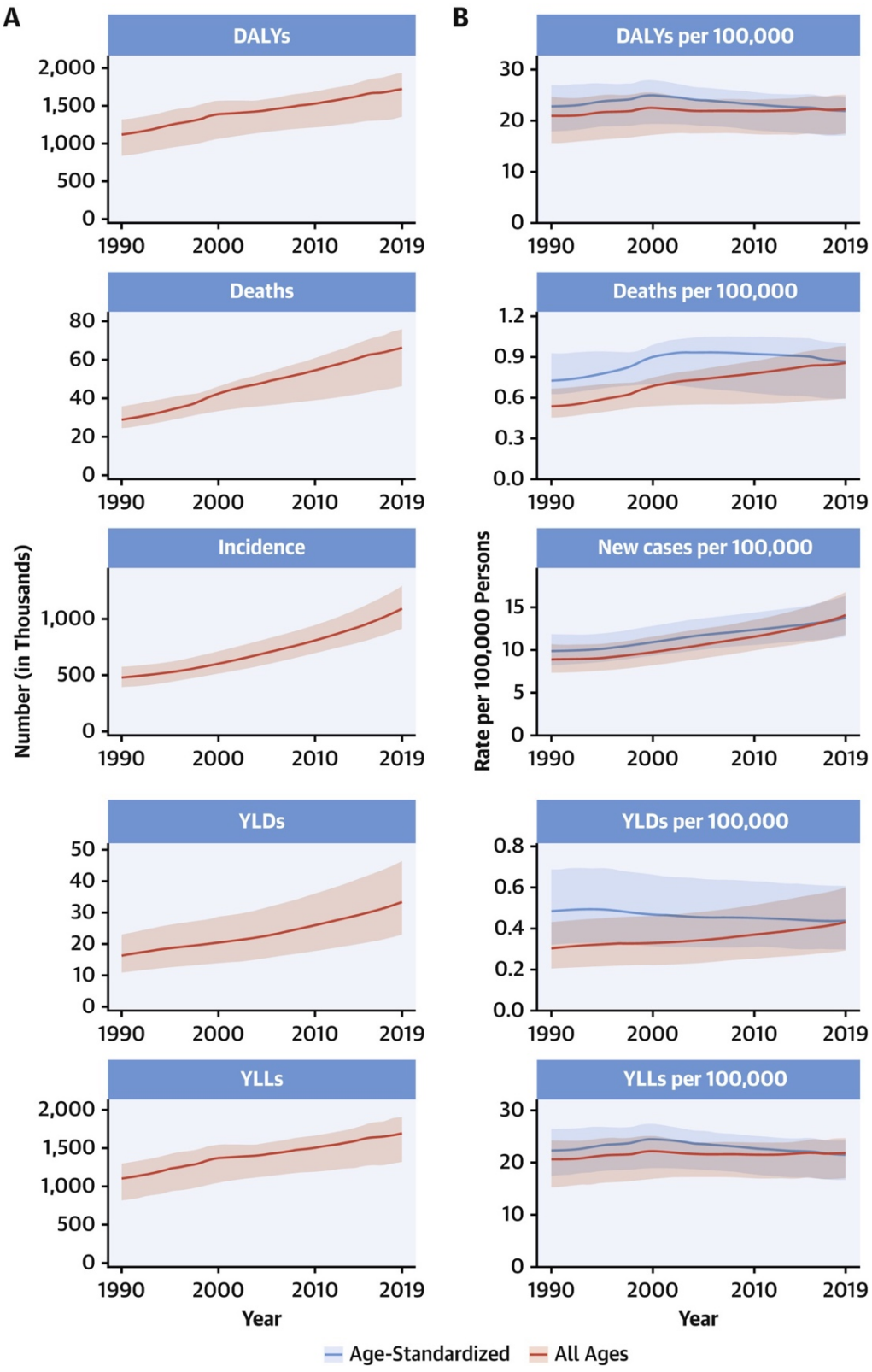

Figure 1: Epidemiology of infective endocarditis

(A) Total number of DALYs, deaths, incident cases, YLDs, and YLLs due to endocarditis between 1990 and 2019. Shaded regions represent 95% CI. (B) Age-standardized and all-ages DALY, death, incidence, YLD, and YLL rates of endocarditis between 1990 and 2019. Shaded regions represent 95% CI. Abbreviations: DALYs: disability-adjusted life-years; YLLs: years of life lost; YLDs: years lived with disability. From Roth et al.[22] with permission.

1.3 Pathophysiology of infective endocarditis

Under normal conditions, the valvular endothelium is resistant to bacterial colonization. The development of IE therefore requires an interaction between cardiac structural damage (valvular or nonvalvular) that results in blood flow turbulence, disruption of the endothelium, and complex host immune reactions.[14,24] Previous studies have suggested that host endothelial damage is the pivotal factor that triggers subsequent platelet-fibrin activation and results in the initial lesion, termed *nonbacterial thrombotic endocarditis* (NBTE). Once bloodstream infection is established, this sterile platelet-fibrin matrix serves as a nidus for adhesion and further proliferation of microorganisms (bacteria or fungi). The interaction between microorganisms and NBTE is mediated by different microbial surface proteins that recognize a wide variety of host receptors present in the NBTE. Typical sources of bacteremia are the periodontal tissue, skin, surgical wounds, urinary and gastrointestinal tracts, and indwelling intravascular catheters. Following microbial colonization, pathogen proliferation and host inflammatory response result in the formation of vegetations and local tissue destruction. Pathogen-specific virulence factors and the host immune response play a prominent role in this process.[14,19,24] Although different types of IE share common pathophysiological mechanisms, the formation of a biofilm formation is unique to prosthetic materials. This phenomenon plays a critical role the pathogenesis of IE on cardiac devices and prosthetic valves, as it hinders clearance of microorganisms by the host immune system, and contributes to device-associated vegetation development and local tissue destruction **(Figure 2)**.[25]

As a systemic disease, IE can involve multiple target organs. Extracardiac manifestations are often the result of small portions of the fibrin-platelet matrix that have detached from infected cardiac vegetations, and are traveling through the bloodstream. These septic emboli may affect any organ, and systemic manifestations result mainly from ischemic events and local invasion of surrounding tissues by microorganisms in satellite areas, with subsequent abscess formation.[26] Similarly, systemic manifestations, such as glomerulonephritis and Osler nodes, are also related to the circulation of immune complexes and complement deposition in target organs.[24]

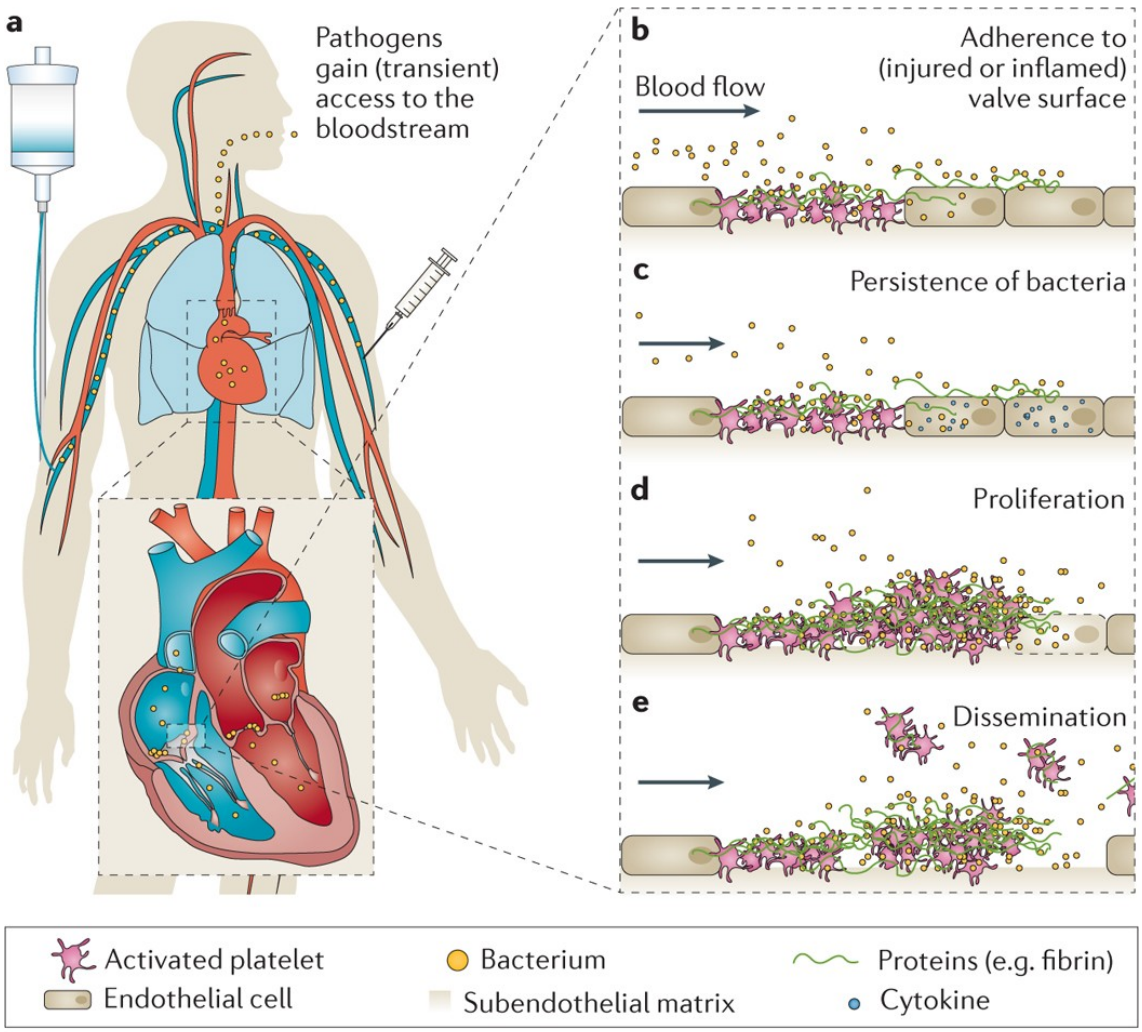

Figure 2: Overview of the pathophysiology of bacterial infective endocarditis
From Holland et al[26] with permission.

1.4 Diagnosis

The diagnosis of IE is often challenging, and is based on a combination of clinical, imaging, and biological findings, in addition to microbiological assessment. Historically, the diagnosis of IE has relied on classical clinical findings, such as the presence of a cardiac murmur, immunological phenomena, and embolic events in association with positive blood cultures. Although these findings remain the mainstay of diagnosis in resource-limited settings, the diagnostic work-up for IE has improved substantially over the last decade, enabling earlier and more accurate diagnosis.

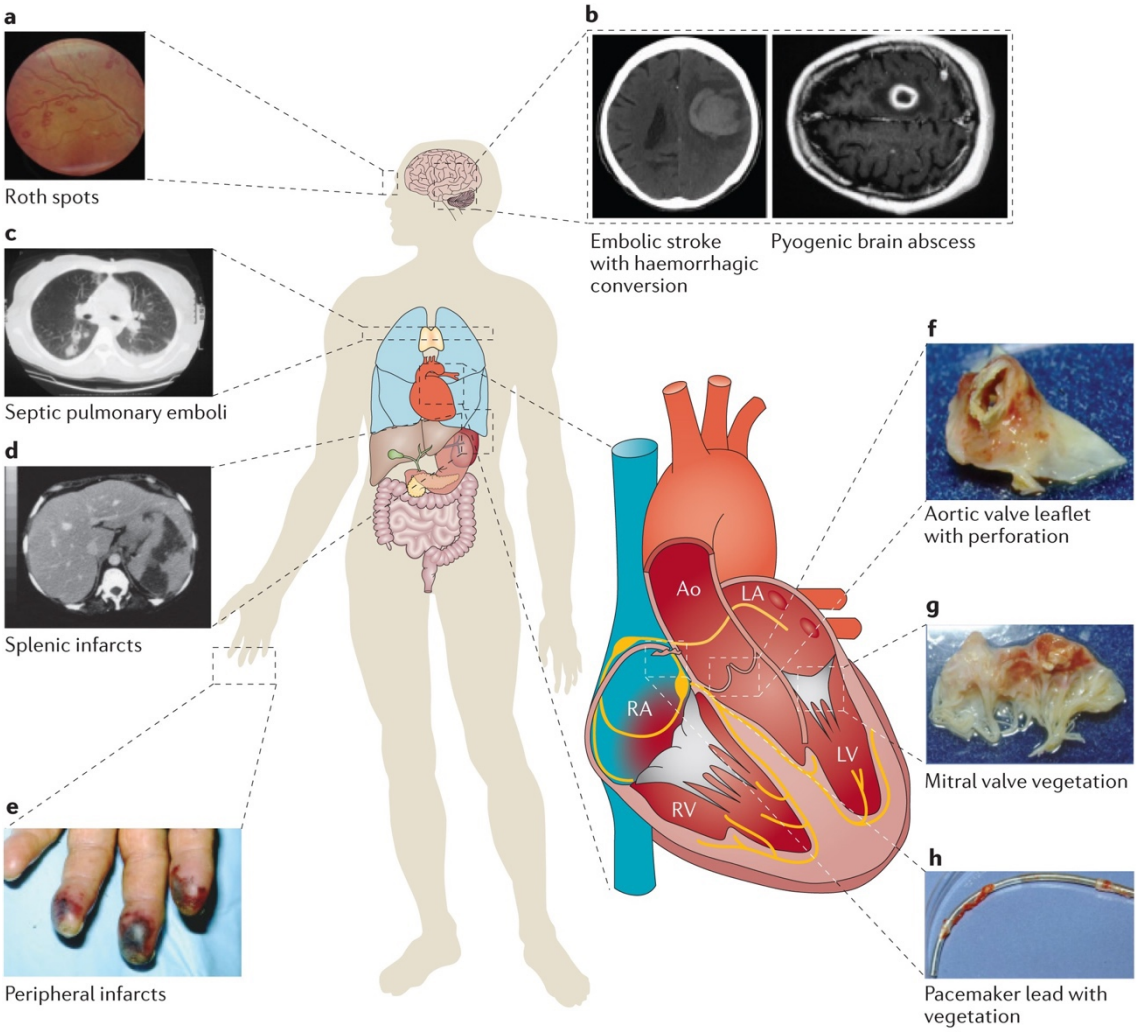

Figure 3: Clinical manifestations of infective endocarditis

(a) Roth spots. (b) CT scans showing an embolic stroke with hemorrhagic conversion and a pyogenic brain abscess. (c) CT scan with multiple septic pulmonary emboli. (d) CT scan showing peripheral wedge-shaped splenic infarcts. (e) Peripheral infarcts affecting multiple fingers. (f) Aortic valve leaflet with vegetation and perforation. (g) Mitral valve with vegetation. (h) Pacemaker leads with vegetation. From Holland et al.26 with permission.

1.4.1 Clinical manifestations

The clinical presentation of IE varies widely. Classical presentation combines the presence of systemic signs of infection without apparent cause and detection of a new regurgitant cardiac murmur **(Figure 3)**. Fever is the most common symptom at presentation (~85%), but is less common in patients who are elderly, immunocompromised, or who have received previous antibiotic therapy.[27] A heart murmur is present in 80-85% of patients, while up to 25% have embolic complications at presentation.[28] Typical peripheral signs, including Osler nodes, Roth spots, purpura, and Janeway lesions are commonly associated with advanced stages of subacute forms, which

are currently extremely uncommon in high-income countries. The wide range of possible clinical presentations and the importance of early diagnosis necessitates a high suspicion index and a low screening threshold, particularly in high-risk patients.

1.4.2 Microbiology

Identifying the causative microorganism is essential for the diagnosis and management of IE. The microbiological spectrum has shifted as patients' risk factors have changed over the last decades. *Staphylococcus aureus (S. aureus)* is the leading cause of native- and prosthetic-valve endocarditis globally,[29–31] accounting for ~30% of total cases.[30,32] The rising incidence of health care–associated IE has led to a steady increase in coagulase-negative staphylococci cases, while IE caused by oral streptococci has declined over time.[12,26] Similarly, enterococci infection cases have risen globally, and are strongly associated with health care exposure and elderly patients.[33] HACEK bacteria (*Haemophilus species, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella* species), fungi, and zoonoses collectively represent around 5% of cases.[34]

The microbiological profile of IE varies with geographical and epidemiological factors. According to a population-based study, the proportion of IE caused by *Streptococcus gallolyticus* (formerly *Streptococcus bovis)* was significantly higher in Europe and South America than in other regions. IE caused by HACEK organisms was also found to be relatively uncommon in North America.[30]

Culture-negative IE is an important subtype, accounting for approximately 10-20% of overall cases. Although it may sometimes be related to previous antibiotic use, "true" culture-negative IE is commonly caused by fastidious, slow-growing pathogens that are difficult to isolate using conventional blood culture techniques. The most frequently implicated microorganisms include *Coxiella burnetti, Bartonella spp., Brucella spp., and Tropheryma whipplei*. It should be noted that early recognition of this type of IE, combined with a comprehensive diagnostic strategy, enables the identification of the causative microorganism in almost two thirds of patients.[35]

1.4.3 Imaging techniques

Echocardiography is the cornerstone of diagnostic imaging for IE, allowing rapid and easy identification of endothelial lesions, structural damage, and valve or ventricular dysfunction. Transthoracic echocardiography (TTE) is recommended as the first-line imaging technique, and should be performed as soon as IE is suspected. Although often performed in combination with TTE, transesophageal echocardiography (TEE) is especially indicated in the presence of inconclusive findings on TTE, when complications are suspected, or in the setting of prosthetic valve endocarditis (PVE) or cardiac-device IE **(Figure 4)**. Echocardiography also provides helpful information on the existence of concomitant valvular heart disease, ventricular function, and pulmonary pressure. TTE has a sensitivity of 50-90% and a specificity of 90% in patients with suspected NVE. However, the sensitivity of TTE is significantly lower (40-70%) in patients with PVE due to shadowing from the prosthetic valve.[34] In contrast, TEE has a sensitivity of 90-100% for detecting vegetations, and is superior to TTE in identifying complications such as abscesses, aneurysms, fistulas, or perforations.[34]

Cardiac computed tomography (CT) has excellent spatial resolution, and is primarily used for the detection of embolic events and assessment of perivalvular extension. CT is also useful for identifying coronary artery disease in patients undergoing cardiac surgery for IE complications. Some studies have reported the superiority of CT compared to TEE in detecting abscesses and pseudoaneurysms, and have found that it provides more accurate anatomical information.[36,37] Importantly, the assessment of paravalvular complications using CT has been included as a major criterion in the latest ESC guidelines for diagnosing IE.[38]

Novel diagnostic modalities based on metabolic imaging play an essential role in IE diagnosis and management. Radionuclide hybrid imaging has emerged as an additional diagnostic tool and is useful in guiding the most appropriate clinical management. The ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and white blood cell single-photon emission computed tomography/computed tomography (WBC SPECT/CT) are two of the most widely used radionuclide imaging modalities. These techniques are based on the uptake of radiolabeled tracers by

inflammatory cells at the site of infection. Previous studies have reported high diagnostic accuracy of these techniques in patients with suspected IE, demonstrating a sensitivity of 73-100%, a specificity of 71-100%, and positive and negative predictive values of 67-100% and 50-100%, respectively.[39] Of note, the sensitivity of the Modified Duke Criteria increases substantially from 52-70% to 91-97% when these diagnostic tools are systematically included in the work-up of IE.[39] Likewise, ^{18}F-FDG PET/CT has been shown to improve the detection of unexpected extracardiac complications and infectious foci.[40] Another study showed that the addition of cardiac CT with ^{18}F-FDG-PET/CT yielded an overall sensitivity of 87%, and concurrently increased the sensitivity of the Modified Duke Criteria from 52% to 91%, resulting in a conclusive diagnosis in 95% of the cases.[41] As a result, the 2015 ESC guidelines included abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT or WBC SPECT/CT as a major criterion.[42] However, the limited availability of these techniques, particularly in resource-limited health systems, remains one of the main barriers to their widespread application **(Table 1)**.

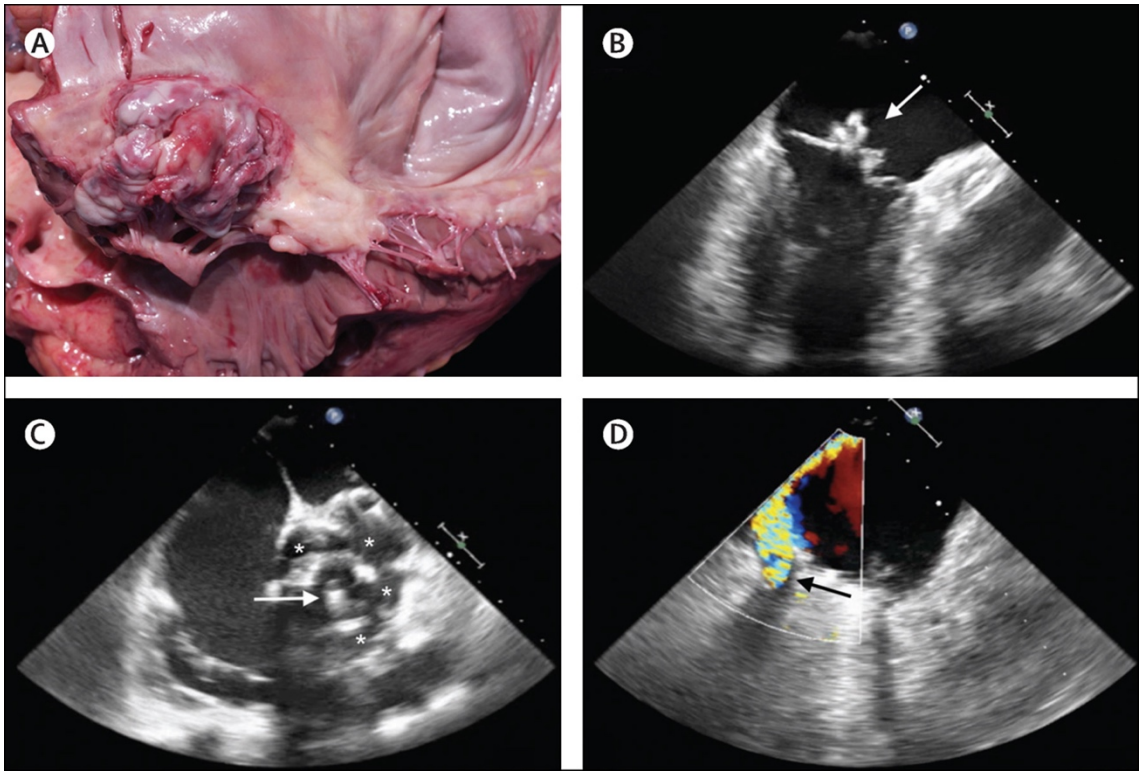

Figure 4. Macroscopic and echocardiographic findings in infective endocarditis.

(A) Vegetation in staphylococcal IE. (B) TEE with vegetation on the mitral valve (arrow). (C) TEE with the aortic valve en face (arrow) surrounded by many abscesses (*). (D) Jet of mitral regurgitation (arrow) arising at the site of new prosthetic mitral valve dehiscence. From Cahill et al.[43] with permission.

Table 1. Comparison of additional imaging modalities in the diagnosis of infective endocarditis.

	TEE	CMR/MRI	CT	^{18}F-FDG	WBC SPECT
Imaging resolution					
Spatial	High	Moderate	High	Low	Low
Temporal	High	High	Rate dependent	N/A	N/A
Diagnosis performance					
NVE	High	Low	High	Low	Low
PVE	Moderate	Low	High	High	High
Perivalvular complications	Moderate	Low	High	High	High
Distal emboli	N/A	High	High	High	High
CIED	High	N/A	High	High	High
Practical considerations					
Availability	Wide	Moderate	Moderate	Low	Low
Patient preparation	Sedation as required	eGFR>30 mL/min/kg for contrast	eGFR>30 mL/min/kg for contrast	HFLC diet over 24 h	In vitro WBC labeling
Radiation dose	None	None	24 mSv	16-24 mSv	

Adapted with permission from Infective Endocarditis: A Multidisciplinary Approach.[44]

1.4.4 Diagnostic criteria

Due to the complexity of IE diagnosis, several efforts have been made to develop probabilistic classifications to improve accuracy. The original Duke criteria, and the modified version developed by Li (the so-called "Modified Duke Criteria"), constitute the diagnostic reference for IE **(Table2)**.[45,46] These criteria have been well-validated in a broad spectrum of patients, and have high sensitivity and specificity, even in geographically and clinically diverse populations.[47,48] The Modified Duke Criteria are comprised of two major and five minor criteria. While the major criteria focus on the causative microorganism and evidence of endocardial involvement (as determined by echocardiography), the minor criteria are related to predisposing conditions, fever, vascular or immunological phenomena, and microbiological evidence that does not meet the major criteria. Based on this classification system, patients presenting with suspected IE can be divided into three categories according to their diagnostic probability: definite, suspected, or rejected. Definite IE is diagnosed when a pathological criterion is met in

addition to clinical criteria. A diagnosis of IE is considered possible when the patient meets one major and one minor criterion, or three minor criteria. Rejected IE is established when there is a firm alternate diagnosis or symptoms disappear within four days of antibiotic therapy, or when there is no pathological evidence of IE at surgery or autopsy prior to the completion of four days of antibiotic therapy.

Despite its thoroughness, the Modified Duke Criteria is less accurate for early diagnosis, particularly in the setting of PVE or cardiac-device IE, where echocardiographic findings are often inconclusive.[49] The recent incorporation of advanced imaging modalities in the work-up of IE has substantially improved the diagnosis of this pathology, particularly in the very early setting. As a result, the 2015 ESC guidelines suggest the inclusion of three additional items in the Modified Duke Criteria:[38] (1) use of CT should be considered a major criterion for identifying paravalvular complications; (2) abnormal radiolabel uptake pattern assessed by ^{18}F-FDG PET/CT or radiolabeled leucocyte SPECT/CT should be considered a major criterion in patients with suspected PVE; and (3) evidence of embolic events or infectious aneurysms by imaging only should be considered a minor criterion. A recent study showed that these new ESC criteria have higher sensitivity in patients with PVE, compared to the classical Duke criteria.[50] In contrast, the 2015 AHA guidelines suggested that further data are required before novel imaging tools can be included in the diagnostic criteria.[31]

Table 2. Definition of terms used in the proposed Modified Duke Criteria for the diagnosis of infective endocarditis.

Major criteria

Blood culture positive for IE

Typical microorganisms consistent with IE from 2 separate blood cultures:

Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus; or

Community-acquired enterococci, in the absence of a primary focus; or

Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:

At least 2 positive cultures of blood samples drawn >12 h apart; or

All of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart)

Single positive blood culture for Coxiella burnetii or antiphase I IgG antibody titer >1:800

Evidence of endocardial involvement

Echocardiogram positive for IE *(TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients),* defined as follows:

Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or

Abscess; or

New partial dehiscence of prosthetic valve

New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

Minor criteria

Predisposition, predisposing heart condition or injection drug use

Fever, temperature >38ºC (100.4°F)

Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions

Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[a] or serological evidence of active infection with organism consistent with IE

Echocardiographic minor criteria eliminated

TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. [a]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis. Proposed modifications are shown in italics.

Adapted from Li et al.[45]

1.5 Management

The management of patients with IE is often challenging and requires a high level of expertise. The latest version of clinical practice guidelines from the European Society of Cardiology and the American Heart Association introduced the concept of an "Endocarditis Team" for a multidisciplinary approach.[31,38] This team should be comprised of cardiologists, infectious diseases specialists, cardiac surgeons, imaging specialists, microbiologists, and neurologists, among others. Some studies have demonstrated that this collaborative approach improves patient outcomes and substantially reduces 1-year mortality.[51,52]

1.5.1 Medical therapy

IE is associated with a poor prognosis, unless treated appropriately. Since the introduction of penicillin in the mid-1940s, the mortality of IE has dramatically declined. Antibiotic therapy is therefore the cornerstone of IE management, and effective treatment typically requires microbial clearance by bactericidal regimens. Generally, medical therapy for infection eradication consists of prolonged, intravenous bactericidal drugs, frequently used in combination. Antibiotic regimens should be longer (at least 6 weeks) in patients with PVE, while 4 weeks may be sufficient for patients with left-sided native valve endocarditis.[31,38]

Initial antibiotic therapy is often empirical, and may be introduced while awaiting blood test results based on suspected pathogens and severity of presentation. Additionally, the type of IE (native- vs. prosthetic-valve IE) and the prevalence of multidrug-resistant microorganisms should be considered when choosing the optimal empiric therapy. Despite the high level of consensus on most pathogen-based antibiotic regimens, the most appropriate empirical therapy for IE remains controversial.

Antibiotic recommendations have evolved over time. Overall, antibiotic regimens for both PVE and NVE are comparable, except for staphylococcal PVE, for which the treatment should always include rifampin if the strain is susceptible. Different antibiotic regimens are extensively detailed in AHA and ESC guidelines on IE.[31,38] However, some

notable changes in recent years include the following: 1) aminoglycosides are no longer indicated for staphylococcal native IE due to their potential renal toxicity and uncertain efficacy. Nevertheless, clinical practice guidelines still support the use of aminoglycosides for enterococcal IE and PVE caused by *Staphylococcus spp*.; 2) rifampin is indicated for PVE due to *Staphylococcus spp.* but is no longer recommended for staphylococcal native-valve IE; and 3) in patients with native-valve, methicillin-sensitive, or methicillin-resistant staphylococcal IE, daptomycin is recommended as an alternative to vancomycin.

One major concern in the treatment of IE is bacterial tolerance. Tolerance appears when microorganisms persist despite appropriate antibiotic therapy, and resume growth and infection after antibiotic discontinuation. Multiple factors are implicated in this phenomenon, including poor antibiotic penetration within vegetations, high bacterial concentration, and the formation of biofilms on bioprosthetic materials.[34] The risk of tolerance is partially addressed by using prolonged and parenteral antibiotic therapies.

The requirement for prolonged intravenous antibiotic regimens is commonly associated with extended hospital stays and eventual complications. As such, there has been increasing interest in alternative treatment strategies. For instance, shortened regimens (2 weeks) of combined intravenous antibiotics have found to be safe and effective in selected patients with viridans group streptococci and uncomplicated IE.[53] Likewise, some studies have demonstrated that intravenous antimicrobial therapy can be administrated safely in an outpatient setting after hospital discharge in selected patients.[54,55] Recently, the POET (Partial Oral Treatment of Endocarditis) randomized trial has shown that changing to oral antibiotic treatment was noninferior to continued intravenous therapy in patients with left-sided IE who were in stable condition.[56]

1.5.2 Surgery

The progression of surgical techniques has expanded the indications for surgery in the management of IE. Globally, the role of surgery is well-established for the management of patients with complicated IE, including heart failure, severe valve

dysfunction, persistent bacteremia despite appropriate medical therapy, IE caused by drug-resistant pathogens or fungi, and a high risk of systemic embolism. Regardless of the type of IE, surgical treatment is associated with an in-hospital survival of ~90%.[57] However, the long-term prognosis of patients undergoing surgery due to IE is inferior to that of patients undergoing elective valve surgery, with a 10-year survival ranging from 40-60%.[58,59]

When surgery is indicated, valve or cardiac device explantation is the treatment of choice, with some series reporting up to 40-50% of surgical interventions during index hospitalization.[60–62] Indeed, some studies have shown improved outcomes with early surgery during IE.[63,64] Although surgery is a well-established option for patients with complicated IE, only one small randomized trial has compared surgery with conventional treatment.[64] In this study, early surgery reduced the composite primary endpoint of all-cause death or embolic events by decreasing the risk of systemic embolism in patients with IE and large vegetations.[64] This benefit is also supported by observational studies showing lower in-hospital mortality in patients undergoing surgery during index hospitalization, compared to patients treated medically.[65,66]

The optimal strategy for surgery in IE remains controversial, and definitions of surgical timing differ between clinical practice guidelines. The 2015 ESC guidelines distinguished three levels of urgency: emergent (within 24 hours), urgent (within a few days), or elective (after 1-2 weeks of antibiotic therapy).[38] By contrast, the AHA guidelines define early surgery as an intervention performed during index hospitalization and before completing of a full course of antibiotics.[31] Despite these differences, both guidelines advocate immediate surgery in the presence of hemodynamic instability, uncontrolled infection, or perivalvular complications, and for the prevention of embolism events **(Table 3)**.

It is important to note that, despite the expansion of indications for surgery, a remarkable proportion of patients do not undergo surgery even in the presence of clear indications. For example, a prospective cohort study that included patients with definite

left-sided IE found that almost 1 in 4 did not undergo surgery, despite surgical indication.[67] Reasons for lack of surgery included poor prognosis regardless of treatment (34%), hemodynamic instability (20%), death before surgery (23%), and severe complications such as stroke (23%) and sepsis (21%).[67] The subjective preoperative risk stratification of these patients also strongly influences clinical decisions. Reliable risk score models for IE are therefore essential to guide the decision-making process. These endocarditis-specific risk scores have shown better prognostic performance than classical surgical risk scores in real-life situations.[68]

Table 3. Indications for surgery in current clinical practice guidelines.

	AHA Guidelines 2015	Class, LOE	ESC Guidelines 2015	Class, LOE	Timing
Heart failure	Early surgery* is indicated in patients with IE who present with valve dysfunction resulting in symptoms or signs of HF	I, B	Aortic or mitral NVE, or PVE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary edema or cardiogenic shock	I, B	Emergency
	Early surgery* is indicated in patients with PVE with symptoms or signs of HF resulting from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction	I, B	Aortic or mitral NVE, or PVE with severe regurgitation or obstruction causing symptoms of HF, or echocardiographic signs of poor hemodynamic tolerance	I, B	Urgent
Uncontrolled infection	Early surgery* is indicated in patients when IE is complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	I, B	Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	I, B	Urgent
	Early surgery* is reasonable for patients with relapsing PVE	IIa, C			
	Early surgery* should be considered, particularly in patients with IE caused by fungi or highly resistant organisms (e.g., VRE, multidrug-resistant gram-negative bacilli)	I, B	Infection caused by fungi or multiresistant organisms	I, C	Urgent/elective
	Early surgery* is indicated for evidence of persistent infection (manifested by persistent bacteremia or fever lasting >5–7 d, and provided that other sites of infection and fever have been excluded) after the start of appropriate antimicrobial therapy	I, B	Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	IIa, B	Urgent
			PVE caused by staphylococci or non-HACEK gram-negative bacteria	IIa, C	Urgent/elective

Prevention of embolism	Early surgery* is reasonable in patients who present with recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy	IIa, B	Aortic or mitral NVE, or PVE with persistent vegetations >10 mm after ≥1 embolic episode despite appropriate antibiotic therapy	I, B	Urgent
	Early surgery* is reasonable in patients with severe valve regurgitation and mobile vegetations >10 mm	IIa, B	Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	IIa, B	Urgent
	Early surgery* may be considered in patients with mobile vegetations >10 mm, particularly when involving the anterior leaflet of the mitral valve and associated with other relative indications for surgery	IIb, C	Aortic or mitral NVE, or PVE with isolated very large vegetations (>30 mm)	IIa, B	Urgent
			Aortic or mitral NVE, or PVE with isolated large vegetations (>15 mm) and no other indication for surgery	IIb, C	Urgent

*Defined as "during initial hospitalization and before completion of a full course of antibiotics." †Defined as: emergency surgery = performed within 24 h; urgent surgery = within a few days; elective surgery = after at least 1 to 2 weeks of antibiotic therapy. HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; HF = heart failure; NVE = native valve infective endocarditis; PVE = prosthetic valve infective endocarditis; VRE = vancomycin-resistant Enterococcus.
Adapted from Cahill et al.[34] with permission.

1.6 Prosthetic valve endocarditis

PVE is the most severe subtype of IE. Previous studies have reported an incidence of 0.3-1.2% per patient-year.[29,61] PVE accounted for more than 20% of all endocarditis cases, and its prevalence has increased in recent years.[29] Patients with prosthetic heart valves are at high risk of infection, and the cumulative risk of IE has been estimated to be 2.8% and 4.5% at 5 and 10 years, respectively.[69] Compared to the general population, patients undergoing prosthetic valve replacement have a 70-fold increase in risk of IE at 5 years.[18]

Diagnosis of PVE is particularly challenging. In general, PVE exhibits a lower incidence of vegetations (particularly in mechanical prostheses) and a greater incidence of paravalvular complications, compared to native valve IE. Consequently, the sensitivity and specificity of some imaging techniques for identifying IE may be lower in the setting of PVE.[31] These difficulties often lead to delayed diagnosis and treatment, which is strongly associated with worse clinical outcomes.[70–72]

PVE is classified as two forms, according to the time of disease: early and late PVE. Although late PVE is widely accepted as an IE episode occurring >1 year after surgery, the definition of early IE varies between studies. Current clinical practice guidelines propose early and late PVE as disease occurring within 1 year and >1 year after surgery, respectively.[31,38] The relevance of this classification relies on the distinct pathogenic mechanisms and microorganism spectrum associated with each form. While late PVE shows a microbiological profile comparable to that of IE in native valves, early PVE is commonly due to health care-associated microorganisms.[73]

In general, PVE is associated with poorer outcomes than native valve IE. In-hospital and long-term mortality are significantly higher in this population, due to the high prevalence of underlying comorbidities, staphylococcal infections, and complicated presentations.[29,65]

2. CALCIFIC AORTIC STENOSIS

2.1 Epidemiology of valvular heart disease

Valvular heart disease (VHD) is a term that encompasses a broad spectrum of disorders that lead to valve dysfunction. VHD is a major cause of morbidity and mortality, and represents a growing health and economic concern in high-income countries as aging populations and life expectancy increase. The epidemiology of VHD has shifted substantially over the past several decades, and varies significantly with geographical regions and epidemiological determinants. Overall, there are two distinct patterns of VHD: 1) valvular involvement caused by rheumatic fever, and 2) non-rheumatic heart valve disease, which includes degenerative and functional VHD. Rheumatic valvular disease is the sequelae of sustained valvular damage resulting from acute rheumatic fever, a disease caused by abnormal host immune response to a group A beta-hemolytic streptococcal infection.[74,75] Rheumatic valvular disease remains the most common manifestation of VHD in middle- and low-income countries, typically affecting young patients. By contrast, the improvement of health systems in high-income countries, with greater access to medical resources, has dramatically reduced the prevalence of this disease etiology. Consequently, non-rheumatic valvular disorders are currently the most prevalent type of VHD in high-income countries, and are increasing in incidence due to the aging population and enhanced screening programs available in these countries.[22]

Worldwide, however, rheumatic valvular disease remains by far the most common form of VHD. According to The Global Burden of Disease study,[76] which collects data from 195 countries, the crude prevalence of rheumatic and non-rheumatic valvular heart disease was estimated to be 39.3 and 29.7 million cases, respectively. Non-rheumatic valvular heart disease caused 144,900 all-age deaths in 2017, representing 0.3% of global deaths. Notably, the mortality related to non-rheumatic valvular heart disease has increased by 31.8% over the past ten years.[23,77]

2.2 Calcific aortic valve disease

Calcific aortic valve disease encompasses a wide variety of clinical presentations, ranging from calcification and thickening of the aortic valve (aortic sclerosis) with minimal clinical relevance, to hemodynamically severe aortic stenosis (AS), which has major prognostic implications. Calcific AS is the most frequent primary VHD requiring

surgery or transcatheter aortic valve replacement in high-income countries.[78,79] Calcific aortic valve disease is commonly associated with an elderly population and a normal trileaflet aortic valve. Its prevalence increases exponentially with age, occurring in 1-2% of adults aged 65 years, and rising to >10% in individuals older than 75 years.[22,80,81]

The prevalence of calcific aortic valve disease has increased progressively in recent decades, particularly in high-income countries. This could be due to the growing prevalence of atherosclerosis risk factors, which is also associated with this pathology, as well as with improved screening programs. The age-standardized prevalence of non-rheumatic calcific aortic valve disease has increased by 155% over the past three decades, from 45.5 cases per 100,000 people in 1990 to 116.3 cases per 100,000 people in 2019.[22] According to recent data, the age-standardized mortality rate is estimated to be 1.76 per 100,000 persons, and 130,000 deaths worldwide were attributable to calcific aortic valve disease in 2019.[79] Notably, the number of patients with AS is expected to increase in the near future, with some studies projecting an increase in prevalence of 2.4-fold by 2040, and of 3-fold by 2060.[82] This will pose a challenge to both health and economic sectors, particularly in high-income countries.

2.3 Pathophysiology of calcific aortic stenosis

Calcific aortic valve disease results from progressive thickening, fibrosis, calcification, and narrowing of the aortic valve leaflets, and the adaptative changes that occur in the left ventricle (LV) to overcome the resulting abnormal increase in afterload. Traditionally, calcific AS has been considered a passive degenerative condition related to aging. However, recent data suggest that this entity is an active process involving highly complex interactions between inflammatory, humoral, metabolic, and genetic components. When present, clinical manifestations in patients with AS are due to both valvular and myocardial impairment.[83]

Two phases may be distinguished in the pathophysiology of AS: (1) an early initiation phase that shares multiple common mechanisms with atherosclerosis, in which endothelial damage, tissue inflammation, and lipid deposition are the most relevant

elements, and (2) a later propagation phase dominated by procalcific and osteogenic mechanisms.[83,84]

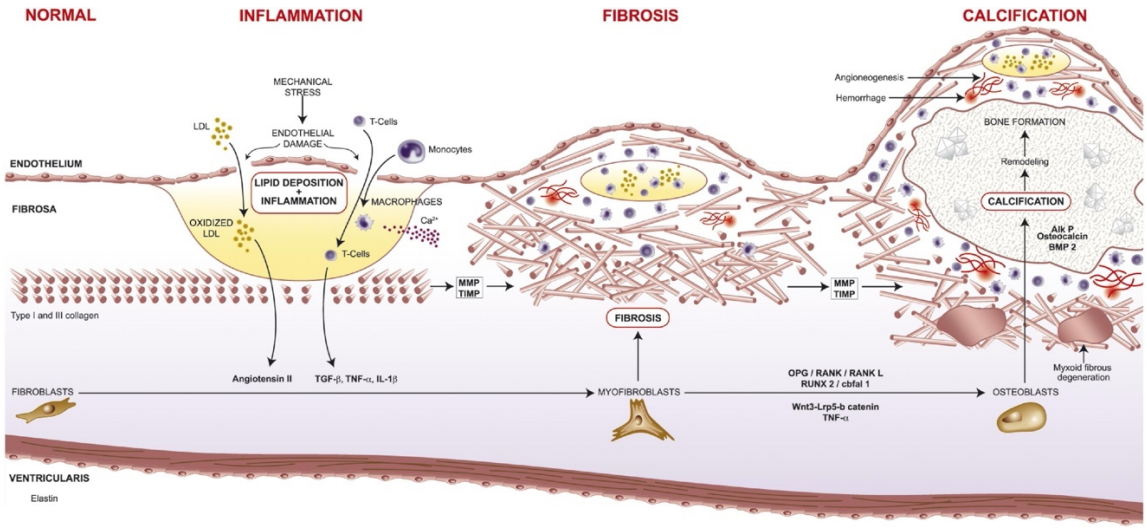

Figure 5: Summary of the pathophysiology of calcific aortic stenosis.
From Dweck et al[83].

The early stages of AS and the onset of atherosclerosis have many pathological features in common. In the initiation phase, endothelial damage resulting from increased mechanical stress and reduced shear stress is considered to be the initiating injury that triggers the entire process. This damage facilitates valvular infiltration by oxidized lipids, T-lymphocytes, mast cells, and macrophages. These inflammatory cells promote the release of proinflammatory mediators, such as cytokines and angiotensin II, and the subsequent activation of fibroblasts into myofibroblast. Consequently, enhanced collagen production and activation of matrix metalloproteinases facilitate extracellular matrix remodeling and valvular fibrosis. Matrix vesicle secretion from macrophages triggers valvular calcification, and this process is promoted by valvular interstitial cells that facilitate differentiation into an osteoblast-like phenotype. Many osteogenic factors, including WNT/b-catenin, RANKL/RANK signaling, and CBFA/RUNX2 are involved in this process. Further calcification is regulated by osteoblast-like cells, and involves many signaling proteins in a pathway comparable to that of skeletal bone formation. In addition, angiogenesis and valvular hemorrhage contribute to accelerated AS progression. The propagation phase is a tightly controlled disease process influenced by osteoblast-

like cells and their osteogenic phenotype. This phase is essentially characterized by continuous calcification and remodeling. Finally, in the end-stage of calcific valvular disease, lamellar bone, microfractures, and hemopoietic tissue can all be identified within the valve (**Figure 5)**.[83–87]

2.4 Risk factors

Available evidence suggests a close relationship between calcific AS and classical and emerging risk factors, such as mineral metabolism, inflammation, and vascular stiffness. Older age, male sex, hypertension, smoking, diabetes, raised cholesterol levels, lipoprotein(a), metabolic syndrome, and chronic kidney disease have all been associated with an increased risk of calcific AS. Additionally, two recently published large-scale cohort studies demonstrated a strong association between obesity and AS.[88,89]

The pathway shared by AS and atherosclerosis, particularly in the early stages of the disease, has encouraged many researchers to investigate whether lipid-lowering therapies may play an essential role in treating this pathology. This hypothesis was supported by promising preliminary results in animal models and nonrandomized studies in humans; however, three independent randomized controlled trials failed to demonstrate that statins were associated with AS regression or delay progression.[90–92]

2.5 Natural history, stages, and clinical manifestations of aortic stenosis

AS is an active condition with a slow progression. In most patients, a prolonged asymptomatic period precedes the development of symptoms.[93] The imbalance between an increased LV afterload and the ability of the LV to overcome this (at rest and during exercise) prompts the onset of symptoms. Although LV hypertrophy may compensate for the increased afterload to maintain LV performance, these adaptive changes usually result in deleterious effects.[94,95]

Clinical manifestations rarely occur in AS patients with normal ventricular systolic function until the AS becomes severe. However, the onset of symptoms varies

significantly between patients.[96] While some develop symptoms when AS is less severe, others remain asymptomatic until critical valvular obstruction is established. Notably, symptom onset represents a turning point in the natural history of AS, and a poor prognosis for survival.[97,98] Even mild symptoms (such as abnormal exertional dyspnea or exercise intolerance) foreshadow a significant change in disease course, with a high risk of heart failure, arrhythmia, and sudden death.[99] Most patients experience symptoms prior to development of LV dysfunction. Nonetheless, in some cases, the sustained increase in LV afterload leads to a progressive impairment of LV function, resulting in decreased stroke volume and cardiac output. Such patients develop predominantly clinical manifestations of heart failure.

Traditionally, AS has been classified as mild, moderate, or severe based on isolated valve hemodynamic parameters. However, this classification has several limitations, as does not reflect the broad spectrum of clinical scenarios. The American College/American Heart Association (ACC/AHA) Guidelines for the Management of Patients with Valvular Heart Disease has therefore proposed a new classification system for AS progression according to valve anatomy, valve hemodynamics, LV function, and the presence of symptoms (**Figure 6 and Table 4**). In brief, stage A refers to patients who have risk factors for developing AS, stage B to asymptomatic patients who have progressive mild to moderate AS, stage C to asymptomatic patients who meet criteria for severe AS and have normal ventricular function (C1) or signs of ventricular dysfunction (C2), and finally stage D, which refers to patients with symptomatic aortic stenosis.[100]

Table 4. Stages of aortic stenosis.

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of AS	BAV (or other congenital valve anomaly) Aortic valve sclerosis	Aortic V_{max} <2 m/s with normal leaflet motion	None	None
B	Progressive AS	Mild to moderate leaflet calcification/fibrosis of a bicuspid or trileaflet valve with some reduction in systolic motion or Rheumatic valve changes with commissural fusion	Mild AS: aortic V_{max} 2.0–2.9 m/s or mean ΔP <20 mm Hg Moderate AS: aortic V_{max} 3.0–3.9 m/s or mean ΔP 20–39 mm Hg	Early LV diastolic dysfunction may be present Normal LVEF	None
C: Asymptomatic severe AS					
C1	Asymptomatic severe AS	Severe leaflet calcification/ fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA typically is ≤1.0 cm^2 (or AVAi 0.6 cm^2/m^2) but not required to define severe AS Very severe AS is an aortic V_{max} ≥5 m/s or mean P ≥60 mm Hg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None Exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV systolic dysfunction	Severe leaflet calcification/ fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA typically ≤1.0 cm^2 (or AVAi 0.6 cm^2/m^2) but not required to define severe AS	LVEF <50%	None

D: Symptomatic severe AS					
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification/ fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA typically ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2) but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present	Exertional dyspnea, decreased exercise tolerance, or HF Exertional angina Exertional syncope or presyncope
D2	Symptomatic severe low-flow, low-gradient AS with reduced LVEF	Severe leaflet calcification/ fibrosis with severely reduced leaflet motion	AVA ≤1.0 cm^2 with resting aortic V_{max} <4 m/s or mean ΔP <40 mm Hg Dobutamine stress echocardiography shows AVA <1.0 cm^2 with V_{max} ≥4 m/s at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF <50%	HF Angina Syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification/ fibrosis with severely reduced leaflet motion	AVA ≤1.0 cm^2 (indexed AVA ≤0.6 cm^2/m^2) with an aortic V_{max} <4 m/s or mean ΔP <40 mm Hg AND Stroke volume index <35 mL/m^2 Measured when patient is normotensive (systolic blood pressure <140 mm Hg)	Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling LVEF ≥50%	HF Angina Syncope or presyncope

AR indicates aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area circulation; AVAi, AVA indexed to body surface area; BAV, bicuspid aortic valve; ΔP, pressure gradient between the LV and aorta HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; and Vmax, maximum velocity.
Adapted from Otto et al.[100] with permission.

Despite several improvements in therapies for severe AS using invasive approaches, no medical therapy has yet been shown to delay the natural progression of the disease or improve clinical outcomes. As such, when symptoms emerge, severe calcific AS is associated with a poor prognosis, with a 5-year mortality rate of 94% if AS remains untreated.[101]

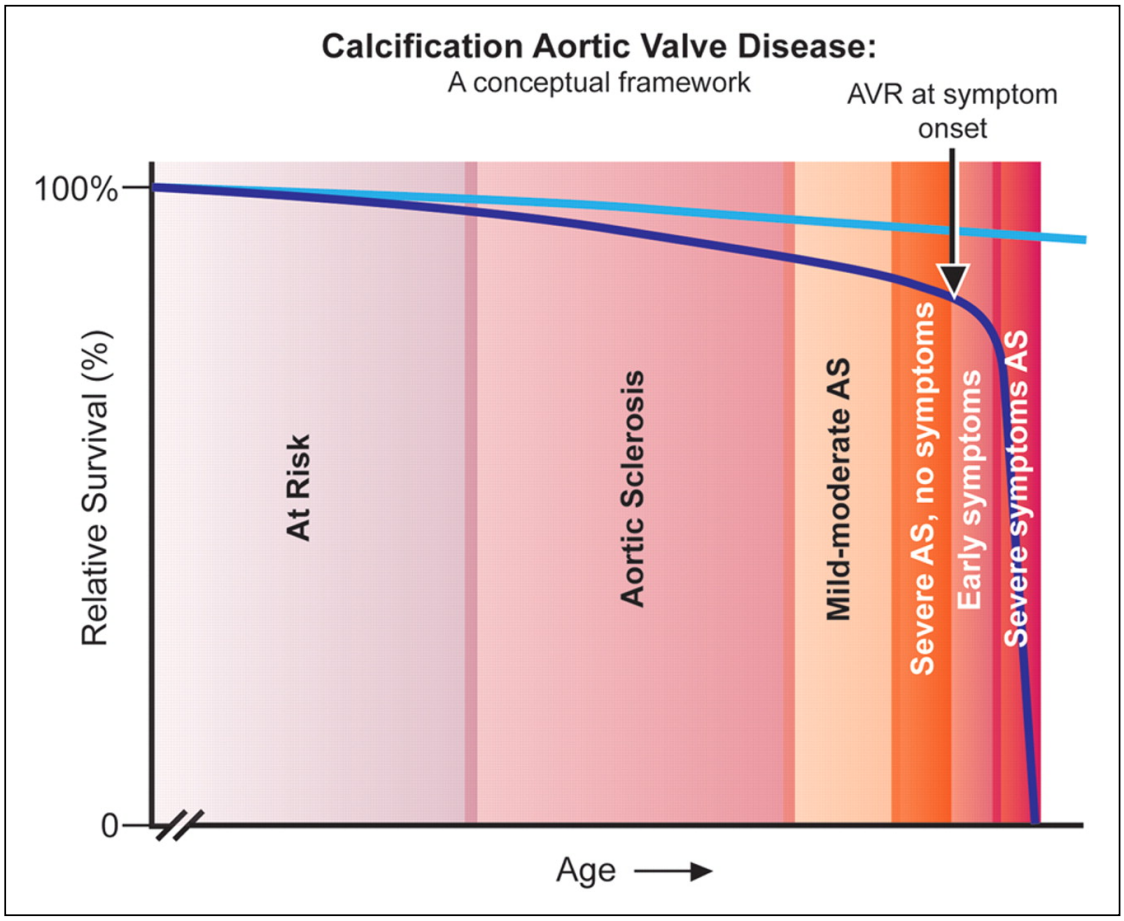

Figure 6. Natural history of aortic valve stenosis
From Otto et al.[98] with permission.

2.6 Evaluation of aortic stenosis

2.6.1 Imaging diagnosis

A comprehensive medical history and physical examination combined with imaging assessment are essential for AS diagnosis. Imaging is the cornerstone for diagnosis and characterization of calcific aortic valve disease. Echocardiography is usually the first-line technique for evaluating AS, and provides crucial information on

etiology, severity, LV function, pulmonary pressure, and the presence of concomitant VHD. TTE is indicated for initial assessment and reevaluation when new symptoms appear. Clinical practice guidelines recommend careful evaluation of transvalvular gradients, peak transvalvular velocity, and valvular area. From these measurements, four categories of AS can be defined:[100,102]

1. High-gradient AS: mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, and valve area ≤1 cm^2 (or ≤0.6 cm^2/m^2). Severe AS can be established regardless of flow conditions and LV function.

2. Low-flow, low-gradient AS with reduced LV ejection fraction (LVEF): mean gradient <40 mmHg, valve area ≤1 cm^2, LVEF<50%, SVi ≤35 mL/m^2. In this scenario, stress echocardiography is recommended to differentiate true severe AS from pseudo-severe AS, and to identify those patients with no contractile reserve.

3. Low-flow, low-gradient AS with preserved LVEF: mean gradient <40 mmHg, valve area ≤1 cm^2, LVEF ≥50%, SVi ≤35 mL/m^2. Diagnosis of severe AS is complex and often requires a meticulous exclusion of other conditions associated with low stroke volume (severe mitral regurgitation or stenosis, severe tricuspid regurgitation, and severe right ventricle dysfunction), as well as the exclusion of measurement errors.

4. Normal-flow, low-gradient AS with preserved LVEF: mean gradient <40 mmHg, valve area ≤1 cm^2, LVEF ≥50%, SVi >35 mL/m^2. This subgroup of patients frequently presents with only moderate AS.

CT is helpful for quantifying aortic valve calcium to determine severity, particularly in patients presenting with low gradients or inconclusive echocardiography findings. CT also provides valuable information on the aortic valve and aortic root anatomy, as well as the degree of valvular and vascular calcification. Evidence-based guidelines propose sex-specific Agaston unit cutoff values for diagnosing severe AS, with more than 1300 AU for women and more than 2000 for men.[100,103] Additionally, a large-scale multicenter

study has shown that severe aortic valve calcification assessed by CT is an independent predictor for mortality in patients with AS.[104] CT may therefore play an increasing role in patient risk-stratification.

Cardiac magnetic resonance (CMR) is a growing imaging modality in the evaluation of patients with AS. CMR provides details of aortic anatomy, LV morphology and function, as well as useful information on extracellular myocardial volume and fibrosis. Late gadolinium enhancement and increased extracellular myocardial volume have been strongly associated with mortality in patients with severe AS.[105–107] Despite this, CMR has not yet been integrated into routine AS assessment in most centers.

2.6.2 Biomarkers

The diagnostic and prognostic value of biomarkers in the setting of AS has generated much interest in recent years. Brain natriuretic peptide (BNP) and its prohormone, the N-terminal pro-brain natriuretic peptide (NT-proBNP) are the best-studied biomarkers, and are released in response to increased LV afterload and myocardial wall stress. Both the ACC/AHA and ESC/EACTS guidelines on VHD management state that early intervention may be considered in patients with asymptomatic AS and significantly elevated BNP levels, if the surgical risk is low.[100,102] In addition, some studies have suggested that natriuretic peptides may predict symptom-free survival and outcomes in patients with normal and low-flow AS.[108,109] Despite encouraging early results, the definitive role of biomarkers is not yet well-established in the decision-making process for AS patients.

2.6.3 Stress testing

Stress tests, using exercise or pharmacologic methods, are useful for therapeutical decision-making when clinical history and resting hemodynamic findings are inconclusive. The classical indication for stress tests is to determine whether a patient with severe AS is truly asymptomatic.[110] Stress tests also yield relevant prognostic information by identifying patients at high risk of adverse clinical events.[111]

2.7 Management

2.7.1 Medical therapy

Despite remarkable progress in understanding the pathophysiology of AS, no medical therapy has been shown to significantly alter disease progression, or to improve clinical outcomes. Thus, clinical practice guidelines only recommend pharmacological therapies to treat concomitant conditions such as hypertension, coronary artery disease, dyslipidemia, or heart failure. Nevertheless, multiple therapeutic targets remain unexplored, and further randomized trials with potential disease-modifying therapies are warranted.

2.7.2 Aortic valve replacement

Severe symptomatic AS is associated with a poor prognosis if left untreated, with >80% mortality at 5 years.[112] Early aortic valve replacement (AVR) is therefore strongly recommended for all patients. Exceptions include patients for whom any intervention is unlikely to improve quality of life or survival due to severe comorbidities, or patients with a survival life expectancy <1 year. Current evidence recommends AVR for treating symptomatic high gradient AS, regardless of LVEF **(Table 5)**. Nevertheless, both the optimal management of patients with low-gradient AS and the role of AVR in asymptomatic patients remain controversial.

Surgical aortic valve replacement (SAVR) has been considered the standard of care for patients with symptomatic AS for many years. During SAVR, native aortic valve leaflets are removed and replaced with either a mechanical or bioprosthetic aortic valve prosthesis in open-heart surgery. There is strong evidence supporting the benefits of AVR for symptom relief, improvement of LV systolic function, and survival.[113–116]

Generally, the type of prosthetic aortic valves used for replacement is either mechanical or biological. Several factors determine the selection of one over the other, including clinical and anatomical features, hemodynamic factors, and patient preferences. The main advantage of mechanical valves is their durability, as they are unlikely to

required reinterventions. By contrast, this type of prosthesis requires long-term anticoagulation therapy with vitamin K antagonists.

Table 5: Indications for AVR in patients with AS.

	ACC/AHA[100]		ESC/EACTS[102]	
Symptomatic severe high gradient AS	**I**	**A**	**I**	**B**
Severe AS with symptoms on exercise testing	**I**	**A**	**I**	**C**
Asymptomatic severe AS (LVEF < 50%)	**I**	**B**	**I**	**B**
Severe AS undergoing cardiac surgery for other indications	**I**	**B**	**I**	**C**
Asymptomatic very severe AS[a] and low surgical risk	**IIa**	**B**	**IIa**	**B**
Asymptomatic severe AS with abnormal exercise test	**IIa**	**B**	**IIa**	**C**
Symptomatic low-flow, low-gradient severe AS (LVEF < 50%)	**I**	**B**	**I**	**B**
Symptomatic low-flow, low-gradient severe AS (LVEF < 50%) without flow (contractile) reserve			**IIa**	**C**
Symptomatic low-flow, low-gradient severe AS (LVEF ≥ 50%) if AS is the most likely cause of symptoms.	**I**	**B**		
Moderate AS undergoing cardiac surgery	**IIb**	**C**	**IIa**	**C**
Asymptomatic severe AS with rapid progression and low surgical risk[c]	**IIa**	**B**	**IIa**	**B**
Asymptomatic severe AS with markedly elevated BNP levels	**IIa**	**B**	**IIa**	**B**

In patients with AS, the 2021 ESC/EACTS guidelines for the management of VHD advocate SAVR (over other interventions) in the presence of lower surgical risk, younger age, active or suspected IE, bicuspid aortic valve, low coronary ostia, heavy leaflet/LVOT calcification, thrombus occurring in the LV or aorta, significant multivessel coronary artery disease requiring surgical revascularization, concomitant severe mitral or tricuspid disease, significant dilatation/aneurysm of the aortic root and/or ascending aorta, or septal hypertrophy requiring myectomy.[102]

Although this surgery has good results, approximately one-third of patients with an indication for SAVR are deemed unsuitable candidates due to their high surgical risk.[117]

2.8 Transcatheter aortic valve replacement

2.8.1 Evidence on transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR), also called transcatheter aortic valve implantation (TAVI), has revolutionized the treatment of patients with symptomatic AS over the past two decades. At present, TAVR is considered a safe, effective, and less-invasive alternative to SAVR in patients with AS. Since the first-in-human TAVR performed in 2002,[118] more than 400,000 TAVR have been performed worldwide, and the number of these procedures is expected to increase by 4 to 10-fold in the next decade.[119] As such, TAVR has become the dominant form of AVR in the United States.[120]

The first TAVR prosthesis was approved in Europe (2007) and the United States (2011) for patients with symptomatic severe AS deemed inoperable. Since then, the safety and efficacy of this procedure have been confirmed across the entire spectrum of surgical risk by multiple randomized clinical trials. Consequently, new indications and approvals of TAVR have expanded to include patients at high-risk (2012), intermediate-risk (2016), and low-risk (2019) for SAVR **(Figure 7 and Table 6)**.[121]

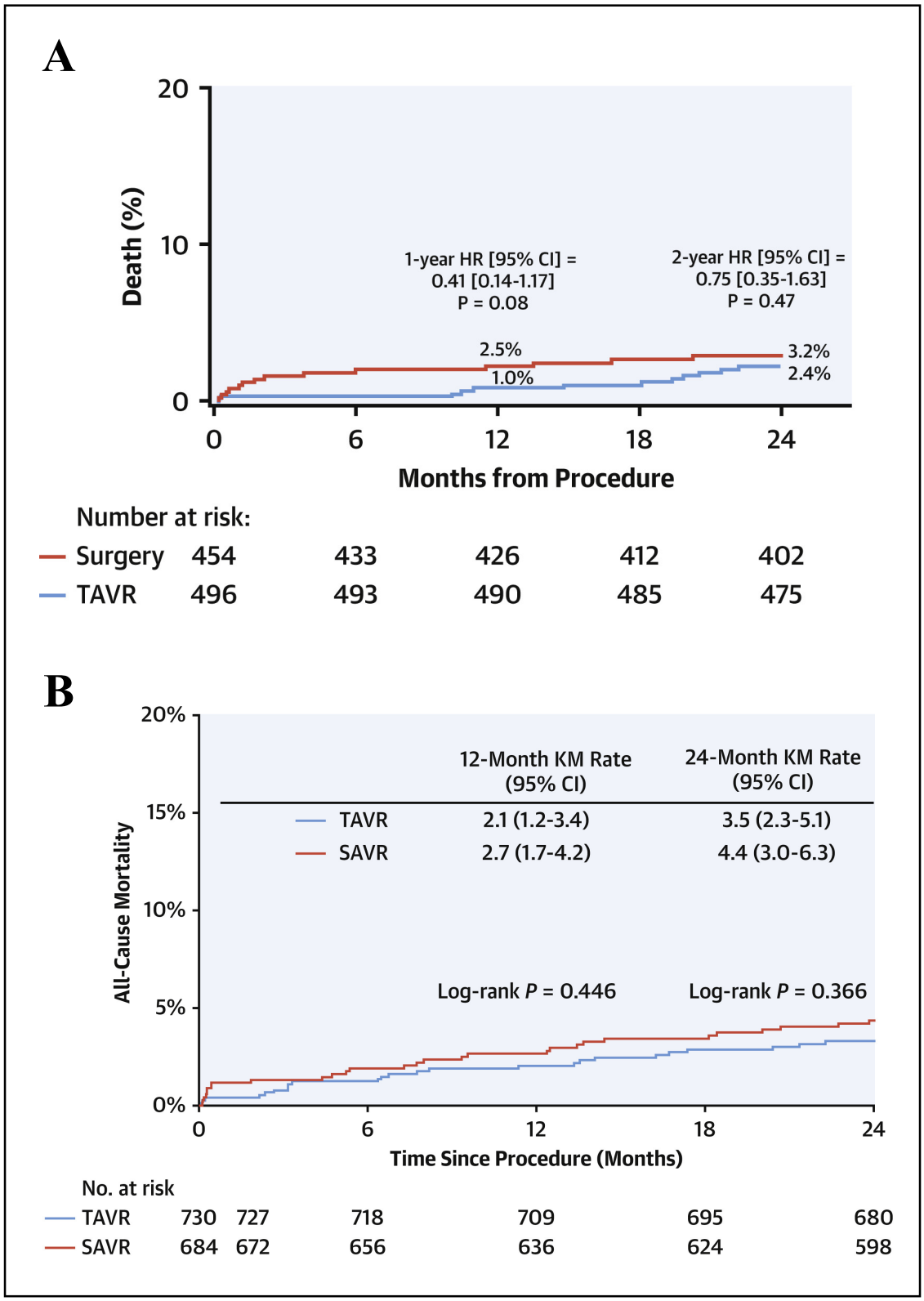

Figure 7. 2-year mortality after transcatheter and surgical aortic valve replacement in low-risk patients.

A) BEV: SAPIEN 3 and B) SEV: CoreValve, Evolut R, or Evolut PRO valve; Medtronic. From Leon et al.[122] and Forrest et al.[123] with permission.

Table 6. Main randomized clinical trials on transcatheter aortic valve replacement.

Trial	Publication Year	No. of Patients	Risk (STS Score %)	Valve type and Comparator	Primary Endpoint	Result
PARTNER[124]	2011	699	High (11.8)	SAPIEN vs. SAVR	All-cause mortality at 1 year	TAVR non-inferior to SAVR
CoreValve[125]	2014	747	High (7.4)	CoreValve vs. SAVR	All-cause mortality at 1 year.	TAVR superior to SAVR
PARTNER 2[126]	2016	2032	Intermediate (5.8)	SAPIEN XT vs. SAVR	All-cause mortality or disabling stroke at 2 years.	TAVR non-inferior to SAVR
SURTAVI[127]	2017	1660	Intermediate (4.5)	CoreValve (84%)/Evolut R (16%) vs. SAVR	Death or disabling stroke at 2 years.	TAVR non-inferior to SAVR
PARTNER 3[128]	2019	1000	Low (1.9)	SAPIEN 3 vs. SAVR	All-cause mortality, stroke, rehospitalization at 1 year.	TAVR superior to SAVR
Evolut Low Risk[129]	2019	1468	Low (1.9)	CoreValve/Evolut R/Evolut PRO vs. SAVR	All-cause mortality or disabling stroke at 2 years.	TAVR non-inferior to SAVR
NOTION[130]	2015	280	Low (3.0)	CoreValve vs. SAVR	All-cause mortality, stroke, or myocardial infarction at 1 year.	TAVR equivalent to SAVR
REPRISE III[131]	2018	912	6.8%	Lotus vs. CoreValve/Evolut R	All-cause mortality, disabling stroke, moderate-to-severe PVL at 1 year.	Lotus non-inferior to CoreValve
SCOPE 1[132]	2019	739	3.5%	Acurate neo vs. SAPIEN 3	Composite endpoint	SAPIEN 3 superior to Acurate neo
SCOPE 2[133]	2020	796	4.6%	Acurate neo vs. CoreValve Evolut	All-cause mortality or stroke at 1-year.	CoreValve superior to Acurate neo
CHOICE[134]	2014	121	High risk (5.8%)	SAPIEN XT vs. CoreValve	Device success.	Sapien XT superior to CoreValve
SOLVE-TAVI[135]	2020	447	High to intermediate (4.7%)	Evolut R vs. SAPIEN 3	All-cause mortality, stroke, moderate/severe PVL, and PPI at 30 days.	SEV equivalent to BEV

Compared to patients undergoing SAVR, TAVR is associated with a higher rate of major vascular complications, moderate or severe paravalvular regurgitation, and permanent pacemaker implantation **(Figure 8)**. According to data from the STS-ACC TVT Registry, the 30-day mortality rate and stroke incidence have decreased over the years, though the rate of permanent pacemaker requirement has remained stable.[120]

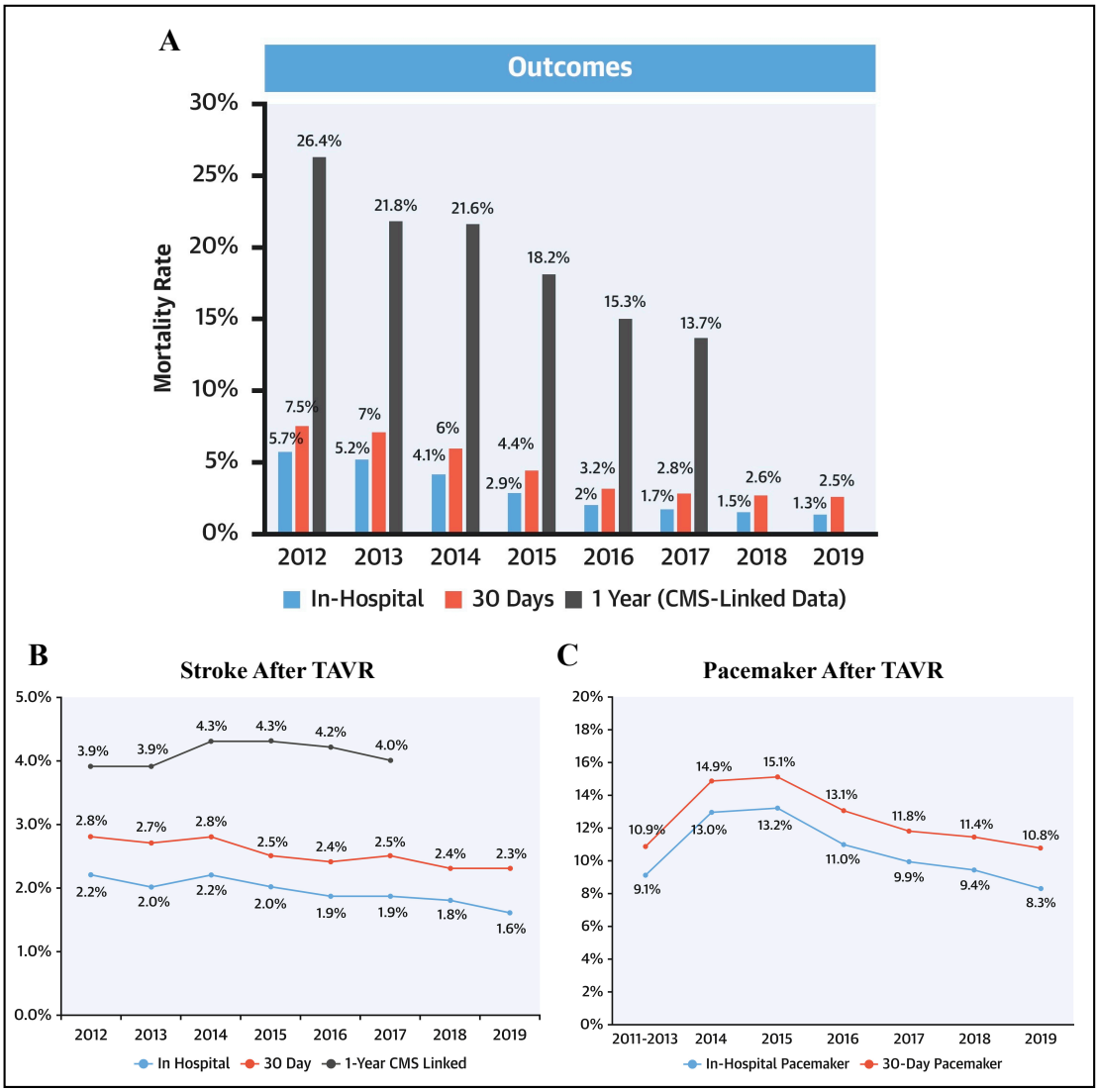

Figure 8. Temporal trends of outcomes after transcatheter aortic valve replacement
A) In-hospital, 30-day and 1-year mortality after TAVR. Temporal trends of stroke (A) and pacemaker (B) after TAVR.
From Carrol et al.[120] with permission.

2.8.2 Peripheral vascular accesses

As a minimally invasive procedure, TAVR requires vascular access for prosthesis implantation. Transfemoral access is the most commonly used approach, as it allows for a fully percutaneous intervention and is associated with a relatively low complication rates.[136] However, despite major iterations on delivery systems profile, 10-20% of TAVR patients remain unsuitable for the transfemoral approach due to severe peripheral artery disease or small iliofemoral arteries.[120,137] Multiple vascular accesses has therefore been described as alternative routes for TAVR, including transcarotid, transaortic, transcaval, transapical, and trans-subclavian.

Vascular access has evolved substantially over the past decade. The transfemoral approach has increased steadily in popularity, and is currently used in >95% of TAVR procedures.[120] The type of alternative vascular access has also changed over time; while transapical and direct aortic approaches were initially preferred, the axillary-subclavian approach is currently the most common nontransfemoral access used in the United States.[120] Nonetheless, some studies suggest that nontransfemoral vascular access is associated with a higher rate of complications than the transfemoral approach.[138] Consequently, available clinical guidelines recommend the transfemoral route as gold standard,[100,102] and even ACC/AHA guidelines advocate considering SAVR or palliative care when transfemoral TAVR is not feasible.[100]

2.8.3 Transcatheter aortic heart valves

TAVR is a minimally invasive procedure that uses a delivery system to implant a bioprosthesis at the level of the dysfunctional aortic valve. There are many THV systems available worldwide. According to the type of deployment, the most frequently used and commercially available TAVR devices are classified as balloon-expandable (BEV), self-expandable (SEV), and mechanically expandable (MEV) valves **(Figure 9)**.

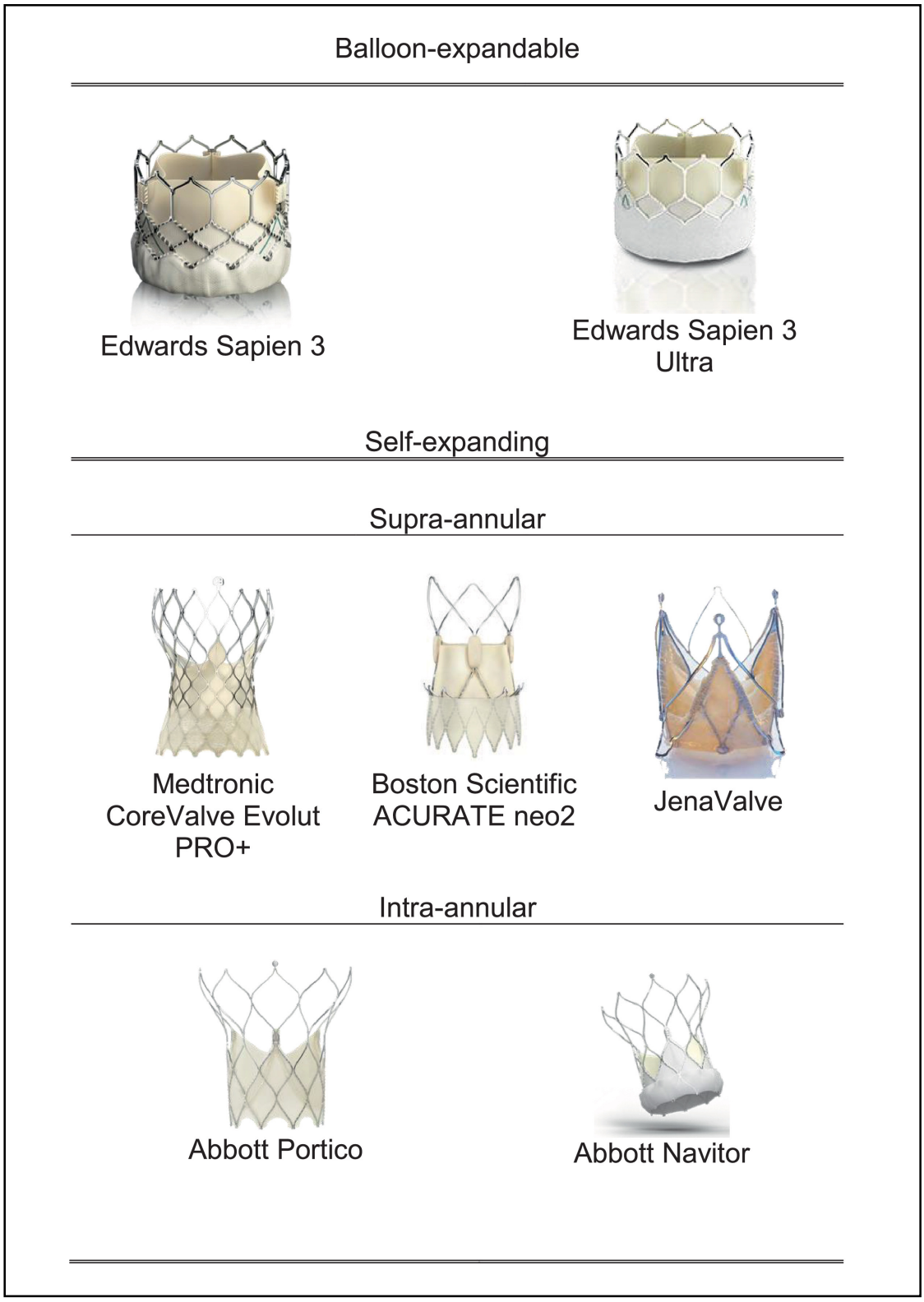

Figure 9. Latest-generation transcatheter aortic valve systems.

From Tugaoen et al.[139] with permission.

The SAPIEN™ family (Edwards Lifesciences, Irvine, CA, USA) is the device with the strongest clinical evidence among BEVs. This device contains a trileaflet bovine pericardial tissue valve sutured to a radiopaque cobalt-chromium alloy frame. An external polyethylene terephthalate fabric seal was later added to the bottom of the stent frame to improve paravalvular sealing. The SAPIEN 3 Ultra valve represents the latest generation of the SAPIEN THV family. The device is currently available in 20 mm, 23 mm, 26 mm, and 29 mm sizes, covering an annulus range from 16-28 mm. This type of valve can be implanted using the transfemoral, trans-subclavian, transapical, transaortic, and transcaval approaches.[136] The device is delivered via the transfemoral approach using the Commander Delivery System (Edwards Lifesciences, Irvine, CA), which provides an ergonomic design that enables a single-operator approach and a stable platform, allowing for controlled coaxial alignment and accurate positioning of the THV within the native valve. The system is compatible with 14F expandable introducer sheaths, and is appropriate for smaller peripheral anatomies (minimum vessel diameter 5 mm). Contemporary data on this device show a 30-day mortality rate of <5%. Roughly 85% of procedures are performed using the transfemoral approach, and the rates of paravalvular regurgitation, major vascular complications, and stroke are <7%, <6%, and <4%, respectively.[136] The rate of permanent pacemaker implantation with devices varies from 4 to 13%.[136]

Of the SEVs, the Medtronic CoreValve™/Evolut™ family (Medtronic, Inc., Minneapolis, MN, USA) is the most widely used device. This valve consists of three porcine pericardium leaflets sutured in a supra-annular position and attached to a compressible, self-expanding nitinol frame. The modified nitinol design at the annulus, which optimizes expansive radial force, and a longer porcine pericardial skirt are designed to enhance paravalvular sealing properties. The Evolut PRO+ system represents the latest generation of self-expanding valves in the Medtronic CoreValve™/Evolut™ family, and incorporates some attractive technical advantages. Currently, four sizes are commercially available: 23 mm, 26 mm, 29 mm, and 34 mm (for an aortic annulus diameter between 18-30 mm). The Delivery Catheter with InLine sheath provides a low profile with a 14F equivalent outer diameter. This low-profile system requires a minimum femoral artery diameter of ≥ 5 mm. The platform is designed to enable partial recapturability (just prior to final valve deployment) and repositionability. Although the Medtronic

CoreValve™/Evolut™ is typically delivered transfemorally, transsubclavian, transaortic, and trans-carotid approaches have been described as alternatives.[140–142] Real-world experience with this device shows a 30-day mortality rate of <5%. Up to 90% of the procedures are performed using the transfemoral approach, and the rates of paravalvular regurgitation, major vascular complications, and stroke are ~5%, <2%, and <4%, respectively.[136,143] Compared to BEVs, multiple studies have found the rate of permanent pacemaker implantation to be consistently higher.[136]

Other transcatheter aortic valve systems are currently available commercially. The characteristics of the main TAVR devices are summarized in **Table 7**.

Table 7. Characteristics of main latest-generation transcatheter aortic valve devices.

Prosthesis	Company	Release	Valve Size (mm)	Stent Frame	Delivery System Diameter	Leaflets Tissue	Repositionable	Supra or intra-annular
SAPEN 3 Ultra	Edwards Lifesciences	BE	20,23,26,29	Co-Cr	14F	Bovine	No	Intra-annular
CoreValve Evolut PRO+	Medtronic	SE	23, 26, 29, 34	Nitinol	14F/16F	Porcine	Yes	Supra-annular
ACURATE neo2	Boston Scientific	SE	23, 25, 27	Nitinol	14F	Porcine	No	Supra-annular
Portico	Abbott	SE	23, 25, 27, 29	Nitinol	18F/19F	Bovine	Yes	Intra-annular
Navitor	Abbott	SE	23, 25, 27, 29	Nitinol	14F	Bovine	Yes	Intra-annular
Myval	Meril	BE	20, 21.5, 23, 24.5, 26, 27.5, 29,30.5, 32	Ni-Co	14F	Bovine	No	Intra-annular
Hydra	SMT	SE	22, 26, 30	Nitinol	18F	Bovine	No	Supra-annular
JenaValve	JenaValve Technology	SE	23, 25, 27	Nitinol	19F	Porcine	Yes	Supra-annular
J-Valve	JC Medical	SE	22, 25, 28	Nitinol	18F	Bovine	Yes	Intra-annular
Lotus Edge	Boston Scientific	ME	23, 25, 27	Nitinol	15F	Bovine	Yes	Intra-annular
Allegra	Biosensors	SE	23, 27, 31	Nitinol	15F	Bovine	Yes	Supra-annular
Venus-A Valve	Venus Medtech	SE	23, 26, 29, 32	Nitinol	19F	Porcine	Yes	Supra-annular
VitaFlow	MicroPort	SE	21, 24, 27, 30	Nitinol	16F/18F	Bovine	Yes	Supra-annular

2.8.4 Transcatheter aortic valve replacement indications and patient selection

AS is a heterogeneous disease, and clinical decision-making should be individualized considering several factors. Based on robust evidence supported by multiple randomized clinical trials, TAVR is accepted by the ACC/AHA and ESC/EACTS guidelines as a class I indication in elderly patients (≥ 75 years in the ESC/EACTS guidelines and > 80 years in the ACC/AHA guidelines), or in patients at high risk or unsuitable for surgery who present with severe symptomatic AS **(Table 8)**.[100,102]

In recent years, two concepts have gained particular relevance in optimizing the management of patients with severe AS and improving outcomes: the Heart Team and the Heart Valve Clinic.[96,144] The Heart Team plays a fundamental role in decisions concerning the appropriateness of treatment and the choice of intervention. This collaborative and multidisciplinary group is comprised of clinical and interventional cardiologists, imaging specialists, cardiac surgeons, anesthesiologists, and other experts (such as geriatrists and heart failure specialists.) The aim of the Heart Team is to carefully evaluate clinical, anatomical, and procedural factors to determine whether SAVR or TAVR is the best treatment option for the patient.

Clinical decision-making should be individualized based on patient- and procedure-specific factors. Clinical practice guidelines suggest favoring TAVR, when transfemoral vascular access is feasible, in patients with high surgical risk, older age or fewer expected remaining years of life, previous cardiac surgery, severe frailty, sequelae of chest radiation, porcelain aorta, severe chest deformation or scoliosis, a high likelihood of significant patient-prosthesis mismatch, a favorable ratio between life expectancy and valve durability, concomitant conditions (severe pulmonary, liver, or renal disease), in addition to patient preferences.[100,102]

Valve durability represents a major concern in TAVR patients, given its increased use in younger patients with longer life expectancies. To date, reliable evidence on valve durability in low-risk patients is limited to a 2-year follow-up. There is a paucity of studies

directly comparing valve durability between surgical and transcatheter bioprostheses. According to the PARNERT 2A data, third-generation SAPIEN 3 has shown similar rates of structural valve deterioration at 5-year compared with bioprosthetic surgical valves in intermediate-risk patients.[145] However, all-cause bioprosthetic valve failure was higher in TAVR compared to SAVR.[145] These results highlight the importance of considering valve durability in the decision-making process for patients undergoing TAVR.

Table 8. Indications for transcatheter aortic valve replacement in the ACC/AHA and ESC/EACTS guidelines.

ESC	Aortic valve interventions must be performed in Heart Valve Centres that declare their local expertise and outcomes data, have active interventional cardiology and cardiac surgical programs on-site, and a structured collaborative Heart Team approach.	I	C
	The choice between surgical and transcatheter intervention must be based upon careful evaluation of clinical, anatomical, and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient, who can then make an informed treatment choice.	I	C
	TAVI is recommended in older patients (≥75 years), or in those who are high risk (STS-PROM/EuroSCORE II>8%) or unsuitable for surgery.	I	A
	SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical, and procedural characteristics	I	B

	For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability.	I	A
	For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR.	I	A
	In asymptomatic patients with severe AS and an LVEF <50% who are ≤80 years of age and have no anatomic contraindication to transfemoral TAVI, the decision between TAVI and SAVR should follow the same recommendations as for symptomatic patients.	I	B
	For symptomatic patients of any age with severe AS and a high or prohibitive surgical risk, TAVI is recommended if predicted post-TAVI survival is >12 months with an acceptable quality of life.	I	C

3. INFECTIVE ENDOCARDITIS AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT

3.1 Epidemiology of infective endocarditis after transcatheter aortic valve replacement.

The incidence of IE after TAVR reported in randomized clinical trials and large observational registries ranges from 0.3 to 2.0 per 100 person-years **(Table 9)**. Patient heterogeneity may partially explain this variability among studies. Data directly comparing IE incidence rates after SAVR and TAVR are scarce, with most studies reporting similar incidence rates.[146–148] A large nationwide observational cohort study including 2,632 TAVR and 3,777 SAVR patients compared the long-term risk of IE following both interventions.[146] During a mean follow-up of 3.6 years, the crude incidence rates of IE were similar in both groups. Likewise, the cumulative 5-year risk of IE in TAVR and SAVR patients was comparable (5.8% vs. 5.1%).[146] A meta-analysis of the most relevant randomized trials comparing TAVR and SAVR found no differences in early, late, and overall IE incidence between both groups.[149] Interestingly, a trend toward a higher risk of IE after TAVR than after SAVR was observed in patients with intermediate surgical risk (2.3% vs. 1.2%, OR 1.92, 95% CI 0.99-3.72, p = 0.05).[149] In contrast, a recent study analyzing a pooled cohort from three randomized clinical trials including patients with a broad spectrum of surgical risk receiving SEV, found a lower cumulative incidence of IE after TAVR compared with SAVR (TAVR: 1.01% vs. SAVR: 1.58%) 5 years after the procedure.[150,151]

Although one might anticipate that TAVR, as a less invasive technique, would be associated with a lower incidence of early IE when compared with SAVR, available evidence suggests otherwise **(Figure 10)**. In an observational cohort study, the risk of IE was greater within the first year post-TAVR than more than 1 year after the procedure (incidence rate of early vs. late IE: 1.48 vs. 0.40 per 100 person-years).[152] Notably, the highest risk of IE was observed during the early peri-procedural period (< 100 days), with an incidence of 2.6 per 100 person-years.[152] This incidence translates into a six-fold higher risk of IE during the early peri-TAVR period than more than 1 year after the procedure. In another study analyzing a limited number of TAVR prosthesis failures, early IE appeared to be more frequent in TAVR patients (80%) compared to SAVR patients (~40%).[73,153] Likewise, a multicenter nationwide cohort study showed that most IE cases (64%) occurred within the first year post-TAVR.[154] In addition, no differences in early IE incidence rates have been found when comparing TAVR and SAVR. In a

propensity-matched cohort of a large number of patients, the rate of early IE was similar with both interventions (TAVR: 1.7% vs. SAVR: 2.5% per person-year).[151,155]

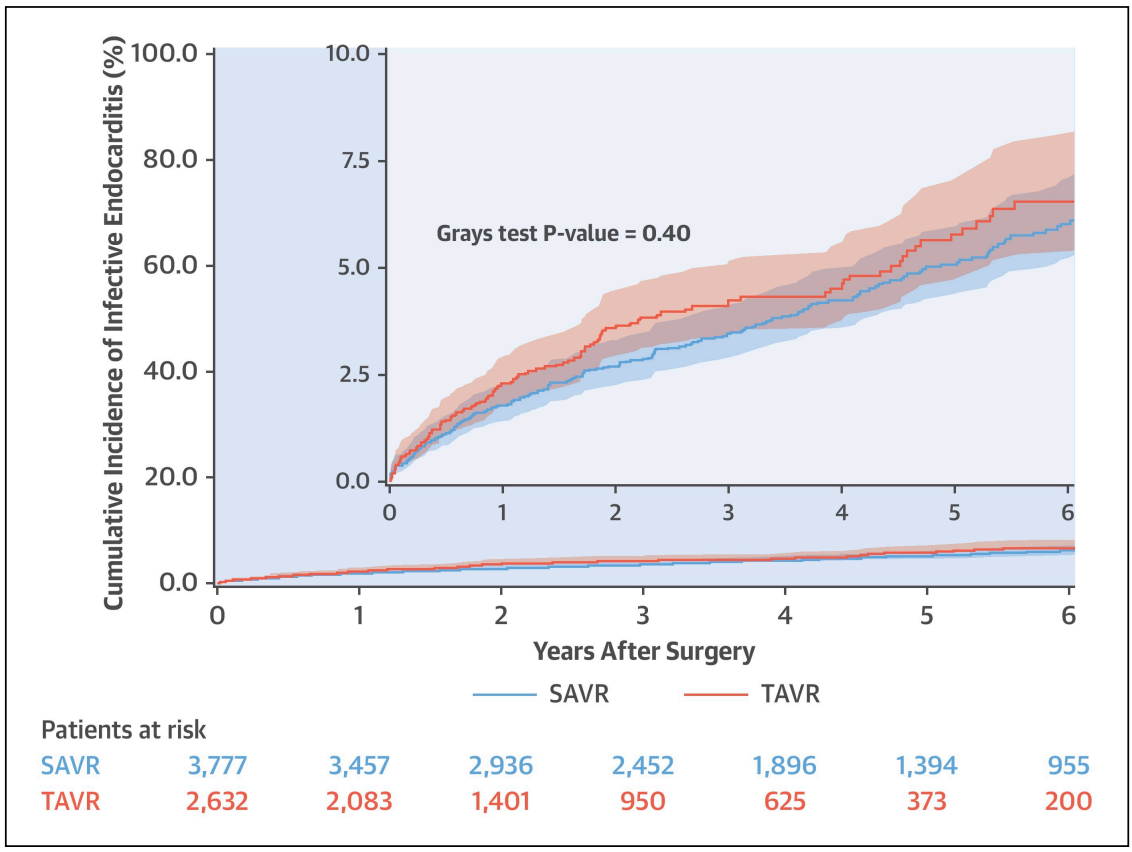

Figure 10. Cumulative incidence of infective endocarditis after transcatheter and surgical valve replacement.
From Butt et al.[146] with permission.

3.2 Risk factors

Multiple risk factors, both patient-related and inherent to the TAVR procedure, may contribute to the development of IE. Although numerous studies have attempted to identify predictors of IE following TAVR, none have consistently demonstrated a strong association with TAVR-IE across different studies.[151]

Patient-related risk factors for IE after TAVR include younger age, male sex, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, prior history of IE before TAVR, pulmonary hypertension, coagulopathy, liver disease,

preexisting atrial fibrillation, blood transfusion during TAVR hospitalization, and anemia.[152,154,156,157]

Procedure-related risk factors include residual moderate or severe aortic regurgitation, cardiac implantable devices, low TAVR valve placement, implantation of more than one prosthetic valve, lack of a balloon aortic valvuloplasty before TAVR, valve-in-valve procedures, and vascular and bleeding complications.[152,154,156,157] Although an increased risk of IE was initially reported in a study evaluating patients receiving SEV,[158] this finding was not confirmed during further analysis of a larger cohort of patients from the same registry. In a direct comparison of BEV and SEV, the 1-year cumulative incidence of IE was comparable between groups (BEV:1.25% vs. SEV: 0.95%).[159] These results were confirmed in a recent meta-analysis showing no differences in IE rates between both types of valves.[151,160]

Whether the location of the intervention influences the risk of IE is controversial. The largest observational studies have shown no evidence of a higher incidence of IE associated with the procedure location (catheterization laboratory vs. operating room or hybrid room).[156] Conversely, results from the Swiss TAVR multicenter registry revealed that the performance of the procedure in a hybrid operating room was independently associated with a reduced incidence of IE following TAVR.[152] Nevertheless, this finding has not yet been corroborated by further studies.[151]

To date, only one study has directly compared the risk factors for IE in TAVR and SAVR populations.[146] In this study, male sex was consistently associated with increased risk in both groups, while a history of chronic kidney disease and diabetes mellitus were associated with a higher risk in the TAVR-IE and SAVR-IE groups, respectively.[146]

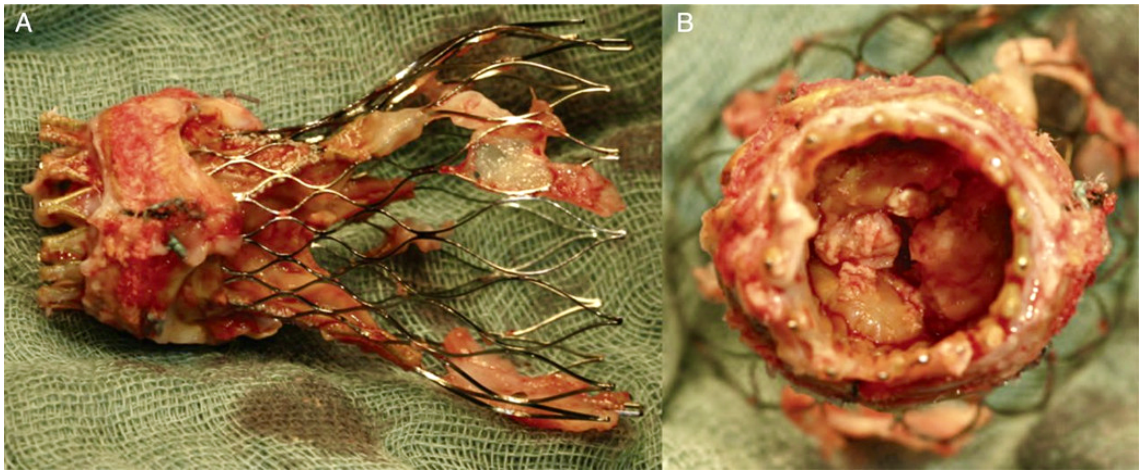

Figure 11. Infective endocarditis after transcatheter aortic valve replacement using self-expanding valve.

(A and B) Explanted Medtronic CoreValve 26 mm. From Seeburger et al.[161] with permission.

3.3 Microbiology

Staphylococci, particularly *Staphylococcus aureus*, are the leading cause of native- and prosthetic-valve IE in high-income countries.[29,31,60] In contrast, IE following TAVR shows a distinct microbiological profile. The most common microorganisms in TAVR-IE are enterococci, *S. aureus,* and coagulase-negative staphylococci **(Table 9)**. While enterococci represent only around 10% of SAVR-IE cases, prior studies have revealed that these microorganisms are the leading cause of IE following TAVR, accounting for more than one in four cases.[156,162] Enterococci have a strong affinity for warm, moist habitats such as the groin region. Hence, the high incidence of IE caused by these pathogens may be explained by the widespread use of the transfemoral approach during TAVR procedures. Enterococci are closely followed by *S. aureus,* which was the most commonly isolated pathogen in some observational studies.[157,163,164] Compared with SAVR-IE, TAVR-IE is less commonly caused by streptococci (6.9% vs 21%).[155–157] Additionally, culture-negative TAVR-IE is relatively uncommon (~5%)[156,157] compared with culture-negative IE in native- and prosthetic-valve IE (10%-20%).[29,30,34,151]

Of growing concern is the rising incidence of health care-associated IE (nosocomial or non-nosocomial) in TAVR patients, which is often associated with multidrug-resistant organisms. According to current data, more than half of TAVR-IE cases could be classified as health care-associated IE,[156,163] more than twice the rate as that observed

among SAVR patients.[29] Intravascular or soft tissue infections are the most frequently identified presumed source of bacteremia, while episodes related to dental procedures are rare. Other typical sources of bacteremia are gastroenterological and urological, which may explain the high prevalence of enterococcal infections seen in TAVI-IE patients. Nevertheless, in almost 7 out of 10 patients, the source of infection is unknown despite a thorough evaluation.[151,156,157]

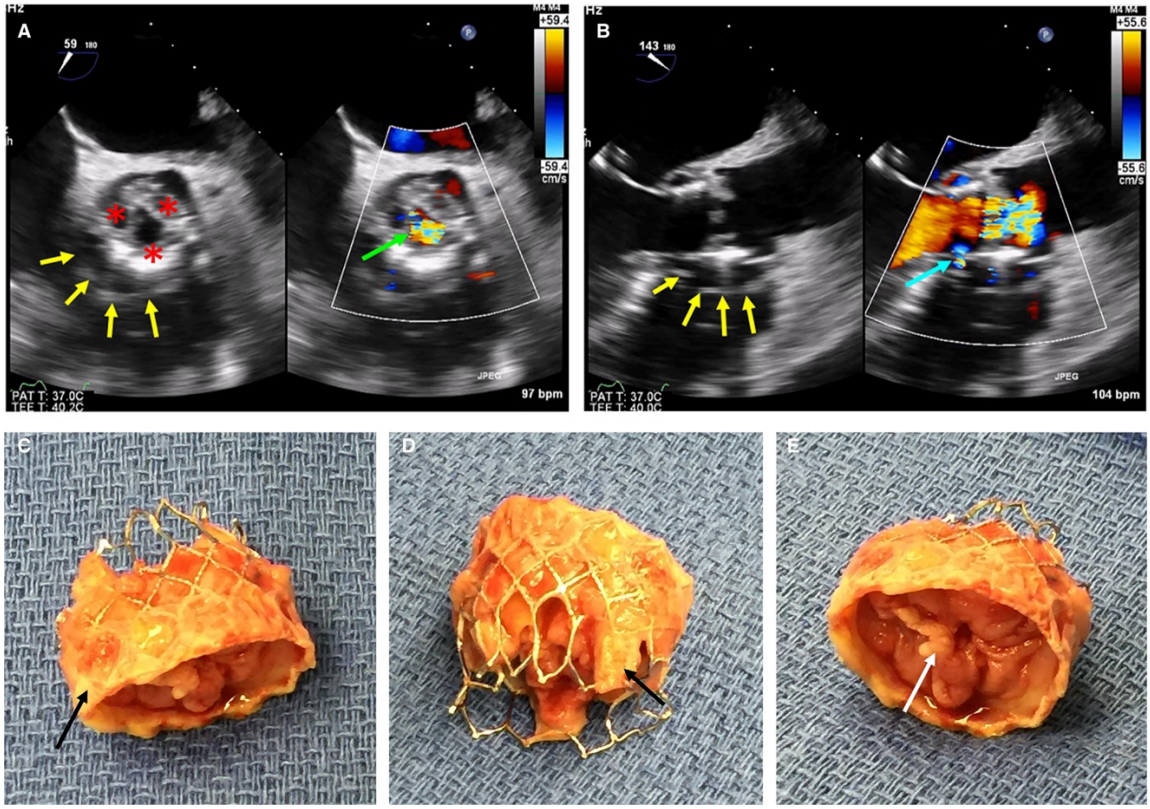

Figure 12. Infective endocarditis after transcatheter aortic valve replacement using balloon-expandable valve.
(A and B) Echocardiographic images. (C-E) Explanted SAPIEN 3. From Alexis et al.[147]

3.4 Clinical features and diagnosis

In general, fever is the most commonly identified presenting symptom, followed by new-onset heart failure, which occurs in around 80% and 40% of cases, respectively.[156,163] Furthermore, systemic embolic events account for ~13% of presenting symptoms in TAVR-IE patients.[156] Nevertheless, it is important to highlight that atypical presentation and nonspecific symptoms are more frequent in TAVR-IE patients. While fever, a

cardinal sign of infection, is present in approximately 90% of IE patients in the general population, this prevalence declines significantly in TAVR patients. This may be explained by the specific profile of the TAVR population, which typically is comprised of elderly patients with a high comorbidity burden. The absence of the classical IE presentation commonly leads to delayed diagnosis and treatment initiation in TAVR-IE patients.[151]

Despite the characteristic features of IE in TAVR population, there are no specific criteria to guide its diagnosis. As in PVE, clinical practice guidelines for IE recommend the use of the Modified Duke Criteria in patients presenting with suspected TAVR-IE. Nevertheless, these criteria have a lower diagnostic accuracy for TAVR-IE compared with native-valve IE, mainly due to a higher rate of negative blood cultures and inconclusive echocardiographic findings.[156,165] Previous studies have revealed that the combined sensitivity of TTE and TEE for diagnosing IE in TAVR patients was 67.8%, in contrast with 73% in patients with conventional PVE and 89.9% in patients with native-valve IE.[29,156] Likewise, atypical lesions, such as leaflet thickening and obstructive patterns with high transvalvular gradients, are more frequent in TAVR-IE.[166] These findings were confirmed in a large nationwide observational study in which echocardiographic studies (TTE and/or TEE) were considered normal or inconclusive in almost half of the patients with TAVR-IE.[151,152]

Although echocardiography remains the mainstay of diagnostic imaging, other imaging modalities, including CT, MRI, and metabolic imaging, have emerged as valuable tools, particularly in challenging scenarios such as TAVR-IE **(Figure 13)**. Some studies have supported the benefit of a multi-imaging approach, showing greater sensitivity in identifying endocardial involvement and extracardiac complications. For instance, in a retrospective analysis, the combination of ^{18}F-FDG-PET and CT enabled the reclassification of 33% of patients with suspected TAVR-IE who had previously been evaluated by the Duke Criteria, primarily as a result of higher accuracy in identifying definite cases.[167] The 2015 ESC evidence-based guidelines for IE included the use of ^{18}F-FDG-PET/CT and cardiac CT in the diagnostic work-up of PVE, which is also applicable to TAVR-IE. In addition, a recent study assessed the value of the multi-imaging approach

according to the 2015 ESC criteria in patients with suspected TAVR-IE.[166] This strategy showed a higher diagnostic value (100% sensitivity for definite IE diagnosis) than the Modified Duke Criteria (50% sensitivity).[151,166]

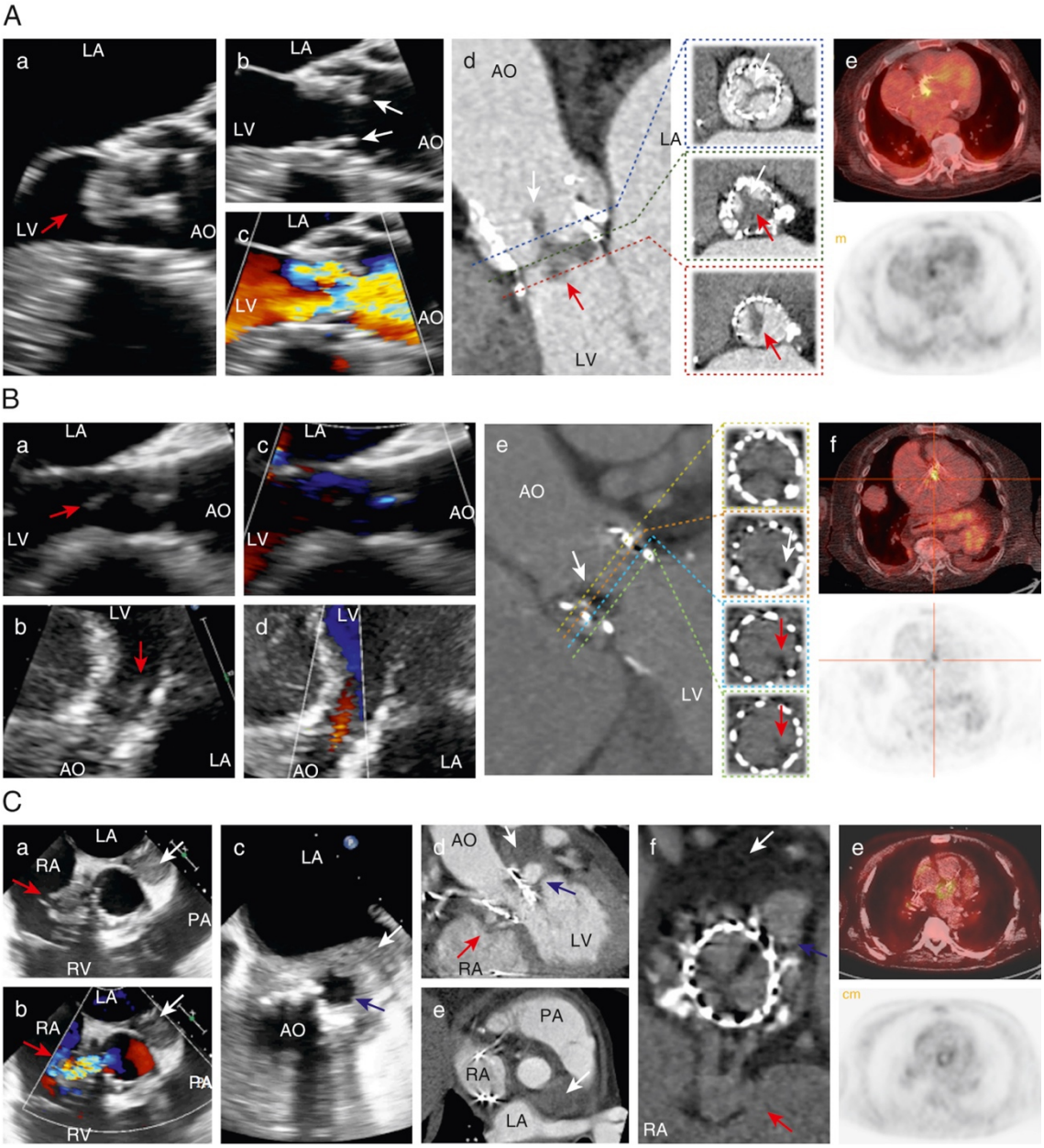

Figure 13. Multi-imaging approach to diagnosing infective endocarditis after transcatheter aortic valve replacement.

(A) An 83-year-old man with definite S. salivarius IE 6 months after 26-mm Edwards Sapien 3 implantation. (B) An 80-year-old woman with definite *S. aureus* IE 17 months after 23-mm Edwards Sapien XT implantation. (C) An 84-year-old man with definite *Enterococcus faecalis* IE 8 months after 26-mm Edwards Sapien 3 implantation. From Salaun et al.[166] with permission.

3.5 Management and outcomes

IE after TAVR is associated with a high rate of serious complications (>70%),[156,157] with acute heart failure, acute renal failure, septic shock, and systemic embolisms being the most common. Additionally, paravalvular complications and abscesses are relatively frequent and more common in TAVR-IE patients than in those with surgical PVE.[168] Numerous studies have shown that, regardless of treatment strategy, IE following TAVR is associated with dramatically high mortality rates (15% to 47% in-hospital mortality, 27% to 74% 1-year mortality) **(Table 9 and Figure 14)**. Although these wide ranges reflect the variability of patients across the surgical risk spectrum included in the different studies, these mortality rates are nevertheless consistently higher than those reported in native-valve and surgical-prosthetic IE.[156,169] The unique profile of the TAVR population (elderly patients with a high comorbidity burden) may partially explain the poor prognosis of TAVR-IE patients.[151]

The management of IE following TAVR is challenging and requires a collaborative approach. In the same way that the "Heart Team" has been shown to be useful in the selection of TAVR patients, evidence also supports the value of a multidisciplinary approach to the management of IE patients. As mentioned previously, the implementation of an "Endocarditis Team" has led to a significant reduction of in-hospital and long-term mortality in this population.[51,52] Thus, a collaborative approach, involving cardiologists, cardiac surgeons, infectious disease specialists, microbiologists, neurologists, neurosurgeons, and geriatric specialists, is critical to the decision-making processes in patients with IE following TAVR.[151]

To date, no randomized clinical trials have directly compared different antibiotic regimens or treatment strategies in TAVR-IE patients. Consequently, there are no specific guidelines for the management of this subset of patients, and antibiotic therapy recommendations are based on available guidelines for PVE.[31,38] Intravenous antibiotic treatment should be guided by the microbiological profile and antimicrobial susceptibility testing. In general, antibiotic regimens in patients with TAVR-IE should be longer in duration (at least 6 weeks) than those used in patients with native IE. Nevertheless, it

should be noted that TAVR patients are usually not well represented in PVE studies, whose results thus cannot be extrapolated to TAVR-IE patients.[151]

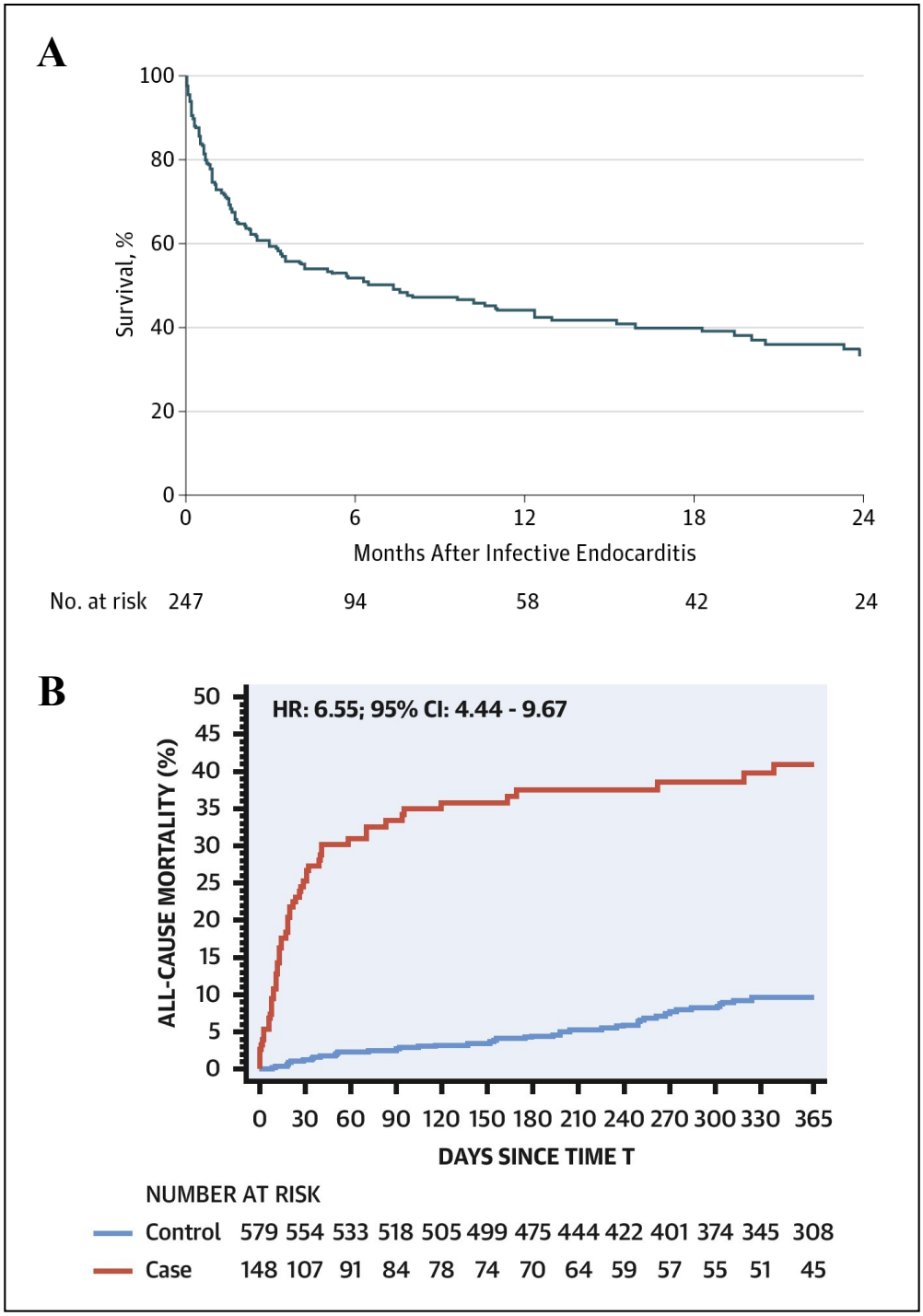

Figure 14: Outcomes of infective endocarditis after transcatheter aortic valve replacement.

(A) Kaplan-Meier estimated survival curve at 2-year follow-up after IE following TAVR. (B) Kaplan-Meier estimated mortality at 1-year follow-up in patients with (red line) and without (blue line) IE after TAVR. From Regueiro et al.[156] and Stortecky et al.[152] with permission.

The most appropriate management of patients with IE post-TAVR remains unclear. Previous studies revealed exceptionally low surgical and valve explantation rates (~15%) in this population.[157,170,171] However, the evidence is rather limited, and surgical indications for PVE cannot always be extrapolated to TAVR-IE patients in real-life practice, as they frequently exhibit an increased comorbidity burden and high-surgical-risk profile. Furthermore, classical surgical risk scores are not accurate in TAVR-IE, and specific risk scores have already been proposed.[172,173] A study including a cohort of high-surgical-risk patients with IE after TAVR showed no difference in mortality rates between surgical and conservative treatment.[174] Therefore, further studies are needed to determine the optimal indications and timing of surgery in this unique population.[151]

Table 9. Major studies reporting on the incidence and main characteristics of infective endocarditis after transcatheter aortic valve replacement.

Study	Period	Study Population	Valve Type	Incidence	Microbiology	TAVR-IE Mortality
Latib et al[163]	2008-2013	2,572	SEV (52%), BEV (48%)	29 pt (1.13%)	staphylococci (31%), enterococci (21%), CoNS (17%), oral streptococci (14%)	Cumulative:18 pt (62%)
Amat- Santos et al[158]	2007-2014	7,944	SEV (19.8%), BEV (80.2%)	53 pt (0.67%) 0.50% at 1-year	CoNS (24%), *S aureus* (21%), enterococci (21%), oral streptococci (5.7%)	In-hospital: 47.2% 1-year: 66% Cumulative: 38 pt (71.7%)
Regueiro et al[156]	2005-2015	20,006	SEV (47.6%), BEV (52.4%)	250 pt (1.2%) 1.1% per person-years	enterococci (25%), *S aureus* (24%), CoNS (17%)	In-hospital: 36% 2-year: 66.7%
Mangner et al[157]	2006-2014	1,820	SEV (~75%)	55 pt (3.0%) 1.82% per person-years	*S aureus* (38.2%), enterococci (30.9%), CoNS (9.1%), oral streptococci (3.6%)	In-hospital: 63.6% 1-year: 41 pt (74.5%)
Kolte et al[155]	2013-2014	29,306	NA	224 pt (0.8%) 1.7% per person-years	staphylococci (30.4%), streptococci (29.9%), and enterococci (20.5%)	In-hospital: 35 (15.6%)
Yeo et al[175]	2012-2014	41,025	NA	120 pt (0.3%) (In-hospital incidence)	Viridans group streptococci (20.8%), *S aureus* (16.7%) and enterococci (8.3%)	Cumulative: 25 pt (20.8%)
Thourani et al[176]	2014	1,077	SAPIEN 3 (100%)	8 pt (0.74%) 0.8% at 1-year	NA	NA
Cahill et al[162,177]	2007-2016	14,195	NA	140 pt (0.99%) 3.57‰ person-year 1.5% at 5-year	enterococci (25.9%),(16.4%), *S aureus* (11.8%)	45.6% at 1-year
Butt et al[146]	2008-2016	2,680	NA	115 pt (4.4%) 1.6% per person-years	NA	1-year: 46 pt (40%)

				5.8% at 5-year		
Ali et al[178]	2008-2018	1,337	NA	13 pt (0.97%)	streptococci (53.8%)	In-hospital: 5 pt (38.5%) Long-term: 7 pt (53.8%)
Bjursten et al[170]	2008-2018	4,336	BEV (42.3%), SEV (52.5%), MEV (5.4%)	103 pt (2.4%) 1.42% at 1-years	Alpha-haemolytic streptococci (34%), S *aureus* (22.3%), *Enterococcus faecalis* (20.4%)	In-hospital: 17 pt (17%) 6-month: 31 pt (30.1%)
Ando et al[149]	2002-2018	1,895 (meta-analysis)	NA	75 pt (2.0%)	NA	NA
Moriyama et al[164]	2008-2017	2,130	NA	15 pt (0.7%) 3.4‰ person-years	streptococci (46.7%), staphylococci (26.7%), enterococci (26.7%)	In-hospital: 3 pt (20%)
Fauchier et al[148]	2010-2018	47,553	BEV: 54.1%	1127 (2.4%) 1.89% per person-years	*S aureus* (15.8%), streptococci (29%), enterococci (22.7%) in the matched cohort	1-year: 32.8%
Mentias et al[154]	2012-2017	134,717	NA	1,868 pt (1.39%) 0.87% per person-years	staphylococci (22%), streptococci (20%), enterococci (15.5%)	1-year: 45.6%
Stortecky et al[152]	2011-2018	7,203	BEV: 44.1%, SEV: 42.7%, MEV: 13.3%	149 pt (5.8%) 1.0% per person-years	streptococci (28.9%), enterococci (26.2.%), *S aureus* (21.5%),	NA
Summers et al[179]		7,273 (pooled data of of 2 RCT)	SAPIEN (50.5%), SAPIEN XT (31.6%), SAPIEN 3 (17.9%)	95 pt (1.31%) 5.21‰ per person-years	staphylococcus (28.4%)	Cumulative: 46.3%
Lanz et al[150]	2011-2018	2,249 (pooled data of 3 RCT)	SEV (100%)	12 pt (0.5%) 2.47‰ per patient-years	streptococci (38.5%), enterococci (23.1.%), *S aureus* (15.4%), CoNS (15.4%),	1-year: 27.3%

HYPOTHESIS AND OBJECTIVES

I. HYPOTHESIS

I.I General hypothesis

IE after TAVR presents a unique epidemiological, clinical, and prognostic profile and constitutes a distinct entity within PVE.

I.II Specific hypotheses

1. The evolution of the TAVR procedure over the last few years (major device iterations combined with simplified and less invasive procedures) has led to a reduction in the incidence of IE after TAVR.

2. Stroke complicating TAVR-IE is an uncommon but serious complication associated with poor in-hospital and late clinical outcomes.

3. IE post-TAVR caused by *Staphylococcus aureus* is relatively frequent and associated with higher in-hospital mortality rates and worse late clinical outcomes compared with other causative microorganisms.

4. In the absence of TAVR-IE, physiological uptake of ^{18}F-Fluorodeoxyglucose occurs in the perivalvular area, and the uptake pattern of noninfected TAVR prostheses varies between different devices.

5. Cardiac surgery during the index hospitalization for IE after TAVR is associated with improved in-hospital and late clinical outcomes.

6. Patients who survive the index episode of IE after TAVR have high recurrence and long-term mortality rates.

II. OBJECTIVES

II.I General objectives

The primary objectives of this Ph.D. research project are: (i) to determine the temporal trends in the incidence, clinical characteristics, management, and outcomes of IE post-TAVR, (ii) to assess the clinical features and outcomes of IE after TAVR in subgroups of patients, and (iii) to determine the role of ^{18}F-FDG PET/CT in the diagnosis of very early IE (within 3 months) after TAVR.

II.II Specific objectives

1. To determine temporal trends in incidence, clinical characteristics, management, and outcomes by comparing a historical and contemporary cohort of patients with IE after TAVR.

2. To assess the incidence, associated risk factors, clinical characteristics, management, and outcomes of patients with IE after TAVR complicated by stroke during the index IE hospitalization.

3. To evaluate the clinical characteristics, management, and in-hospital and late outcomes of patients with IE caused by *Staphylococcus aureus* after TAVR.

4. To characterize the uptake pattern of ^{18}F-FDG in noninfected transcatheter aortic valves 3 months after TAVR and assess differences in the uptake pattern between the two most widely used types of prostheses.

5. To compare the characteristics and outcomes of patients with IE after TAVR treated with cardiac surgery compared with patients treated with antibiotics alone.

6. To evaluate the long-term (>2 years) outcomes and prognostic factors associated with patients with IE post-TAVR who survived index hospitalization.

CHAPTER 1. Temporal Trends, Characteristics, and Outcomes of Infective Endocarditis After Transcatheter Aortic Valve Replacement.

David del Val,[1] Mohamed Abdel-Wahab,[2,3] Axel Linke,[2,4] Eric Durand,[5] Nikolaj Ihlemann,[6] Marina Urena,[7] Costanza Pellegrini,[8] Francesco Giannini,[9,10] Martin Landt,[3] Vincent Auffret,[11] Jan Malte Sinning,[12] Asim Cheema,[13,14] Luis Nombela-Franco,[15] Chekrallah Chamandi,[16] Francisco Campelo-Parada,[17] Antonio Munoz-Garcia,[18] Howard C. Herrmann,[19] Luca Testa,[20] Kim Won-Keun,[21] Juan Carlos Castillo,[22] Alberto Alperi,[23] Didier Tchetche,[24] Antonio Bartorelli,[25] Samir Kapadia,[26] Stefan Stortecky,[27] Ignacio Amat-Santos,[28] Harindra C Wijeysundera,[29] John Lisko,[30] Enrique Gutiérrez-Ibanes,[31] Vicenç Serra,[32] Luisa Salido,[33] Abdullah Alkhodair,[34] Ugolino Livi,[35] Tarun Chakravarty,[36] Stamatios Lerakis,[30,37] Victoria Vilalta,[38] Ander Regueiro,[39] Rafael Romaguera,[40] Marco Barbanti,[41] Jean-Bernard Masson,[42] Frédéric Maes,[43] Claudia Fiorina,[44] Antonio Miceli,[45,46] Susheel Kodali,[47] Henrique B. Ribeiro,[48] Jose Armando Mangione,[49] Fabio Sandoli de Brito Jr,[48] Guglielmo Mario Actis Dato,[50] Francesco Rosato,[51] Maria-Cristina Ferreira,[52] Valter Correia de Lima,[53] Alexandre Siciliano Colafranceschi,[54] Alexandre Abizaid,[55] Marcos Antonio Marino,[56] Vinicius Esteves,[57] Julio Andrea,[58] Roger R. Godinho,[59] Helene Eltchaninoff,[5] Lars Søndergaard[6], Dominique Himbert,[7] Oliver Husser,[8,60] Azeem Latib,[9,61] Hervé Le Breton,[11] Clement Servoz,[17] Isaac Pascual,[23] Saif Siddiqui,[24] Paolo Olivares,[25] Rosana Hernandez-Antolin,[33] John G. Webb,[34] Sandro Sponga,[35] Raj Makkar,[36] Annapoorna S. Kini,[37] Marouane Boukhris,[42] Norman Mangner,[2,4] Lisa Crusius,[2,4] David Holzhey,[2] and Josep Rodés-Cabau[1]

[1]Quebec Heart and Lung Institute, Laval University, Quebec City, Canada, [2]Heart Center Leipzig at University of Leipzig, Leipzig, Germany, [3]Heart Center, Segeberger Kliniken, Bad Segeberg, Germany, [4]Herzzentrum Dresden, Technische Universität Dresden, Dresden, Germany, [5]Hôpital Charles Nicolle, University of Rouen, Rouen, France, [6]Righospitalet, Copenhagen, Denmark, [7]Bichat Hôpital, Paris, France, [8]Deutsches Herzzentrum München, Munich, Germany, [9]Ospedale San Raffaele, Milan, Italy, [10]Maria Cecilia Hospital, GVM Care and Research, Cotignola RA, Italy, [11]Centre Hospitalier Universitaire de Rennes, Rennes, France, [12]Heart Center Bonn, Bonn, Germany, [13]St Michaels Hospital, Toronto, Canada, [14]Southlake Regional Health Centre, Newmarket, Canada, [15]Cardiovascular Institute, Hospital Clínico San Carlos, IdISSC, Madrid, Spain, [16]Hôpital Européen Georges Pompidou, Paris, France, [17]Hôpital Rangueil, Toulouse, France, [18]Hospital Universitario Virgen de la Victoria, Malaga, Spain, [19]Hospital of the University of Pennsilvania, Philadelphia, Pennsylvania, USA, [20]IRCCS Pol San Donato, Milan, Italy, [21]Kerckhoff Klinik, Bad Nauheim, Germany, [22]Hospital Universitario Reina Sofia, Cordoba, Spain, [23]Hospital Universitario Central de Asturias, Oviedo, Spain, [24]Clinique Pasteur, Toulouse, France, [25]Centro Cardiologico Monzino, IRCCS, University of Milan, Italy, [26]Cleveland Clinic, Cleveland, Ohio, USA, [27]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Switzerland (on behalf of SwissTAVI), [28]CIBERCV, Hospital Clinico Universitario de Valladolid, Valladolid, Spain, [29]Sunnybrook Health Science Center, Toronto, Canada, [30]Emory University School of Medicine, Atlanta, Georgia, USA, [31]Instituto de Investigación Universitaria Gregorio Marañón, Hospital Gregorio Marañón, Madrid, Spain, [32]Hospital Vall d'Hebron, Barcelona, Spain, [33]Hospital Universitario Ramón y Cajal, Madrid, Spain, [34]St Paul's Hospital, Vancouver, Canada, [35]University Hospital of Udine, Udine, Italy, [36]Cedars-Sinai Heart Institute, Los Angeles, California, USA, [37]Mount Sinai Hospital, New York, New York, USA, [38]Hospital Germans Trias i Pujol, Badalona, Spain, [39]Hospital Clinic, Barcelona, Spain, [40]Hospital de Bellvitge, L'Hospitalet de Llobregat, Spain, [41]A.O.U. Policlinico Vittorio Emanuele, University of Catania, Catania, Italy, [42]Centre Hospitalier de l'Universite de Montreal, Montreal, Canada, [43]Cliniques Universitaires Saint-Luc, Brussels, Belgium, [44]ASST-Spedali Civili di Brescia, Brescia, Italy, [45]Fondazione Toscana G. Monasterio, Massa, Italy, [46]Istituto Clinico Sant'Ambrogio, Milan, Italy, [47]Columbia University Medical Center, New York, New York, USA, [48]Instituto do Coraçao (Incor), Heart Institute, University of São Paulo, Sao Paulo, Brazil, [49]Hospital Beneficencia Portuguesa, Sao Paulo, Brazil, [50]Ospedale Mauriziano, Torino, Italy, [51]Azienda Ospedaliera Santa Croce e Carle, Cuneo, Italy, [52]Hospital Naval Marcilio Dias, Rio de Janeiro, Brazil, [53]Hospital São Francisco-Santa Casa de Porto Alegre, Porto Alegre, Brazil, [54]Hospital Pró-cardíaco, Rio de Janeiro, Brazil, [55]Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil, [56]Hospital Madre Teresa, Belo Horizonte, Brazil, [57]Hospital São Luiz, Sao Paulo, Brazil, [58]Clinica São Vicente, Rio de Janeiro, Brazil, [59]Hospital Samaritano Paulista, Sao Paulo, Brazil, [60]St-Johannes-Hospital, Dortmund, Germany, and [61]Montefiore Medical Center, New York, New York, USA.

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1.1 RÉSUMÉ

Contexte : Les améliorations procédurales combinées à l'évolution du profil clinique des patients bénéficiant d'un remplacement valvulaire aortique percutané (TAVR) pourraient avoir eu une influence sur l'incidence et les complications de l'endocardite infectieuse (EI) après le TAVR.

Objectifs : Nous avons cherché à déterminer les tendances temporelles, les caractéristiques et les résultats de l'EI après le TAVR.

Méthodes : Étude observationnelle incluant 552 patients présentant une EI certaine après le TAVR. Les patients ont été divisés en deux groupes selon le moment où le TAVR a été effectué (cohorte historique [HC] : avant 2014; cohorte contemporaine [CC] : après 2014).

Résultats : Le taux d'incidence globale d'EI était similaire dans les deux cohortes (CC vs HC : 5,45 vs 6,52 pour 1000 personnes-années ; p=0,12), mais le taux d'EI précoce était plus faible dans la CC (2,29‰ vs 4,89‰, p<0,001). Les entérocoques étaient les micro-organismes les plus fréquemment impliqués. La plupart des patients présentaient une EI compliquée (CC : 67,7% ; HC : 69,6% ; p=0,66), mais le taux de traitement chirurgical restait faible (CC : 20,7% ; HC : 17,3% ; p=0,32). Les patients de la CC présentaient un taux plus faible d'insuffisance rénale aiguë (35,1 % vs. 44,6 % ; p=0,036) et de mortalité pendant l'hospitalisation (26,6 % vs. 36,4 % ; p=0,016) et à un an (37,8 % vs. 53,5 % ; p<0,001). Un EuroSCORE logistique plus élevé, une EI causée par *Staphylococcus aureus* et la survenue d'une complication (accident vasculaire cérébral, insuffisance cardiaque et insuffisance rénale aiguë) étaient associés à la mortalité hospitalière dans l'analyse multivariée (p<0,05 pour tous).

Conclusions : Bien que l'incidence globale des EI soit restée stable, la fréquence de survenue des EI précoces a diminué ces dernières années. Les micro-organismes impliqués, le taux élevé de complications et le très faible taux de traitement chirurgical sont restés stables. Les taux de mortalité pendant l'hospitalisation et à un an étaient élevés mais ont progressivement diminué au fil du temps.

1.2 ABSTRACT

Background: Procedural improvements combined with the contemporary clinical profile of patients undergoing transcatheter aortic valve replacement (TAVR) may have influenced the incidence and outcomes of infective endocarditis (IE) following TAVR. We aimed to determine the temporal trends, characteristics, and outcomes of IE post-TAVR.

Methods: Observational study including 552 patients presenting definite IE post-TAVR. Patients were divided in 2 groups according to the timing of TAVR (historical cohort [HC]: before 2014; contemporary cohort [CC]: after 2014).

Results: Overall incidence rates of IE were similar in both cohorts (CC vs HC: 5.45 vs 6.52 per 1000 person-years; p=0.12), but the rate of early IE was lower in the CC (2.29‰ vs 4.89‰, p<0.001). Enterococci were the most frequent microorganism. Most patients presented complicated IE (CC: 67.7%; HC: 69.6%; p=0.66), but the rate of surgical treatment remained low (CC: 20.7%; HC: 17.3%; p=0.32). The CC exhibited lower rates of in-hospital acute kidney injury (35.1% vs 44.6%; p=0.036) and in-hospital (26.6% vs 36.4%; p=0.016) and 1-year (37.8% vs 53.5%; p<0.001) mortality. Higher logistic EuroSCORE, *Staphylococcus aureus* etiology, and complications (stroke, heart failure, and acute renal failure) were associated with in-hospital mortality in multivariable analyses (p<0.05 for all).

Conclusions: Although overall IE incidence has remained stable, the incidence of early IE has declined in recent years. The microorganism, high rate of complications, and very low rate of surgical treatment remained similar. In-hospital and 1-year mortality rates were high but progressively decreased over time.

1.3 INTRODUCTION

Infective endocarditis (IE) following transcatheter aortic valve replacement (TAVR) is a rare but life-threatening complication. The incidence of IE post-TAVR ranges between 0.9% and 3.1% at 1-year follow-up, similar to that reported following surgical aortic valve replacement.[149,165] Transcatheter aortic valve replacement has revolutionized the treatment of severe aortic stenosis and is currently expanding towards the treatment of younger patients with a lower surgical risk.[180] Thus, the number of patients at risk of developing IE after TAVR is growing exponentially. Infective endocarditis post-TAVR is associated with high in-hospital mortality and patients who survive the index IE episode showed a poor long-term prognosis, with nearly two-thirds dying at 5-year follow-up.[156,179,181]

In the last few years, there has been an increasing interest in simplifying and reducing invasive healthcare procedures in TAVR. The potential benefits of both device iterations and procedural changes (e.g., no general anesthesia) are a shorter hospital length of stay, earlier patient ambulation, lower risk for nosocomial infections, and lower in-hospital mortality.[182,183] However, it remains unknown whether such improvements combined with the contemporary clinical profile of patients undergoing TAVR have impacted the incidence and outcomes of IE episodes in this particular population. Thus, the objectives of this study including a large cohort of patients with definite IE after TAVR were to determine the temporal trends regarding the incidence, clinical characteristics, management, and outcomes of IE episodes post-TAVR.

1.4 METHODS

Data from the Infectious Endocarditis After TAVR International Registry were used for this study. Details about the design of this retrospective, multicenter, international registry have been published previously.[156] Briefly, the registry collected data from 552 patients with definite IE after TAVR from 56 TAVR centers in 10 countries across Europe, North America, and South America between June 2005 and May 2020.

1.4.1 Patient Selection and Data Collection

Patients were retrospectively identified by each center according to the modified Duke criteria. Only patients with definite IE were included, irrespective of the structure affected (native/prosthetic valve or implantable cardiac device). Also, only the first episode of IE recorded for an individual patient was included in the analysis. A dedicated database was used in all sites for data collection including baseline and periprocedural TAVR features, IE characteristics, and in-hospital and follow-up outcomes. Based on the TAVR date, the global cohort was divided into 2 cohorts of patients. The division date (31 December 2013) was prespecified on the basis of the following criteria: (1) to reflect a new era for TAVR with important platform iterations (second-generation valves) and procedural changes that may have influenced IE epidemiology and (2) to divide the entire cohort into 2 similar (numerically) groups of patients. A total of 285 patients were included in the historical cohort (HC; June 2005 to December 2013) and 263 patients in the contemporary cohort (CC; January 2014 to May 2020). Four patients were excluded from the final analysis because of missing data of TAVR date. Also, participating sites were asked to provide data on the total number of TAVR procedures (overall and according to TAVR time) and individual data concerning TAVR patients' follow-up. The flowchart of the study population is depicted in **Figure 1.1**. Data from up to 250 patients (45%) included in the present study have been reported in a prior study (203 and 47 patients corresponding to the HC and CC, respectively).[156]

1.4.2 Definitions

The definition of definite IE was based on the modified Duke criteria.[45] Clinical endpoints were defined according to the Valve Academic Research Consortium-2 criteria.[184] Perioperative mortality risk was defined according to the logistic EuroSCORE.[185] Transcatheter aortic valve type was divided into 2 groups: balloon-expandable valves and self- or mechanically expandable valves. Infective endocarditis with no TAVR platform affection was defined as any IE episode not involving the TAVR prosthesis. Early prosthetic valve endocarditis (PVE) was defined as occurring within 60 days of TAVR.[27,29] Healthcare associated IE was defined using Friedman et al criteria.[186] Persistent bacteremia was defined as bacteremia despite appropriate antibiotic therapy for more than 7 days. Periannular complications and other systemic embolization were defined as previously reported.[156]

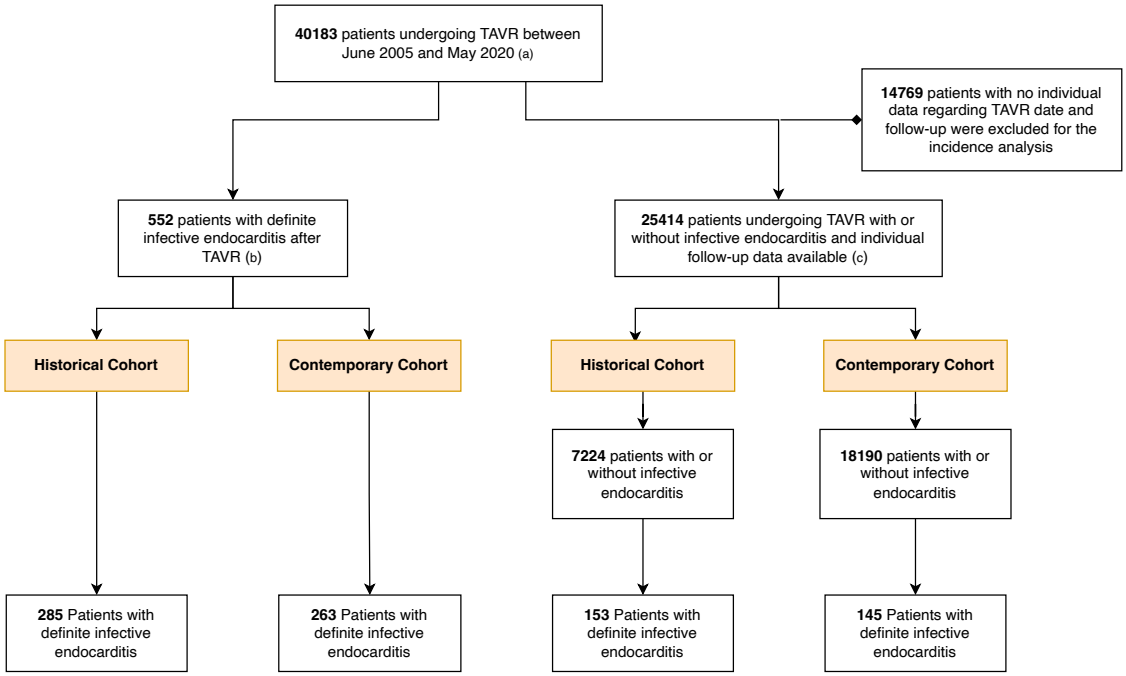

Figure 1.1. Flowchart of the study population.

(a) Forty-three centers reporting data on the total number of TAVR procedures, overall and according to the occurrence of infective endocarditis post-TAVR. (b) Time of TAVR was missing in 4 patients. (c) Thirty-two centers reporting individual data regarding TAVR patients' follow-up. Patients with definite infective endocarditis to determine the incidence estimation were also part of the overall study cohort. Abbreviation: TAVR, transcatheter aortic valve replacement.

1.4.3 Statistical Analysis

Continuous variables were expressed as means ± standard deviations or medians (interquartile ranges [IQRs]) depending on the variable distribution, which was assessed using the Kolmorogov-Smirnov test. Incidence rates and incidence rate ratios were calculated using a subsample of centers that provided individual data from all the patients undergoing TAVR, irrespective of the occurrence of IE. Categorical variables were expressed as numbers (%). Group comparison was analyzed using the Student's *t* test or Wilcoxon rank-sum test for continuous variables and chi-square or Fisher's exact test for categorical variables. A multivariable Cox proportional hazards model was performed to determine the factors independently associated with in-hospital mortality. The variables considered a priori to contribute to in-hospital mortality and with a p value less than 0.10 in the bivariate analysis were included in the model. The model was built by backward stepwise (likelihood ratio) selection. The proportional hazards assumption was tested by assessing log-minus-log survival plots and scaled Schoenfeld residuals. The Kaplan-Meier method was used to provide survival estimates with differences assessed by the

log-rank test. Event times were measured from the date of initial IE symptoms to the date of death or last follow-up. A 2-sided p value of less than 0.05 was considered statistically significant. Data analyses were performed using the Stata software (StataCorp, College Station, TX, USA) and Prism (GraphPad Software, San Diego, CA, USA).

1.5 RESULTS

1.5.1 Baseline and Procedural Characteristics

The main baseline and procedural characteristics of the study population, overall and according to the timing of the TAVR procedure (CC and HC groups), are shown in **Table 1.1**. Definite IE was diagnosed in 552 patients following TAVR. The median follow-up of the entire TAVR population was 16.2 months (IQR, 10.0–36.2 months). The median age of the patients was 80.7 years (IQR, 74.6–85.1 years), with 61.2% men (95% confidence interval [CI], 57.2–65.3%) and a median logistic EuroSCORE of 14.5% (IQR, 8.6–24.2%). Most procedures (87.9%; 95% CI, 85.1–90.6%) were performed through transfemoral approach.

Table 1.1. Baseline Characteristics, Procedural Details, and In-Hospital Transcatheter Aortic Valve Replacement (TAVR) Outcomes, Overall and According to the Time of TAVR (Historical vs Contemporary Cohort).

	Overall (n=552)[a]	Historical Cohort (n=285)	Contemporary Cohort (n=263)	Unadjusted P value
Baseline characteristics				
Age, years	80.7 (74.6-85.1)	79.3 (73.9-84.1)	81.7 (75.6-85.7)	0.010
Female	214 (38.8)	118 (41.4)	94 (35.7)	0.174
Body mass index, (kg/m2)	27.0 (24-30.8)	27.1 (24.2-31.1)	26.8 (24-31)	0.616
Diabetes mellitus	202 (36.6)	105 (36.8)	96 (36.5)	0.934
COPD	150 (27.2)	83 (29.1)	67 (25.5)	0.339
Atrial fibrillation	232 (42.0)	105 (36.8)	126 (47.9)	0.010
Chronic renal failure	216 (39.1)	121 (42.5)	94 (35.7)	0.163
Previous Stroke	75 (13.6)	35 (12.3)	40 (15.2)	0.319
Previous valve surgery	64 (11.6)	28 (9.8)	36 (13.7)	0.159
Previous infectious endocarditis	9 (1.6)	3 (1.1)	6 (2.3)	0.324
Logistic EuroSCORE, %	14.5 (8.6-24.2)	16.1 (9.6-25.2)	12.6 (8.0-23)	0.030

High risk (>20%)	169 (30.6)	103 (36.1)	66 (25.1)	0.012
Low risk (<10%)	154 (27.9)	71 (24.9)	83 (31.6)	0.033
LVEF, %	53.8 (13.5)	53.9 (13.5)	53.7 (13.5)	0.868
Mean transaortic gradient, mmHg	45.3 (16.0)	45.2 (16.6)	45.3 (15.4)	0.715
Aortic valve area, cm2	0.73 (0.23)	0.72 (0.22)	0.74 (0.24)	0.316
Periprocedural characteristics				
Implantation site				
Catheterization laboratory	249 (45.1)	133 (46.7)	116 (44.1)	0.548
Operating or hybrid room	303 (54.9)	152 (53.3)	147 (55.9)	
Approach				
Transfemoral	485 (87.9)	239 (83.9)	243 (92.4)	<0.001
Transapical	43 (7.8)	35 (12.3)	7 (2.7)	
Transaortic	13 (2.4)	7 (2.5)	6 (2.3)	
Other	11 (2.0)	4 (1.4)	7 (2.7)	
Endotracheal intubation	239 (43.3)	154 (54.0)	82 (31.2)	<0.001
Prosthesis type				
Balloon-expandable	292 (52.9)	149 (52.3)	139 (52.9)	0.798
Self-expandable	246 (44.6)	130 (45.6)	116 (44.1)	
Antibiotic prophylaxis				
B-Lactam alone	438 (79.4)	220 (77.2)	217 (82.5)	0.012
Vancomycin (alone or in combination)	23 (4.2)	18 (6.3)	4 (1.5)	
In-hospital Outcomes (TAVR)				
Acute renal failure	72 (13.0)	40 (14.0)	32 (12.2)	0.569
Stroke	26 (4.7)	14 (4.9)	12 (4.6)	0.883
Major vascular complication	39 (7.1)	25 (8.8)	14 (5.3)	0.130
Major bleeding	55 (10.0)	33 (11.6)	22 (8.4)	0.236
New pacemaker implantation	96 (17.4)	56 (19.7)	40 (15.2)	0.185
Length of hospital stay, days	8 (6-14)	9 (7-15)	7 (5-13)	<0.001

Data are presented as n (%), median (IQR), or mean (SD). Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF: left ventricular ejection fraction; SD, standard deviation. [a]Time of TAVR was missing in 4 patients.

Infective endocarditis following TAVR was diagnosed in 285 patients in the HC (incidence rate of 6.52 [95% CI, 5.54–7.67] per 1000 patient-years) and 263 patients in the CC (incidence rate of 5.45 [95% CI, 4.65–6.38] per 1000 patient-years). There was no significant temporal variation regarding the overall IE incidence between both cohorts (incidence rate ratio of 0.84 [95% CI, .66–1.05]; p=0.123), but the incidence of early IE

(within 60 days of the procedure) was significantly lower in the CC (incidence rate in HC vs CC: 4.89 vs 2.29 per 1000 patients; difference, 2.7; 95% CI, 1.0–4.2; p <0.001). Patients in the CC were older (HC vs CC: 79.3 vs 81.7 years; difference, −2.4 years; p<0.01) and exhibited a lower risk profile for TAVR as determined by the logistic EuroSCORE (HC vs CC:16.1% vs 12.6%; difference, 3.5%; p=0.03). Transcatheter aortic valve replacement procedures in the CC were more frequently performed through transfemoral approach (HC vs CC: 83.9% vs 92.4%; difference, −8.5%; 95% CI, −13.9% to −3.2%; p<0.001), without general anesthesia/endotracheal intubation (HC vs CC: 54.0% vs 31.2%; difference, 22.9%; 95% CI, 14.8% to 30.9%; p<0.001), but there were no differences between cohorts regarding transcatheter valve type. A significant reduction in the use of vancomycin for antibiotic prophylaxis was observed in the CC (HC vs CC: 6.3% vs 1.5%; difference, 4.8%; 95% CI, 1.6–8.0%; p=0.012). The median hospitalization length of stay was much shorter in the CC (7 [IQR, 5–13] days) versus the HC (9 [IQR, 7–15] days) (p<0.001).

1.5.2 Characteristics and Clinical Outcomes of the Infective Endocarditis Episode Post–Transcatheter Aortic Valve Replacement

The characteristics and outcomes of the IE episode post-TAVR for the entire population and according to the timing of the TAVR procedure (CC and HC) are shown in **Table 1.2**. Overall, the IE episode was diagnosed after a median of 6.5 months (IQR, 2.0–15.9 months) following TAVR. Fever was the most frequent symptom at admission in both groups, but the proportion of patients presenting without fever was higher in the CC (HC vs CC: 21.1% vs 31.2%; difference, −10.1%; 95% CI, −17.5%% to −2.8%; p=0.004). Acute heart failure at admission was common (HC vs CC: 42.5% vs 37.3%), while neurological symptoms (HC vs CC: 17.5% vs 15.6%) and systemic embolism (HC vs CC: 14.0% vs 9.9%) were less frequent (no differences between groups, p>0.05 for all). The presumed source of entry was only identified in 280 patients (HC vs CC: 48.8% vs 52.5%) and urological infection was the most frequent source of bacteremia in both cohorts. Vegetations were identified in nearly two-thirds of the patients with no differences between groups regarding valve-involved distribution. Enterococci were the most common microorganisms in both cohorts, followed closely by *Staphylococcus aureus*. The episodes caused by methicillin-resistant coagulase-negative staphylococci were higher in the CC (HC vs CC: 3.0% vs 7.9%; difference, −4.9; 95% CI, −8.7% to

−0.9%; p=0.036). Among patients with early IE, a tendency toward an increased incidence of enterococci (HC vs CC: 25.5 vs 38.7; p=0.136) along with a decreased proportion of *S. aureus* (HC vs CC: 35.3% vs 29.0%; P = .477) was observed.

Table 1.2. Main clinical characteristics, management, and outcomes of infective endocarditis after TAVR, overall and according to the time of TAVR (historical vs. contemporary cohort).

	Overall (n=552)[a]	Historical Cohort (n=285)	Contemporary Cohort (n=263)	Unadjusted P value
Incidence of IE (per 1000 patients-year), [95% CI)	5.92 [5.28-6.63]	6.52 [5.54-7.67]	5.45 [4.65-6.38]	p=0.123
Incidence of early IE (per 1000 patients) [95% CI]	3.02 [2.41-3.63]	4.89 [3.44-6.36]	2.29 [1.66-2.92]	p<0.001
Initial symptoms				
Fever	409 (74.1)	225 (78.9)	181 (68.8)	0.004
New-onset heart failure	219 (39.7)	121 (42.5)	98 (37.3)	0.207
Neurological	92 (16.7)	50 (17.5)	41 (15.6)	0.524
Systemic embolism	66 (12.0)	40 (14.0)	26 (9.9)	0.130
Cutaneous	26 (4.7)	11 (3.9)	15 (5.7)	0.320
Health care–associated infection	229 (41.5)	112 (39.3)	113 (43.0)	0.383
Echocardiographic findings				
Vegetation	325/515 (63.1)	167/266 (62.8)	154/245 (62.9)	0.986
No TAVR platform involvement	216 (39.1)	111 (39.0)	104 (39.5)	0.862
Periannular complication	94/393 (23.9)	43/186 (23.1)	50/204 (24.5)	0.747
New aortic regurgitation	54/421 (12.8)	27/190 (14.2)	27/217 (11.9)	0.483
New mitral regurgitation	69/408 (16.9)	35/182 (19.2)	32/222 (14.4)	0.195
Valves involved				
Isolated TAVR prosthesis	265 (48.0)	138 (48.4)	125 (47.5)	0.983
Mitral (native- or prosthetic)	77 (14.0)	38 (13.3)	38 (14.5)	
Cardiac device	21 (3.8)	10 (3.5)	11 (4.2)	
Right-sided IE	7 (1.3)	4 (1.4)	3 (1.1)	
Other	182 (33.0)	95 (33.3)	86 (32.7)	
Causative microorganisms				
Staphylococcus aureus	125/521 (24.0)	64/263 (24.3)	59/254 (23.2)	0.768
Methicillin Sensitive	105/521 (20.2)	49/263 (18.6)	55/254 (21.3)	0.077
Methicillin Resistant	20/521 (3.8)	15/263 (5.7)	5/254 (2.0)	
Coagulase-negative Staphylococci	95/521 (18.2)	47/263 (17.9)	48/254 (18.9)	0.763
Methicillin Sensitive	61/521 (11.7)	35/263 (13.3)	26/254 (10.2)	0.036

Methicillin Resistant	28/521 (5.4)	8/263 (3.0)	20/254 (7.9)	
Enterococci	131/521 (25.1)	66/263 (25.1)	65/254 (25.6)	0.897
Streptococci				
Oral streptococci	74/521 (14.2)	30/263 (11.4)	43/254 (16.9)	0.071
S. gallolyticus (S. bovis)	26/521 (5.0)	12/263 (4.6)	14/254 (5.5)	0.622
Others	23/521 (4.4)	16/263 (6.1)	6/254 (2.4)	0.036
Culture negative	31/521 (6.0)	16/263 (6.1)	15/254 (5.9)	0.923
Presumed source of entry				
Unknown	272 (49.3)	146 (51.2)	125 (47.5)	
Procedural TAVR related	10 (1.8)	5 (1.8)	5 (1.9)	
Urological	47 (8.5)	18 (6.3)	29 (11.0)	
Odontological	22 (4.0)	8 (2.8)	12 (4.6)	0.467
Pacemaker implantation	12 (2.2)	7 (2.5)	5 (1.9)	
Skin infection	20 (3.6)	12 (4.2)	8 (3.0)	
Vascular access	15 (2.7)	9 (3.2)	5 (1.9)	
Other	154 (27.9)	80 (28.1)	74 (28.1)	
Complications during IE				
Any complication	354/517 (68.5)	185/266 (69.6)	168 (67.7)	0.659
Heart failure	216/515 (41.9)	115/266 (43.2)	100/246 (40.7)	0.554
Acute renal failure	191/476 (40.1)	112/251 (44.6)	78/222 (35.1)	0.036
Septic shock	135/513 (26.3)	75/264 (28.4)	59/246 (24.0)	0.257
Stroke	51/512 (10.0)	32/264 (12.1)	19/245 (7.8)	0.101
Other systemic embolization	53/513 (10.3)	26/265 (9.8)	27/245 (11.0)	0.655
Persistent bacteremia	125/450 (27.8)	57/214 (26.6)	68/233 (29.2)	0.549
Surgery during IE hospitalization	100/532 (18.8)	48/277 (17.3)	52/251 (20.7)	0.321
Time to surgery, days	16.5 (6.5-35)	17 (5-36)	14 (8-35)	0.845
TAVR explantation	64/96 (66.7)	30/47 (63.8)	34/49 (69.4)	
Leads removed	18/96 (18.8)	7/47 (14.9)	11/49 (22.5)	0.160
Other	14/96 (14.6)	10/47 (21.3)	4/49 (8.2)	
Follow-up outcomes				
Follow-up, months	14.4 (4.7-32.2)	20.6 (5.8-44.5)	11.6 (3.7-25.9)	
Total person-year	674			
In-hospital mortality[b]	170 (32.0)	102 (36.4)	66 (26.6)	0.016
1-year mortality, % (95% CI)	46.6 (42.3-51.3)	53.5 (47.6-59.6)	37.8 (31.5-44.9)	<0.001[c]
Recurrence of IE	46/382 (12.0)			
Surgery during follow-up	11/382 (2.9)			

Values are n (%), median (IQR), or n/N (%) unless otherwise indicated. Abbreviations: CI, confidence interval; IE, infective endocarditis; IQR, interquartile range. [a]Time of TAVR was missing in 4 patients. [b]Data available in 532 patients. [c]Log-rank.

The proportion of patients presenting with complicated IE (including heart or renal failure, systemic embolisms, or uncontrolled infection) for the entire population was 68.5% (95% CI, 64.5–72.5%). The complication rate was similar in both groups except for a lower rate of acute renal failure in the CC (HC vs CC: 44.6% vs 35.1%; difference, 9.5%; 95% CI, .7–18.3%; p=0.036). The vast majority of patients were treated with antibiotics alone with no differences between groups in surgical intervention rates (HC vs CC: 17.3% vs 20.7%; p=0.321) despite the high percentage of patients with surgery indication in both groups (HC: 82.1%; CC: 79.5%). There was no substantial temporal variation concerning the distribution of antibiotic regimens: β-lactam antibiotics alone (HC vs CC: 20.5% vs 24.4%), β-lactam in combination with aminoglycosides (HC vs CC: 30% vs 31.7%), or vancomycin alone or in combination with other antibiotics (HC vs CC: 32.9% vs 28.3%). Among those patients undergoing surgery, TAVR explantation was the most frequent intervention (HC vs CC: 63.8% vs 69.4%; p=0.160). In-hospital death occurred in 170 patients, leading to an in-hospital mortality rate of 32.0% (95% CI, 28.0–35.9%) with a median survival of 22 days (IQR, 8–50 days). In-hospital mortality was lower in the CC (HC vs CC: 36.4% vs 26.6%; difference, 9.8%; 95% CI, 1.9–17.7%; p=0.016). Patients who survived the index hospitalization in the CC presented lower 1-year mortality rates (17.4%; 95% CI, 11.8–25.2%) compared with those who survived in the HC (28.1%; 95% CI, 21.8–35.8%; log-rank p<0.001) **(Figure 1.2).**

1.5.3 Factors Associated With Clinical Outcomes

The uni- and multivariable-adjusted Cox model determining the independent factors associated with in-hospital mortality are shown in **Table 1.3**. A higher risk profile for TAVR as determined by the logistic EuroSCORE (adjusted hazard ratio [HRadj], 1.02; 95% CI, 1.01–1.03; p=0.001), *S. aureus* etiology (HRadj, 1.71; 95% CI, 1.16–2.52; p=0.006) and IE-related complications such as stroke (HRadj, 1.77; 95% CI, 1.11–2.80; p=0.016), new-onset heart failure (HRadj, 2.07; 95% CI, 1.36–3.15; p=0.001), and acute renal failure during index hospitalization (HRadj, 2.54; 95% CI, 1.69–3.80; p<0.001) were independently associated with in-hospital mortality during the index IE episode.

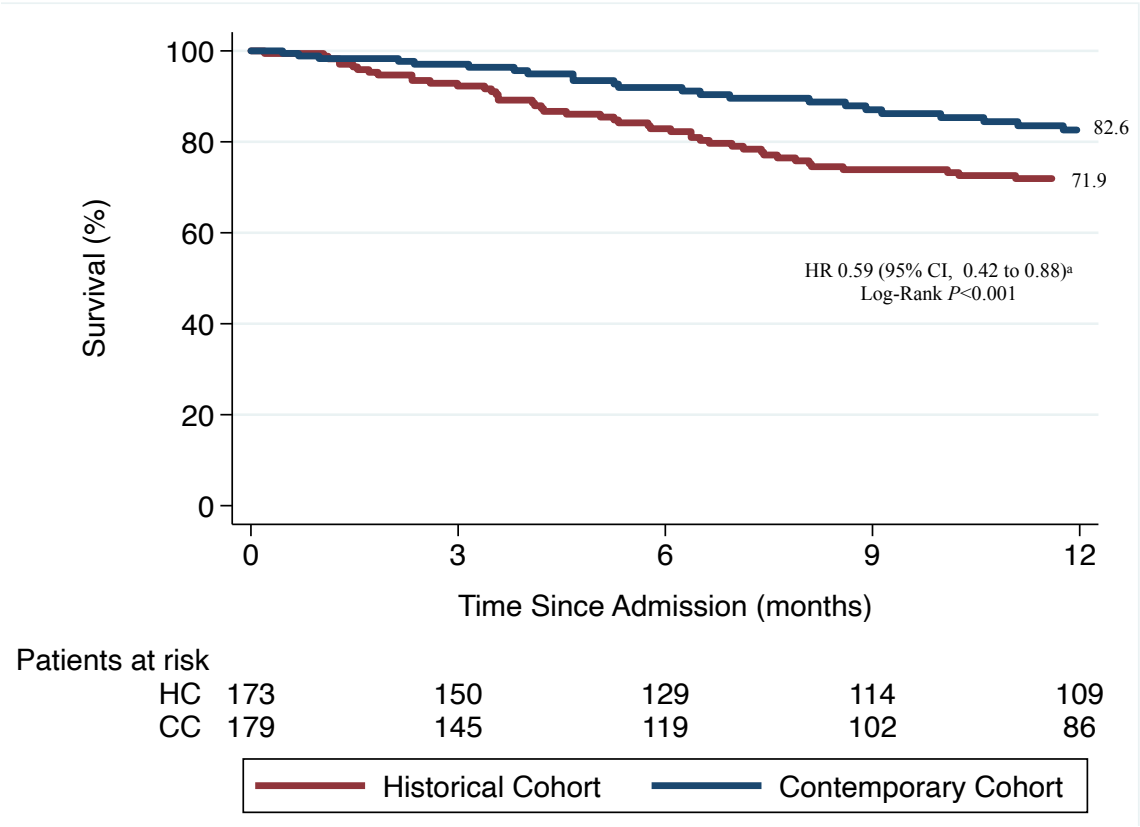

Figure 1.2. Kaplan–Meier estimate survival curve at the 1-year follow-up of patients who survived the infective endocarditis episode, comparing the HC and CC.

[a]HC as reference. Abbreviations: CC, contemporary cohort; CI, confidence interval; HC, historical cohort; HR, hazard ratio.

Although the number of TAVR procedures has increased exponentially in the last years, the incidence of IE has remained comparable over time. Nevertheless, our findings reveal a significant downward trend in the rate of early IE (within 60 days post- TAVR). Early IE is essentially related to the TAVR procedure, in-hospital period, and very early follow-up. The combination of 2 important factors may partially explain the decline in early IE incidence: first, the evolution of the TAVR procedure over the last years with simplified (and less invasive) procedures and device iterations that have translated into earlier patient ambulation and shorter hospital stay; and second, the profile of TAVR recipients has evolved towards patients with a lower comorbidity burden, who are generally exposed to fewer invasive diagnostic and therapeutic procedures, and therefore have a potentially lower risk of IE. Our data show that patients in the HC presented more comorbidities leading to a higher surgical risk and longer hospitalization length. In

contrast, despite being slightly older, low-to-moderate-risk patients were more represented in the CC.

Table 1.3. Factors associated with In-Hospital Mortality in Patients With Infective Endocarditis After Transcatheter Aortic Valve Replacement

	Univariate Analysis Hazard Ratio (95% CI)	Unadjusted p Value	Multivariate Analysis Hazard Ratio (95% CI)	Adjusted p Value
Baseline and TAVR features				
Logistic EuroSCORE[a]	1.02 (1.00-1.03)	0.0099	1.02 (1.01-1.03)	0.001
Chronic renal failure	1.71 (1.26-2.33)	0.0007		-
Implantation site				
Catheterization laboratory	1 [Reference]	-		-
Operating or hybrid room	1.57 (1.14-2.16)	0.0049		-
Approach				
Other	1 [Reference]	-		-
Transfemoral	0.56 (0.35-0.90)	0.0257		-
Post-TAVR acute renal failure	1.72 (1.17-2.55)	0.0102		-
Presenting symptoms				
Neurological	1.82 (1.27-2.60)	0.0020		-
New-onset heart failure	2.12 (1.55-2.91)	<0.0001	1.40 (0.95-2.06)	0.086
Microorganism				
Staphylococcus aureus	2.24 (1.62-3.10)	<0.0001	1.71 (1.16-2.52)	0.006
Oral streptococci	0.47 (0.26-0.84)	0.0047		-
S. gallolyticus (S. bovis)	0.92 (0.86-0.99)	0.0023		-
In-hospital complication				
Heart failure	3.29 (2.36-4.59)	<0.001	2.07 (1.36-3.15)	0.001
Acute renal failure	3.30 (2.35-4.63)	<0.001	2.54 (1.69-3.80)	<0.001
Stroke	2.14 (1.41-3.25)	0.0010	1.77 (1.11-2.80)	0.016

Abbreviations: CI, confidence interval; TAVR, transcatheter aortic valve replacement. [a]Per 1% increase.

Infective endocarditis post-TAVR was associated with a very high rate (~70%) of overall IE-related complications during the index hospitalization. Although heart failure, stroke, and persistent bacteremia rates were similar in both cohorts, there was a substantial decline in acute renal failure incidence over time. This aspect may be partially explained by the lower rate of pre-existing renal impairment in the CC group. Also, aminoglycosides (associated with nephrotoxicity) were no longer recommended as first-line therapy for

enterococci and methicillin-susceptible *S. aureus* in the latest American Heart Association and European Society of Cardiology guidelines,[31,38] and this may have also contributed to lowering the risk of acute renal failure. Of note, new-onset heart failure, acute renal failure, and stroke were independent predictors of in-hospital mortality. This highlights the importance of early identification of patients at high risk for complications who might benefit from aggressive therapies to improve clinical outcomes.

Previous studies on definite PVE have reported in-hospital mortality rates of approximately 20%.[29] The current study showed an even worse prognosis in TAVR recipients, with up to one-third of patients dying during the IE index hospitalization. The causes of such a high in-hospital mortality are probably multifactorial: first, the clinical profile of TAVR recipients, commonly elderly patients with a high comorbidity burden; second, IE diagnosis may be particularly challenging, with patients frequently presenting with atypical symptoms leading to a delay in treatment initiation; and third, the sensitivity of conventional imaging techniques for detecting vegetations seems relatively low compared with that reported in prior studies.[187] Nevertheless, there was a decreasing rate over time regarding in-hospital mortality, with a 9.8% absolute reduction in the most recent (vs HC) cohort. Although patients in the CC were older than those in the HC, they presented a much lower surgical risk profile, which likely reflects a better clinical status. Also, the growing use of novel imaging techniques (especially nuclear imaging) in recent years may have contributed to a more accurate diagnosis, leading to early treatment and improved outcomes in the CC. Unfortunately, data regarding time from initial symptoms to definite diagnosis were not available in most patients. Despite these improvements, the prognosis of patients who survived the initial IE episode remained uncertain, with a high mortality rate (close to 50%) at 1-year follow-up.

The most appropriate management of IE in patients post-TAVR remains unclear. Conservative treatment with only antibiotic therapy, even in the presence of severe IE-related complications, was the most frequent strategy (>80%), with no significant temporal trend changes. These results were in accordance with previous studies, which also reported very low rates of surgery and valve explantation (<15%).[157,170] Globally, surgery is the mainstay for the management of patients with complicated IE. Valve or

cardiac device explantation is the treatment of choice, with some series reporting up to 40–50% of surgical interventions during IE index hospitalization[60–62]. Nevertheless, the evidence in TAVR patients is limited and surgical recommendations cannot always be extrapolated to this population, who frequently exhibit an increased comorbidity burden and high-risk profile. One study, including a high-risk cohort of patients developing IE post-TAVR, showed no benefit in terms of mortality between surgery and conservative management.[174] Our study shows that, despite the presence of surgery criteria in more than 8 out of 10 patients, only those with lower risk underwent surgery, irrespective of underlying IE-related complications. Further studies are needed to determine the optimal indications and timing of surgery in this challenging population.

1.5.4 Study Limitations

This is an observational, retrospective study, with the limitations and potential bias of data collection inherent in this design. Also, there was no external monitoring committee to verify the accuracy of data reported by each center. Finally, since the study included only individual data on patients with definite IE, the determination of risk factors for developing IE was not feasible. Although a large subsample including all TAVR patients (with and without IE post-TAVR) with individual follow-up data was used to evaluate the incidence of IE, the lack of follow-up information in the overall TAVR population from all participating centers is a limitation that could lead to potential bias.

1.6 CONCLUSIONS

Infective endocarditis after TAVR can be considered as a distinct entity among patients with PVE, with a singular microbiological profile, high incidence of IE-related complications, an unresolved role of surgery, and a poor prognosis. Data from the historical and contemporary cohorts showed similar IE incidence rates but temporal improvements regarding the incidence of early IE and clinical outcomes, with lower in-hospital and 1-year mortality rates in recent times. Further studies are needed to further improve the prevention and management of IE post-TAVR.

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1.8 POTENTIAL CONFLICTS OF INTEREST

J. R.-C. has received institutional research grants from Edwards Lifesciences, Medtronic, and Boston Scientific. D. T. has reported consulting fees from Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic. J. G. W. has reported that he has received consulting fees from Edwards Lifesciences and St Jude Medical. R. M. has reported that he has received research grants from Edwards Lifesciences, Medtronic, Abbott, Capricor, and St Jude Medical; has served as a proctor for Edwards Lifesciences; and has received consulting fees from Medtronic. F. S. d. B. has reported that he has received honoraria from Medtronic and Edwards Lifesciences for symposium speeches and proctoring cases. S. L. has reported that he has received consulting fees from Edwards Lifesciences. H. L. B. reports lecture fees from Edwards Lifesciences, outside the submitted work. J. M. S. reports speaker honoraria from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic and research grants from Boston Scientific, Edwards Lifesciences, and Medtronic, outside the submitted work. K. W.-K. reports personal fees from Boston Scientific, Edwards Lifesciences, Abbott, Medtronic, and Meril, outside the submitted work. S. S. reports grants to the institution from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott and personal fees from Boston Scientific, BTG, and Teleflex, outside the submitted work. O. H. reports personal fees from Boston Scientific and payments from Abbott. N. M. reports personal fees from Edwards Lifesciences, Medtronic, Biotronik, Novartis, Sanofi Genzyme, AstraZeneca, Pfizer, and Bayer, outside the submitted work. All other authors report no potential conflicts. Howard C. Herrmann: Institutional research grants from Abbott, Boston Scientific, Edwards Lifesciences and Medtronic. Consulting fees from Edwards Lifesciences, and Medtronic. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

CHAPTER 2. Stroke Complicating Infective Endocarditis After Transcatheter Aortic Valve Replacement

David del Val, MD,[a] Mohamed Abdel-Wahab, MD,[b,c] Norman Mangner, MD,[b,d] Eric Durand, MD,[e] Nikolaj Ihlemann, MD,[f] Marina Urena, MD,[g] Costanza Pellegrini, MD,[h] Francesco Giannini, MD,[i,j] Tomasz Gasior, MD,[d] Wojtek Wojakowski, MD,[k] Martin Landt, MD,[c] Vincent Auffret, MD,[l] Jan Malte Sinning, MD,[m] Asim N. Cheema, MD,[n,o] Luis Nombela-Franco, MD,[p] Chekrallah Chamandi, MD,[q] Francisco Campelo-Parada, MD,[r] Erika Munoz-Garcia, MD,[s] Howard C. Herrmann, MD,[t] Luca Testa, MD,[u] Kim Won-Keun, MD,[v] Juan Carlos Castillo, MD,[w] Alberto Alperi, MD,[x] Didier Tchetche, MD,[y] Antonio L. Bartorelli, MD,[z] Samir Kapadia, MD,[aa] Stefan Stortecky, MD,[bb] Ignacio Amat-Santos, MD, PHD,[cc] Harindra C. Wijeysundera, MD,[dd] John Lisko, MD,[ee] Enrique Gutiérrez-Ibanes, MD,[ff] Vicenç Serra, MD,[gg] Luisa Salido, MD,[hh] Abdullah Alkhodair, MD,[ii] Ugolino Livi, MD,[jj] Tarun Chakravarty, MD,[kk] Stamatios Lerakis, MD,[ee,ll] Victoria Vilalta, MD,[mm] Ander Regueiro, MD,[nn] Rafael Romaguera, MD,[oo] Utz Kappert, MD,[d] Marco Barbanti, MD,[pp] Jean-Bernard Masson, MD,[qq] Frédéric Maes, MD,[rr] Claudia Fiorina, MD,[ss] Antonio Miceli, MD,[tt,uu] Susheel Kodali, MD,[vv] Henrique B. Ribeiro, MD,[ww,xx] Jose Armando Mangione, MD,[yy] Fabio Sandoli de Brito Jr, MD,[ww] Guglielmo Mario Actis Dato, MD,[zz] Francesco Rosato, MD,[aaa] Maria-Cristina Ferreira, MD,[bbb] Valter Correia de Lima, MD,[ccc] Alexandre Siciliano Colafranceschi, MD,[ddd] Alexandre Abizaid, MD,[ww] Marcos Antonio Marino, MD,[eee] Vinicius Esteves, MD,[fff] Julio Andrea, MD,[ggg] Roger R. Godinho, MD,[xx] Fernando Alfonso, MD,[hhh] Helene Eltchaninoff, MD,[e] Lars Søndergaard, MD,[f] Dominique Himbert, MD,[g] Oliver Husser, MD,[h,iii] Azeem Latib, MD,[i,jjj] Hervé Le Breton, MD,[l] Clement Servoz, MD,[r] Isaac Pascual, MD,[x] Saif Siddiqui, MD,[y] Paolo Olivares, MD,[z] Rosana Hernandez-Antolin, MD,[hh] John G. Webb, MD,[ii] Sandro Sponga, MD,[jj] Raj Makkar, MD,[kk] Annapoorna S. Kini, MD,[ll] Marouane Boukhris, MD,[qq] Philippe Gervais, MD,[a] Axel Linke, MD,[b,d] Lisa Crusius, MD,[b,d] David Holzhey, MD,[b] Josep Rodés-Cabau, MD, PHD[a,nn]

[a]Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada; [b]Heart Center Leipzig at University of Leipzig, Leipzig, Germany; [c]Heart Center, Segeberger Kliniken, Bad Segeberg, Germany; [d]Herzzentrum Dresden, Technische Universität Dresden, Dresden, Germany; [e]Normandie Univ, UNIROUEN, U1096, CHU Rouen, Department of Cardiology, FHU CARNAVAL, F-76000 Rouen, France; [f]Righospitalet, Copenhagen, Denmark; [g]Bichat Hôpital, Paris, France; [h]Deutsches Herzzentrum München, Munich, Germany; [i]Ospedale San Raffaele, Milan, Italy; [j]Maria Cecilia Hospital, GVM Care and Research, Cotignola RA, Italy; [k]Medical University of Silesia, Katowice, Poland; [l]Univ Rennes, CHU Rennes, Inserm, LTSI - UMR1099, F 35000 Rennes, France; [m]Heart Center Bonn, Bonn, Germany; [n]St Michaels Hospital, Toronto, Ontario, Canada; [o]Southlake Hospital, Newmarket, Ontario, Canada; [p]Cardiovascular Institute, Hospital Clínico San Carlos, IdISSC, Madrid, Spain; [q]Hôpital Européen Georges-Pompidou, Paris, France; [r]Hôpital Rangueil, Toulouse, France; [s]Hospital Universitario Virgen de la Victoria, Malaga, Spain; [t]Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [u]IRCCS Pol. San Donato, Milan, Italy; [v]Kerckhoff Heart and Thorax Centre, Bad Nauheim, Germany; [w]Hospital Universitario Reina Sofia, Cordoba, Spain; [x]Hospital Universitario Central de Asturias, Oviedo, Spain; [y]Clinique Pasteur, Toulouse, France; [z]Centro Cardiologico Monzino, IRCCS and Department of Biomedical and Clinical Sciences "Luigi Sacco," University of Milan, Milan, Italy; [aa]Cleveland Clinic, Cleveland, Ohio, USA; [bb]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (on behalf of Swiss TAVI); [cc]CIBERCV, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [dd]Sunnybrook Health Science Center, Toronto, Ontario, Canada; [ee]Emory University School of Medicine, Atlanta, Georgia, USA; [ff]Instituto de Investigación Universitaria Gregorio Marañón, Hospital Gregorio Marañón, Madrid, Spain; [gg]Hospital Vall d'Hebron, Barcelona, Spain; [hh]Hospital Universitario Ramón y Cajal, Madrid, Spain; [ii]St Paul's Hospital, Vancouver, British Columbia, Canada; [jj]University Hospital of Udine, Udine, Italy; [kk]Cedars-Sinai Heart Institute, Los Angeles, California, USA; [ll]Mount Sinai Hospital, New York, New York, USA; [mm]Hospital Germans Trias i Pujol, Badalona, Spain; [nn]Hospital Clínic de Barcelona, Barcelona, Spain; [oo]Hospital de Bellvitge, L'Hospitalet de Llobregat, Spain; [pp]A.O.U. Policlinico Vittorio Emanuele, University of Catania, Catania, Italy; [qq]Centre Hospitalier de l'Université de Montreal, Montreal, Quebec, Canada; [rr]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [ss]ASST-Spedali Civili di Brescia, Brescia, Italy; [tt]Istituto Clinico Sant'Ambrogio, Milan, Italy; [uu]University Hospital Galway, Galway, Ireland; [vv]Columbia University Medical Center, New York, New York, USA; [ww]InCor, Heart Institute, University of São Paulo Medical School, Sao Paulo, Brazil; [xx]Hospital Samaritano Paulista, Sao Paulo, Brazil; [yy]Hospital Beneficencia Portuguesa, Sao Paulo, Brazil; [zz]Ospedale Mauriziano, Torino, Italy; [aaa]Azienda Ospedaliera Santa Croce e Carle, Cuneo, Italy; [bbb]Hospital Naval Marcilio Dias, Rio de Janeiro, Brazil; [ccc]Hospital São Francisco-Santa Casa de Porto Alegre, Porto Alegre, Brazil; [ddd]Hospital Pró-cardíaco, Rio de Janeiro, Brazil; [eee]Hospital Madre Teresa, Belo Horizonte, Brazil; [fff]Hospital Sao Luiz, Sao Paulo, Brazil; [ggg]Clínica São Vicente, Rio de Janeiro, Brazil; [hhh]Hospital Universitario La Princesa, Madrid, Spain; [iii]St.-Johannes-Hospital, Dortmund, Germany; and the [jjj]Montefiore Medical Center, New York, New York, USA.

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2.1 RÉSUMÉ

Contexte : L'accident vasculaire cérébral (AVC) est une des complications les plus fréquentes et potentiellement invalidantes de l'endocardite infectieuse (EI). Cependant, il existe peu de données sur les AVC compliquant une EI après un remplacement valvulaire aortique percutané (TAVR).

Objectifs : L'objectif de cette étude était de déterminer l'incidence, les facteurs de risque, les caractéristiques cliniques, la prise en charge et les résultats des patients présentant une EI après TAVR compliquée d'un AVC.

Méthodes : Les données du registre international Infectious Endocarditis after TAVR (comprenant 569 patients ayant développé une EI certaine après un TAVR dans 59 centres de 11 pays) ont été analysées. Les patients ont été divisés en deux groupes en fonction de la survenue d'un AVC pendant l'hospitalisation pour EI (accident vasculaire cérébral [AVC-EI] ou non [NAVC-EI]).

Résultats : Au total, 57 (10 %) patients ont présenté un AVC pendant l'hospitalisation pour EI, sans que le micro-organisme responsable ne diffère entre les groupes. Les patients AVC-EI présentaient des taux plus élevés d'insuffisance rénale aiguë, d'embolisation systémique et de bactériémie persistante ($p < 0,05$ pour tous). Un AVC antérieur à l'EI, une régurgitation aortique résiduelle ≥ modérée après le TAVI, l'utilisation d'une valve expansible par ballonnet, la survenue d'une EI dans les 30 jours après le TAVI et une taille de végétation > 8 mm étaient associés à un risque plus élevé d'AVC pendant l'hospitalisation pour EI ($p < 0,05$ pour tous). Le taux d'AVC chez les patients ne présentant aucun facteur de risque était de 3,1 % et augmentait jusqu'à 60 % en présence de plus de 3 facteurs de risque. Les patients atteints d'AVC présentaient des taux plus élevés de mortalité pendant l'hospitalisation (54,4 % vs. 28,7 % ; $p < 0,001$) et de mortalité toutes causes à un an (66,3 % vs. 45,6 % ; $p < 0,001$). Le traitement chirurgical n'était pas associé à une amélioration des résultats chez les patients AVC-EI (mortalité hospitalière : 46,2 % en cas de traitement chirurgical vs. 58,1 % en l'absence de traitement chirurgical ; $p = 0,47$).

Conclusions : Un AVC est survenu chez 1 patient sur 10 présentant une EI après un TAVR. Un antécédent d'AVC, un court délai entre le TAVR et l'EI, la taille de la végétation, le type de prothèse valvulaire et la régurgitation aortique résiduelle étaient associés à un risque accru

d’AVC. La survenue d'un AVC était associée à une augmentation de la mortalité pendant l’hospitalisation et à un an, et le recours à un traitement chirurgical ne permettait pas d’améliorer le pronostic.

2.2 ABSTRACT

Background: Stroke is one of the most common and potentially disabling complications of infective endocarditis (IE). However, scarce data exist about stroke complicating IE after transcatheter aortic valve replacement (TAVR).

Objectives: The purpose of this study was to determine the incidence, risk factors, clinical characteristics, management, and outcomes of patients with definite IE after TAVR complicated by stroke during index IE hospitalization.

Methods: Data from the Infectious Endocarditis after TAVR International Registry (including 569 patients who developed definite IE following TAVR from 59 centers in 11 countries) was analyzed. Patients were divided into two groups according to stroke occurrence during IE admission (stroke [S-IE] vs. no stroke [NS-IE]).

Results: A total of 57 (10%) patients had a stroke during IE hospitalization, with no differences in causative microorganism between groups. S-IE patients exhibited higher rates of acute renal failure, systemic embolization, and persistent bacteremia ($p<0.05$ for all). Previous stroke before IE, residual aortic regurgitation ≥ moderate after TAVR, balloon-expandable valves, IE within 30 days after TAVR, and vegetation size >8 mm were associated with a higher risk of stroke during the index IE hospitalization ($p<0.05$ for all). Stroke rate in patients with no risk factors was 3.1% and increased up to 60% in the presence of >3 risk factors. S-IE patients had higher rates of in-hospital mortality (54.4% vs. 28.7%; $p<0.001$) and overall mortality at 1 year (66.3% vs. 45.6%; $p<0.001$). Surgical treatment was not associated with improved outcomes in S-IE patients (in-hospital mortality: 46.2% in surgical vs. 58.1% in no surgical treatment; $p=0.47$).

Conclusions: Stroke occurred in 1 of 10 patients with IE post-TAVR. A history of stroke, short time between TAVR and IE, vegetation size, valve prosthesis type, and residual aortic regurgitation determined an increased risk. The occurrence of stroke was associated with increased in-hospital and 1-year mortality rates, and surgical treatment failed to improve clinical outcomes.

2.3 INTRODUCTION

Infective endocarditis (IE) after transcatheter aortic valve replacement (TAVR) is a rare but serious complication associated with a high mortality rate.[165] This entity is often accompanied by life-threatening complications associated with a notoriously poorer prognosis. Neurological events, especially stroke, remain one of the most common and potentially disabling IE-related complications. In previous studies on native and surgical prosthetic-valve infective endocarditis (PVE), the incidence of acute stroke ranged from 20% to 40%, with associated mortality as high as 58%.[34] Although stroke occasionally represents the initial symptom that precipitates the diagnosis of IE, it is frequently identified during index IE hospitalization as the result of a cardioembolic event or intracranial cerebrovascular mycotic aneurysm rupture. Numerous studies have extensively evaluated the stroke risk in patients with native and/or PVE.[188–191] However, to date, no study has attempted to evaluate the predictors of stroke and outcomes in patients with IE following TAVR. Thus, current evidence concerning this particular complication has been extrapolated from data on surgical PVE. Nevertheless, this evidence is not always applicable to TAVR-IE patients, who represent a particular population with a unique clinical profile and a high comorbidity burden. The aim of this study was to determine the incidence, associated risk factors, clinical characteristics, management, and outcomes of patients with definite IE after TAVR complicated by stroke during the index IE hospitalization.

2.4 METHODS

2.4.1 The Infectious Endocarditis after TAVR International Registry

For this study, we used data from The Infectious Endocarditis After TAVR International Registry. Details concerning the design of this observational, multicenter, international registry have been reported previously.[156] Briefly, the registry included data from 604 patients with definite IE determined by the modified Duke criteria after TAVR from 59 centers in 11 countries across Europe, North America, and South America between June 2005 and November 2020. Informed consent was obtained from all patients before the procedure, and individual anonymized data sharing was performed according to the local ethics committee of each center.

2.4.2 Patient selection and data collection

Patients were identified retrospectively by each center according to the modified IE Duke criteria. Only TAVR patients developing definite IE were included regardless of the cardiac structure affected (native/ prosthetic valve and/or implantable cardiac device). To avoid duplicities, only the first episode of IE recorded for an individual patient was included in the analysis. A uniform dedicated case report form (database) was used at all sites for data collection that included baseline and periprocedural TAVR features as well as IE characteristics, microbiological profile, management, and in-hospital and follow-up outcomes. The global cohort was divided into 2 groups: 1) patients presenting stroke during the index infective endocarditis hospitalization (S-IE); and 2) patients without stroke during infective endocarditis admission (NS-IE). In total, 569 patients were finally included in the analysis (35 patients were excluded from the analysis because of missing data of stroke).

2.4.3 Definitions

The definition of definite IE was based on the modified Duke criteria.[45] Stroke was defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.[192] Perioperative mortality risk was defined according to the logistic EuroSCORE.[185] Transcatheter aortic valve type was divided into 2 groups: balloonexpandable (Edwards Sapien, Sapien XT, and Sapien 3 valve systems; Edwards Lifesciences, Irvine, California) and self-expanding or mechanically expandable valves (Medtronic CoreValve and Evolut R systems [Medtronic, Minneapolis, Minnesota], Lotus Valve System [Boston Scientific, Marlborough, Massachusetts], Portico valve [Abbott Vascular, Abbott Park, Illinois], Symetis Accurate [TA and neo] valve systems [Symetis SA, a Boston Scientific company, Ecublens, Switzerland], Direct flow valve [Direct Flow Medical Inc., Santa Rosa, California], JenaValve [JenaValve Technology Inc., Irvine, California], Medtronic Engager [Medtronic], and Centera valve [Edwards Lifesciences]). Clinical events were defined according to the Valve Academic Research Consortium-2 criteria.[184] Health care–associated IE was defined using Friedman et al. criteria.[186] Periannular complications and other systemic embolization were defined as previously reported.[156] Persistent bacteremia was defined as positive blood cultures despite appropriate antibiotic therapy for >7 days. Very early PVE was defined as occurring within 30 days after TAVR. Late endocarditis was defined as IE occurring >1 year following TAVR.[27,29,73]

2.4.4 Statistical analysis

Continuous variables were expressed as mean ± SD or median (interquartile range [IQR]) depending on variable distribution (assessed with the Kolmogorov-Smirnov test), and categorical variables as number (%). Group comparisons were performed using the Student's *t*-test or Wilcoxon rank-sum test for continuous variables, and chi-square or Fisher exact test for categorical variables. A multivariable logistic model was performed to determine the predictors of stroke in patients with IE post-TAVR. Baseline, TAVR procedure, and IE episode-related variables considered a priori to contribute to stroke during IE admission were included in the multivariable model. The variables with a p value <0.20 in the bivariate analysis were included in the multivariable model. Moreover, a multivariable Cox proportional hazard model was performed to determine the factors independently associated with 1-year mortality among patients with S-IE. Likewise, this model included all baseline, TAVR procedure, and IE episode-related variables considered a priori to contribute to 1-year mortality among this group of patients. The variables with a p value <0.20 in the bivariate analysis were included in the multivariable Cox model, with the only exception of the IE management (surgery vs. antibiotics alone) that was forced into the final model due to its potential relevance. Both models were built by backward stepwise (likelihood ratio) selection. The Kaplan-Meier method was used to provide survival estimates, and event times were measured from the date of initial IE symptoms to the date of death or last follow-up. Differences in the incidence of mortality were determined using the log-rank test. A 2-sided p value <0.05 was considered statistically significant. Data analyses were performed using Stata software version 15.1 (Stata Corp, College Station, Texas).

2.5 RESULTS

2.5.1 Baseline and TAVR procedural characteristics

A total of 569 patients with definite IE were identified of 40,183 patients undergoing TAVR. Among these patients, 57 (10%) had a stroke during the index IE hospitalization. The flowchart of the study population is shown in **Figure 2.1**. The main baseline and procedural characteristics comparing patients with and without stroke during IE admission are detailed in **Table 2.1**. Baseline characteristics were well-balanced with no differences between groups. TAVR procedures in S-IE patients were more frequently performed under general anesthesia/endotracheal intubation (S-IE: 63.2% vs. NS-IE: 46.9%; difference, 16.3; 95% CI: 3.0 to 29.5; p=0.023) and these patients were less likely to undergo TAVR through a

transfemoral approach (S-IE: 79.0% vs. NS-IE: 89.3%; difference, -10.3; 95% CI: -21.2 to -0.6; p=0.022). There were no differences between groups regarding valve type, but a tendency toward a higher proportion of stroke in patients treated with balloon-expandable valves was observed (S-IE: 63.2% vs. 51.0%; p=0.081). The rate of TAVR-related complications was similar between groups, except for a higher rate of periprocedural stroke in S-IE patients (S-IE: 15.8% vs. NS-IE: 3.3%; difference, 12.5; 95% CI: 2.9 to 22.1; p<0.001).

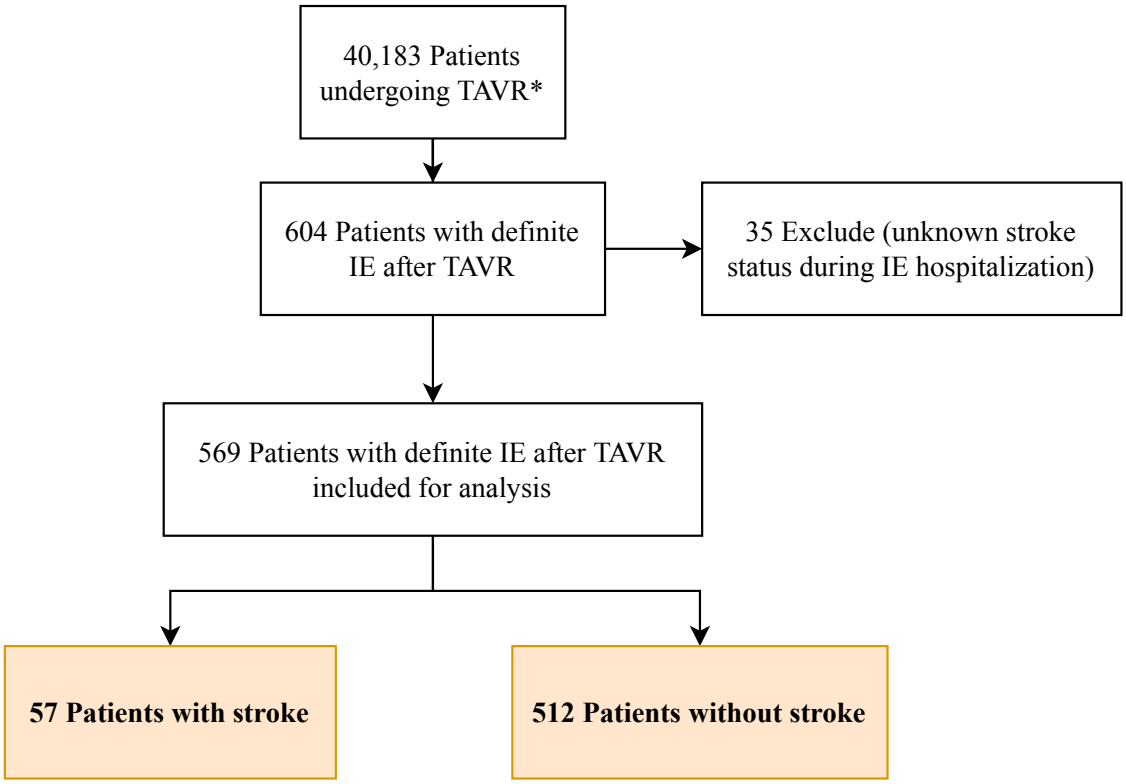

Figure 2.1. Flowchart of the Study Population

A total of 569 patients with definite infective endocarditis (IE) after transcatheter aortic valve replacement (TAVR) were included in the analysis. A total of 57 patients had a stroke during index IE hospitalization. *43 centers reported data on the total number of TAVR procedures.

Table 2.1. Baseline characteristics, procedural details, and in-hospital TAVR outcomes, comparing patients with and without stroke at index IE.

	No Stroke during IE admission (n=512)	Stroke during IE admission (n=57)	Unadjusted P value
Baseline characteristics			
Age, median (IQR), years	81 (76-85)	80 (74-83)	0.208
Female	191 (37.3)	20 (35.1)	0.742
Body mass index, (kg/m2)	26.7 (23.9-30.1)	28.4 (24.9-32.5)	0.085
Diabetes mellitus	187 (36.5)	23 (40.4)	0.570
COPD	137 (26.8)	18 (31.6)	0.438
Atrial fibrillation	215 (42.0)	25 (43.9)	0.796
Chronic renal failure	215 (42.0)	24 (42.1)	0.936
Previous Stroke	64 (12.5)	11 (19.3)	0.150
Previous valve surgery	61 (11.9)	4 (7.0)	0.267
Previous infectious endocarditis	8 (1.6)	1 (1.8)	0.915
Logistic EuroSCORE, %	13.6 (8.4-23.2)	14.7 (8.4-19.5)	0.879
Left ventricular ejection fraction, %	53.3 (13.6)	55.7 (12.7)	0.283
Mean transaortic gradient, mmHg	44.6 (15.9)	46.6 (15.5)	0.508
Aortic valve area, cm2	0.73 (0.23)	0.72 (0.21)	0.999
Periprocedural characteristics			
Implantation site			
Catheterization laboratory	203 (39.7)	27 (47.4)	0.260
Operating or hybrid room	309 (60.4)	30 (52.6)	
Approach			
Transfemoral	457 (89.3)	45 (79.0)	0.099
Transapical	36 (7.0)	8 (14.0)	
Transaxillary/subclavian	7 (1.4)	2 (3.5)	
Transaortic	10 (2.0)	2 (3.5)	
Prosthesis type			
Balloon-expandable	261 (51.0)	36 (63.2)	0.081
Self-expanding	251 (49.0)	21 (36.8)	
Antibiotic prophylaxis			
B-Lactam alone	428 (83.6)	43 (75.4)	0.122
Other	84 (16.4)	14 (24.6)	
Orotracheal intubation	240 (46.9)	36 (63.2)	0.023
In-hospital Outcomes (TAVR)			
Acute renal failure	63 (12.3)	6 (10.5)	0.645
Stroke	17 (3.3)	9 (15.8)	<0.001

Major vascular complication	36 (7.0)	1 (1.8)	0.160
Major bleeding	46 (9.0)	5 (8.8)	0.908
Sepsis	49 (9.6)	7 (12.3)	0.730
New pacemaker implantation	97 (19.0)	5 (8.8)	0.056
Residual aortic regurgitation ≥2 at discharge	64 (12.5)	12 (21.1)	0.091
Mean residual transaortic gradient, mmHg	11.2 (6.5)	10.6 (4.3)	0.945
Length of hospital stay, days	9 (6-14)	7 (5-16)	0.393

Values are median (interquartile range), n (%), or mean ± SD.
IE = infective endocarditis; TAVR = transcatheter aortic valve replacement.

2.5.2 Characteristics and clinical outcomes of the IE episode post-TAVR

The main features, management, and outcomes of the index IE episode after TAVR according to the occurrence of stroke are summarized in **Table 2.2**. Whereas the median time between TAVR and IE diagnosis was comparable between groups, the rate of very early IE (within 30 days) was higher in S-IE patients (S-IE: 26.3% vs. NS-IE: 15.6%; difference, 10.7; 95% CI: 1.2 to 22.5; p=0.04). Fever was the most common presenting symptom in both groups, but S-IE patients exhibited higher rates of any neurological symptoms (S-IE: 56.1% vs. NS-IE: 14.5%; difference, 41.6; 95% CI: 28.4 to 54.9; p<0.001) and systemic embolism other than stroke (S-IE: 42.1% vs. NS-IE: 9.6%; difference, 32.5; 95% CI: 19.5 to 45.6; p<0.001) at admission. Patients not presenting symptoms of infection represented only 4.0%. There were no differences concerning the anticoagulant treatment at presentation between groups. S-IE patients showed larger vegetations (S-IE: 12 mm [IQR: 10 to 18 mm] vs. NS-IE: 10 mm [6 to 15 mm]; p=0.003), but the incidence of periannular complications along with new-onset aortic or mitral valve regurgitation were similar in both groups. Isolated TAVR prosthesis was the most common cardiac structure affected, but the mitral valve was more frequently involved in S-IE patients (S-IE: 24.7% vs. NS-IE: 14.1%; difference, 10.6; 95% CI: 1.1 to 22.1; p=0.036). There were no differences regarding the causative microorganism, except for a higher proportion of *Staphylococcus aureus* methicillin-resistance in S-IE patients (S-IE: 37.5% vs. NS-IE: 15.1%; difference, 22.4; 95% CI: 2.2 to 47.0; p=0.028). Despite the high proportion of patients with unknown infection foci, the presumed entry source was similar between groups. Overall IE-related complications were high, but the proportion of patients presenting with acute renal failure (S-IE: 54.4% vs. NS-IE: 36.3%; difference, 18.1; 95% CI: 4.5 to 31.6; p=0.008), systemic embolization (S-IE: 54.4% vs. NS-IE: 13.9%; difference, 40.5; 95% CI: 27.3 to 53.8;

p<0.001) and persistent bacteremia (S-IE: 38.6% vs. NS-IE: 25.2%; difference, 13.4; 95% CI: 0.2 to 26.6; p=0.030) was substantially higher among S-IE patients.

Table 2.2 Main Clinical Characteristics, Management, and Outcomes of IE After TAVR, Comparing Patients With and Without Stroke at Index IE

	No Stroke during IE admission (n=512)	Stroke during IE admission (n=57)	Unadjusted P value
Time from TAVR, months	5.7 (1.8-14.5)	6.7 (1.0-12.5)	0.565
Very Early IE (<30 days)	80 (15.6)	15 (26.3)	0.040
Initial symptoms			
Fever	408 (79.7)	40 (70.2)	0.079
New-onset heart failure	211 (41.2)	24 (42.1)	0.953
Neurological	74 (14.5)	32 (56.1)	<0.001
Systemic embolism	49 (9.6)	24 (42.1)	<0.001
Skin lesions	24 (4.7)	2 (3.5)	0.999
Health care–associated infection	220 (43.0)	31 (54.4)	0.100
Anticoagulation treatment	191/440 (43.4)	25/52 (48.1)	0.521
Echocardiographic findings			
Vegetation	328/500 (65.6)	37/56 (66.1)	0.944
Transcatheter aortic valve stent frame*	61/220 (27.7)	3/25 (12.0)	0.090
Transcatheter aortic valve leaflets†	159/220 (72.7)	22/24 (88.0)	
Vegetation size, mm	10 (6-15)	12 (10-18)	0.003
Periannular complication	93/393 (23.7)	12/44 (27.3)	0.595
New aortic regurgitation	58/411 (14.1)	4/49 (8.2)	0.249
New mitral regurgitation	64/397 (16.1)	11/49 (22.5)	0.264
Valves involved			
Isolated TAVR prosthesis	248 (48.4)	27 (47.4)	0.878
Mitral (native- or prosthetic valve)	72 (14.1)	14 (24.7)	0.036
Cardiac device	20 (3.9)	3 (5.2)	0.622
Right-sided IE	7 (1.4)	1 (1.8)	0.814
Multi (2 localization at least)	165 (32.2)	12 (21.1)	0.084
Causative microorganisms			
Staphylococcus aureus	119/494 (24.1)	16/57 (28.1)	0.508
Methicillin Sensitive	101/119 (84.9)	10/16 (62.5)	0.028
Methicillin Resistant	18/119 (15.1)	6/16 (37.5)	
Coagulase-negative Staphylococci	87/494 (17.6)	8/57 (14.0)	0.499

Methicillin Sensitive	63/87 (72.4)	5/8 (62.5)	0.684
Methicillin Resistant	24/87 (27.6)	3/8 (37.5)	
Enterococci	127/494 (25.7)	14/57 (24.6)	0.851
Streptococci			
Oral streptococci	70/494 (14.2)	6/57 (10.5)	0.450
S. gallolyticus (S. bovis)	26/494 (5.3)	1/57 (1.8)	0.344
Others	17/494 (3.4)	5/57 (8.8)	0.066
Culture negative	29/494 (5.9)	6/57 (10.5)	0.160
Presumed source of entry			
Unknown	207 (40.3)	28 (49.1)	0.206
Procedural TAVR related	20 (3.9)	4 (7.0)	0.268
Urological	47 (9.2)	4 (7.0)	0.588
Odontological	22 (4.3)	2 (3.5)	0.779
Pacemaker implantation	11 (2.2)	1 (1.8)	0.844
Skin/soft tissue infection	16 (3.1)	4 (7.0)	0.130
Vascular access	18 (3.5)	0 (0.0)	0.240
Other	171 (33.4)	14 (24.6)	0.177
Complications during IE hospitalization			
Heart failure	211 (41.2)	28 (49.1)	0.251
Acute renal failure	186 (36.3)	31 (54.4)	0.008
Septic shock	135 (26.4)	21 (36.8)	0.093
Other systemic embolization‡	71 (13.9)	31 (54.4)	<0.001
Persistent bacteremia	129 (25.2)	22 (38.6)	0.030
Any complication	339 (66.2)	45 (79.0)	0.052
Management and Outcomes			
Antibiotic treatment alone	414 (80.9)	44 (77.2)	0.508
Antibiotic + Surgery during IE hospitalization	98 (19.1)	13 (22.8)	
Time to surgery, days	18 (7-36)	17 (8-47)	0.754
Valve replacement (TAVR and/or mitral)	66 (12.9)	12 (21.1)	0.089
Leads removed	17 (3.3)	1 (1.8)	0.522
In-hospital mortality	147 (28.7)	31 (54.4)	<0.001
Follow-up, months§	15.3 (4.7-34.6)	6.4 (2.3-20.2)	0.040
30-day mortality rate, (95% CI), %	20.1 (16.8-23.9)	28.2 (18.3-41.8)	0.113‖
1-year mortality rate, (95% CI), %	45.6 (41.1-50.3)	66.3 (53.2-79.0)	<0.001‖
Recurrence of IE	45/356 (12.6)	3/25 (12.0)	0.694
Surgery during follow-up	11/356 (3.1)	0/25 (0.0)	0.785

Values are median (interquartile range), n (%), or n/N (%). *Vegetations anchored to the transcatheter aortic valve stent frame. †Vegetations anchored to the transcatheter aortic valve leaflets. ‡Included patients presenting systemic embolism either at admission or during the index IE hospitalization. §Patients who survived in-hospital period. ‖By log-rank test. CI = confidence interval; other abbreviations as in Table 2.1.

2.5.3 Factors associated with stroke

The multivariable analysis for determining the factors associated with stroke among patients with IE post-TAVR are shown in **Figure 2.2**. The factors independently associated with stroke complicating IE post-TAVR were any history of previous stroke before IE episode (adjusted odds ratio [ORadj]: 2.56; 95% CI: 1.34 to 4.90; p=0.004), residual aortic regurgitation (AR) ≥moderate after TAVR (ORadj: 2.10; 95% CI: 1.01 to 4.40; p=0.048), balloon-expandable valves (ORadj: 1.90; 95% CI: 1.03 to 3.51; p=0.039), very early (within 30 days) IE (ORadj: 2.85; 95% CI: 1.41 to 5.74; p=0.003) and vegetation size >8 mm (ORadj: 2.99; 95% CI: 1.67 to 5.36; p<0.001). The incidence of stroke in patients with none of these risk factors was 3.1% (95% CI: 1.1% to 8.6%), whereas the incidence in patients with 1 to 4 risk factors was 6.1% (95% CI: 3.7% to 9.9%), 13.1% (95% CI: 8.9% to 18.8%), 28.9% (95% CI: 17.7% to 43.4%), and 60% (95% CI: 23.1% to 88.2%), respectively (**Figure 2.3**).

2.5.4 Management and outcomes.

The vast majority of patients were treated with antibiotics alone, and no differences were observed in the overall surgical treatment comparing S-IE (22.8%) and NS-IE (19.1%) patients (p=0.508). In-hospital death occurred in 178 (31.8%) patients. Patients with stroke had a higher in-hospital mortality compared with those patients without stroke (S-IE: 54.4% vs. NS-IE: 28.7%; difference, 25.7; 95% CI: 12.2 to 39.2; p<0.001). The median follow-up of patients who survived the in-hospital period was 14.6 months (IQR: 4.7 to 33.5 months). The Kaplan-Meier estimate survival curve at 1-year follow-up comparing patients with and without stroke is shown in **Figure 2.4**. The overall mortality rate at 1 year was higher in S-IE patients (66.3% vs. 45.6%; p<0.001 by log-rank test). The univariable and multivariable adjusted Cox models for determining the independent factors associated with 1-year mortality in patients with S-IE are shown in **Table 2.3**. Heart failure at admission (adjusted hazard ratio [HRadj]: 2.11%; 95% CI: 1.03 to 4.33; p=0.041), health care-associated infection (HRadj: 2.33%; 95% CI: 1.06 to 5.13; p=0.036) and persistent bacteremia despite appropriate antibiotic therapy (HRadj: 2.14; 95% CI: 1.04 to 4.39; p=0.038) were the independent factors associated with 1-year mortality in patients with S-IE. Surgical treatment was performed in 25% of S-IE patients at index IE hospitalization, but it was not associated with improved outcomes (in-hospital mortality: 46.2% and 58.1% in surgical vs. no surgical treatment; p=0.446). The rate of IE recurrence and surgery during follow-up was low (S-IE: 12% vs. NS-IE: 12.6% and S-IE: 0% vs. NS-IE: 3.1%, respectively), with no differences between groups (p>0.05).

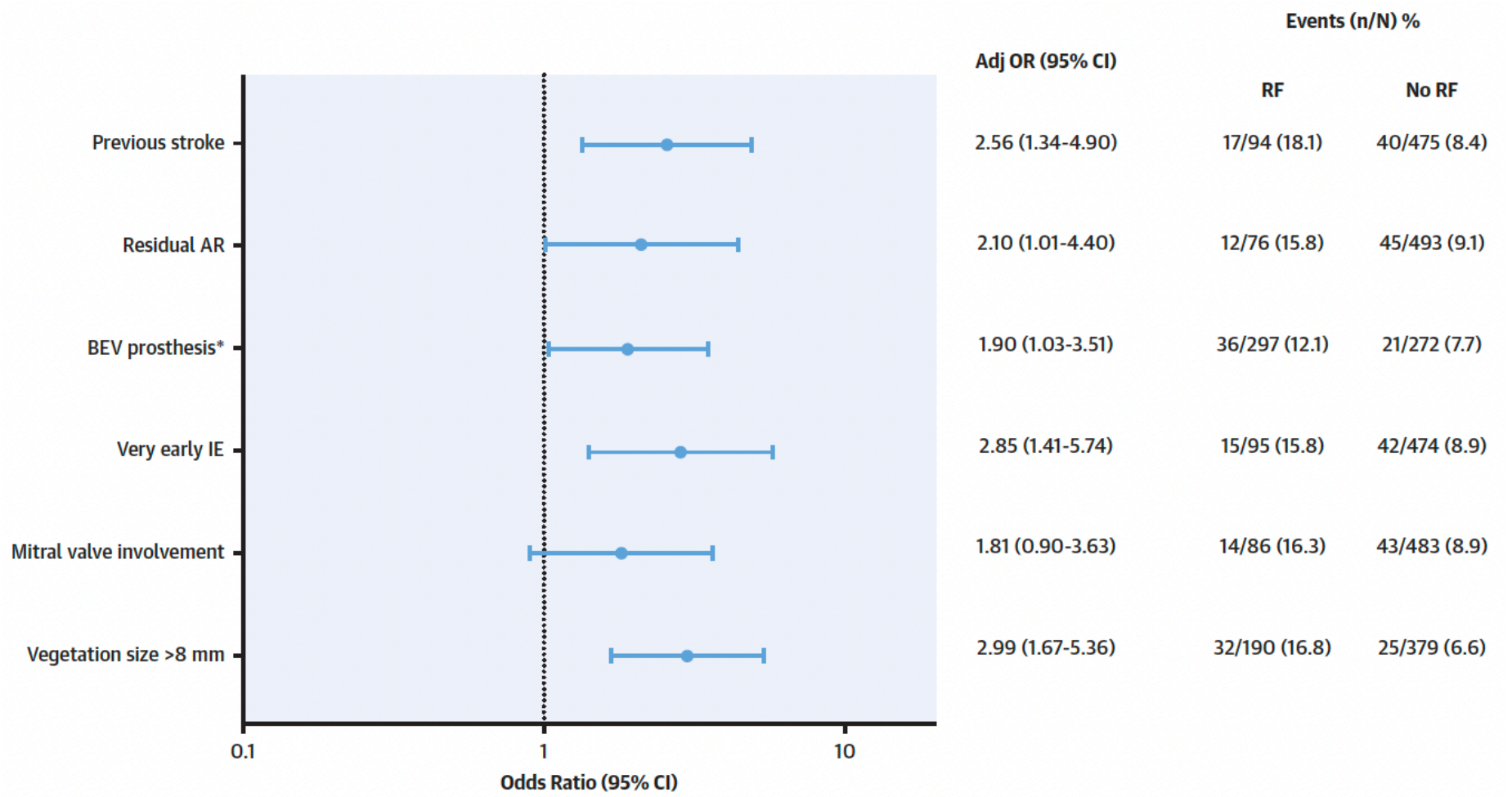

Figure 2.2 Factors Associated With Stroke in Patients With Infective Endocarditis After Transcatheter Aortic Valve Replacement

Predictors of stroke in patients with definite infective endocarditis (IE) after transcatheter aortic valve replacement (TAVR) in a multivariate logistic model. *Self-expanding valve as reference. AR = aortic regurgitation, BEV = balloon-expandable valve; CI = confidence interval; OR = odds ratio; RF = risk factor.

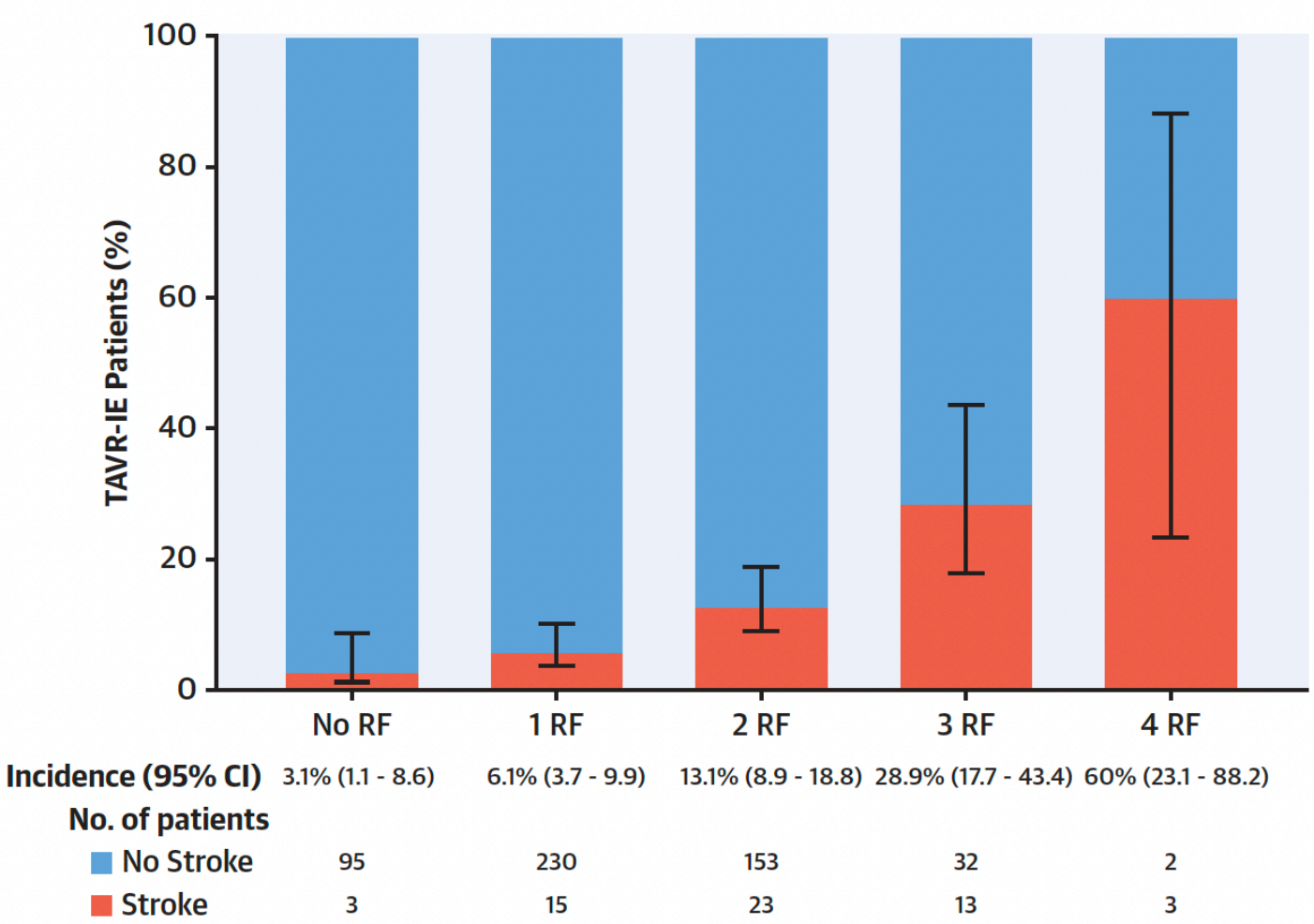

Figure 2.3. Stroke Incidence According to the Presence of RFs

Figure representing the incidence of stroke in patients with IE after TAVR according to the presence of RFs. The incidence of stroke in patients with no RFs was low, whereas the incidence progressively increases in patients with 1 to 4 RFs. Abbreviations as in Figure 2.2.

2.6 DISCUSSION

This is the first study evaluating patients who experienced stroke (as an IE-related complication) in a large and well-defined multicenter cohort of definite IE after TAVR. Our study yielded 5 major findings: 1) the incidence of stroke during IE admission was ~10%; 2) previous stroke (either at baseline or periprocedural TAVR stroke), residual AR ≥moderate after TAVR, balloon-expandable valves, IE within 30 days after TAVR, and vegetation size >8 mm were associated with an increased risk of stroke during index IE hospitalization; 3) the incidence of stroke in TAVR-IE patients with none of these risk factors was relatively low (3.1%), but the presence of risk factors determined a very high risk (6 of 10 TAVR-IE patients with >3 risk factors had a stroke during the index IE hospitalization); 4) S-IE patients showed an ominous prognosis, with >50% dying during index hospitalization and two-thirds within the first year; and 5) surgery rates were low (25%) even in the presence of stroke and failed to improve outcomes in this population **(Figure 2.4).**

TAVR has revolutionized the treatment of aortic stenosis and is currently moving toward less complex and younger patients with lower surgical risk. Despite the relatively low incidence of IE after TAVR, the number of procedures is expected to grow exponentially, increasing the number of patients at risk of developing this life-threatening complication. Therefore, detailed knowledge of this disease and its complications is essential to improve outcomes. Neurological events are the most frequent extracardiac complications in patients with IE, with series reporting an incidence up to 40%.[188,193,194] Although neurological complications comprise a wide clinical spectrum, acute brain embolization is one of the most common neurological events in patients with native- or surgical PVE. Our results showed a stroke incidence of ~10% during the index admission for IE after TAVR, substantially lower compared with those reported by the largest surgical PVE registries.[29] In the same direction, other IE-TAVR registries have reported a stroke incidence <10%.[154,170] Nevertheless, this rate may be underestimated, and some factors could explain these differences. First, elderly patients more frequently present with nonspecific symptoms, and stroke presentation can be misleading in the setting of systemic infection.[195] Second, this study included patients with clinical diagnosis of stroke combined with routine imaging techniques. However, prior studies have reported that advanced imaging modalities may detect subclinical cerebrovascular embolization in up to

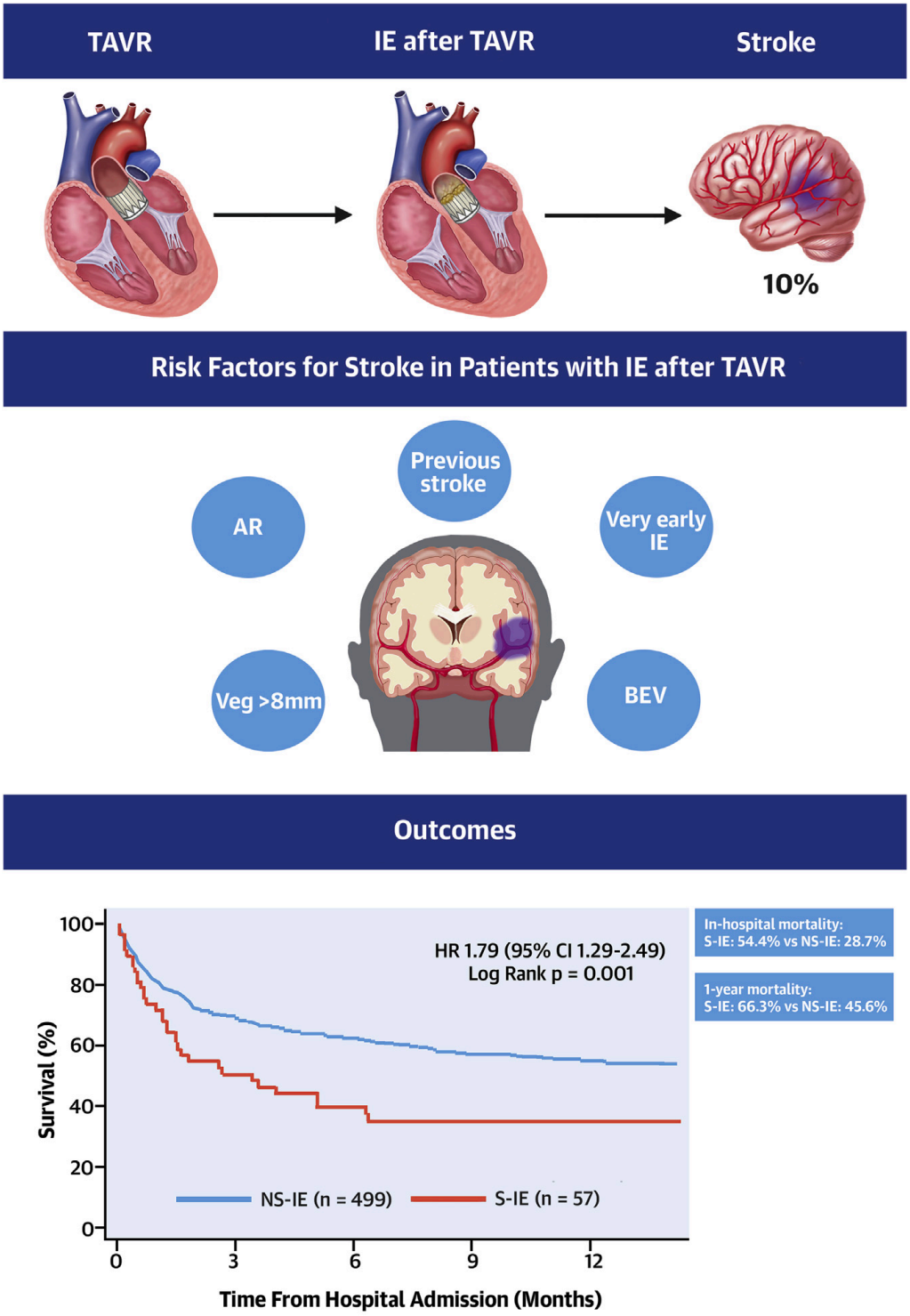

Figure 2.4. Stroke Complicating Infective Endocarditis After Transcatheter Aortic Valve Replacement.

The incidence of stroke during infective endocarditis (IE) admission after transcatheter aortic valve replacement (TAVR) was 10% (top). Previous stroke (either at baseline or periprocedural TAVR stroke), residual aortic regurgitation ≥2 after TAVR, balloon-expandable valves, IE within 30 days after TAVR, and vegetation size >8 mm were associated with a higher risk of stroke during the index IE hospitalization (middle). Impact on survival of stroke as a complication of IE after TAVR. Kaplan-Meier estimate survival curve at 1-year follow-up comparing patients with and without stroke at IE admission after TAVR (bottom). Statistical differences between groups were assessed using the log-rank test. Higher in-hospital and 1-year mortality rates were observed in patients with stroke at index IE hospitalization.

50% of IE patients.[196] Third, stroke diagnosis may be particularly challenging in patients with a high comorbidity burden, especially in the setting of septic shock or multiorgan failure. Therefore, the unique clinical profile of TAVR patients may lead to an underdiagnosis of stroke and might have influenced the apparently low incidence of stroke. Fourth, unlike IE in native or surgical bioprosthetic valves, a high proportion of patients with IE post-TAVR exhibit vegetations at the level of the stent valve frame (and not at the leaflet level), which may be less prone to embolize.

Numerous studies have determined the risk factors associated with stroke in patients with IE.[188,190,191] However, to our knowledge, this is the first study identifying the predictors of stroke in patients with IE after TAVR. Previous stroke (either at baseline or periprocedural TAVR stroke), residual AR ≥moderate after TAVR, balloon-expandable valves, IE within 30 days after TAVR, and vegetation size >8 mm were associated with a higher risk of stroke during the index IE hospitalization. These findings show similarities with those reported in previous studies, including patients with native- or surgical PVE. However, some aspects deserve particular attention. First, although controversial, vegetation size is a well-recognized predictor of stroke in patients with IE. Large vegetations, particularly those involving the mitral and aortic valves, have been associated with an increased risk of embolic events and mortality.[8] Also, a recent meta-analysis including patients with native valve IE showed a significant increase odd of embolism and mortality in patients presenting vegetations >10 mm.[197] Similarly, our findings also suggest a significant association of vegetation size and stroke, particularly in those patients presenting vegetations >8 mm. Second, the causative microorganism, especially *Staphylococcus aureus*, has been frequently associated with an increased risk of stroke in non-TAVR IE patients. In contrast, our data showed no evidence of this association in TAVR patients. The distinct microbiological profile of IE-TAVR population, with enterococci as the leading microorganism, may have influenced these results. Moreover, the present study may be underpowered to detect this association due to the relatively low number of patients in the S-IE group. Therefore, further studies are required to assess the association of *Staphylococcus aureus* and stroke in IE-TAVR patients. Third, prior stroke, before or during TAVR admission, was a strong predictor of stroke during IE hospitalization. As is well known, patients who survive an ischemic stroke are at increased risk of recurrent events, especially in those cases with a cardioembolic etiology.[198] In our cohort, almost 30% of the S-IE patients had a history of previous stroke before the IE episode.

Additionally, the proportion of patients on oral anticoagulation in our cohort was high (44%), mainly due to underlying atrial fibrillation. Thus, this represented a high-risk population for cerebrovascular events in addition to the supplemental embolic risk inherent to IE. Indeed, anticoagulant therapy has been associated with a deleterious effect during acute IE.[188,189] Although no association between any antithrombotic strategy and stroke risk in IE-TAVR patients was observed in our study, treatment decisions should balance the potential hazards of recurrent cardioembolic events against neurological complications related to IE. Fourth, our results suggest that valve type and valve performance may have an impact on the stroke risk in patients with IE after TAVR. Balloon-expandable valves and the presence of significant residual AR were associated with an increased risk of neurological events. Although previous studies have reported no differences in IE incidence rates comparing balloon- and self-expanding valves,[159] differences in mechanical and hemodynamic stress distribution inherent to platform design may influence the vegetation's location and development. In patients with native IE, a mechanical effect has been proposed as a propensity factor of vegetation embolization, with a greater risk of embolism associated with more mobile cardiac structures.[31] This mechanical effect could also modulate the risk of embolism in patients with IE post-TAVR. Therefore, the presence of a higher proportion of patients presenting vegetations anchored to the valve leaflets in balloon-expandable valve recipients may partially explain our findings. Also, given the low frame height of balloon-expandable prostheses, vegetations anchored to the stent frame tend to be in close proximity to valve leaflets, leading to an increased likelihood of vegetation fragment detachment and neurological events. The turbulent blood flow frequently associated with AR and the hyperdynamic circulatory state may also contribute to vegetation embolization and stroke. Nevertheless, these findings should be interpreted with caution, and further studies are warranted to confirm our results.

Previous studies, including native- and surgical PVE-IE patients, have reported that ~50% of the patients underwent surgery.[29,60,62] Consensus guidelines for managing patients with IE recommend surgery along with antibiotic treatment for patients developing systemic embolism, particularly stroke.[31,38] Surgery may be lifesaving in some specific conditions by reducing irreversible structural damage and severe complications, but it also carries a risk. This surgery-associated risk may explain the repeatedly low rates of surgical interventions reported in IE-TAVR studies.[156,174,179] The current study reveals that the low incidence of surgery in IE-

TAVR patients is also confirmed in those patients complicated by stroke. Although stroke should be considered per se a surgical indication in IE patients, our data showed that less than one-fourth of patients with such complication finally underwent surgery. Also, surgical interventions in S-IE patients seemed to be more complex, with more patients undergoing TAVR explantation and/or mitral valve replacement. Of note, surgery was not associated with a benefit in terms of mortality compared with conservative management in S-IE patients. These findings emphasize that surgery recommendations may not be extrapolated to TAVR-IE patients, and specific guidelines are warranted for this particular population. Furthermore, the possibility of early surgery in those patients with factors increasing the risk of stroke should be evaluated in future studies.

IE post-TAVR is associated with a poor prognosis with high in-hospital and late mortality rates.[165,181] Our study reveals that patients with IE after TAVR complicated by stroke showed an even worse prognosis, with more than one-half dying in the hospital after diagnosis and less than one-third still alive at 1 year. The progressive implementation of advanced imaging modalities for early IE diagnosis, especially nuclear imaging, may translate into a better prognosis in coming years. Close attention should be paid to early recognition of stroke-associated factors to improve clinical outcomes.

2.6.1 Study limitations

First, this was an observational study of retrospective nature, with the limitations and potential bias on data collection inherent to this design. Centers participated voluntarily, and there was no external monitoring committee to verify the accuracy of data reported by each center. Second, although stroke diagnosis was based on a harmonized definition, imaging techniques were used following local guidelines. Studies based on CT have reported a ~30% of undetected events compared with magnetic resonance imaging. For this reason, centers not including a systematic magnetic resonance imaging in the workup of suspected stroke might have underdiagnosed this IE-related complication. Third, due to the nature of the dataset, information concerning imaging findings was not available, and an appropriate description of brain injury was not possible. Fourth, data on specific stroke severity classification along with consequent disability were not available.

2.7 CONCLUSIONS

Stroke occurred in ~10% of the patients with IE after TAVR and was associated with dismal in-hospital and late outcomes. The rate of surgical treatment was low (~25%) and failed to improve patient survival. Previous stroke (either at baseline or periprocedural TAVR stroke), residual AR ≥moderate after TAVR, balloon-expandable valves, IE within 30 days after TAVR, and vegetation size >8 mm were associated with an increased risk of stroke in IE-TAVR patients. The presence of such factors (particularly in combination) may be considered for determining an earlier and more aggressive (medical or surgical) treatment in these patients. Future studies are warranted.

2.8 PERSPECTIVES

Competency in patient care and procedural skills: Stroke in patients with IE after TAVR is associated with poor in-hospital and late outcomes.

Translational outlook: Further research is needed to determine whether early surgical intervention based on specific risk factors can improve outcomes in patients with IE after TAVR.

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CHAPTER 3. Infective Endocarditis Caused by Staphylococcus aureus After Transcatheter Aortic Valve Replacement

David del Val, MD,[a] Mohamed Abdel-Wahab, MD,[b,c] Norman Mangner, MD,[b,d] Eric Durand, MD,[e] Nikolaj Ihlemann, MD,[f] Marina Urena, MD,[g] Costanza Pellegrini, MD,[h] Francesco Giannini, MD,[i,j] Tomasz Gasior, MD,[d] Wojtek Wojakowski, MD,[k] Martin Landt, MD,[c] Vincent Auffret, MD,[l] Jan Malte Sinning, MD,[m] Asim N. Cheema, MD,[n,o] Luis Nombela-Franco, MD,[p] Chekrallah Chamandi, MD,[q] Francisco Campelo-Parada, MD,[r] Erika Munoz-Garcia, MD,[s] Howard C. Herrmann, MD,[t] Luca Testa, MD,[u] Kim Won-Keun, MD MD,[v] Juan Carlos Castillo, MD,[w] Alberto Alperi, MD,[x] Didier Tchetche, MD,[y] Antonio L. Bartorelli, MD,[z] Samir Kapadia, MD,[aa] Stefan Stortecky, MD,[bb] Ignacio Amat-Santos, MD, PhD,[cc] Harindra C. Wijeysundera, MD,[dd] John Lisko, MD,[ee] Enrique Gutiérrez-Ibanes, MD,[ff] Vicenç Serra, MD,[gg] Luisa Salido, MD,[hh] Abdullah Alkhodair, MD,[ii] Igor Vendramin, MD,[jj] Tarun Chakravarty, MD,[kk] Stamatios Lerakis, MD,[ee,ll] Victoria Vilalta, MD,[mm] Ander Regueiro, MD,[nn] Rafael Romaguera, MD,[oo] Utz Kappert, MD,[d] Marco Barbanti, MD,[pp] Jean-Bernard Masson, MD,[qq] Frédéric Maes, MD,[rr] Claudia Fiorina, MD,[ss] Antonio Miceli, MD,[tt,uu] Susheel Kodali, MD,[vv] Henrique B. Ribeiro, MD,[ww,xx] Jose Armando Mangione, MD,[yy] Fabio Sandoli de Brito, Jr, MD,[ww] Guglielmo Mario Actis Dato, MD,[zz] Francesco Rosato, MD,[aaa] Maria-Cristina Ferreira, MD,[bbb] Valter Corriea de Lima, MD,[ccc] Alexandre Siciliano Colafranceschi, MD,[ddd] Alexandre Abizaid, MD,[ww] Marcos Antonio Marino, MD,[eee] Vinicius Esteves, MD,[fff] Julio Andrea, MD,[ggg] Roger R. Godinho, MD,[xx] Fernando Alfonso, MD,[hhh] Helene Eltchaninoff, MD,[e] Lars Søndergaard, MD,[f] Dominique Himbert, MD,[g] Oliver Husser, MD,[h,iii] Azeem Latib, MD,[i,jjj] Hervé Le Breton, MD,[l] Clement Servoz, MD,[r] Isaac Pascual, MD,[x] Saif Siddiqui, MD,[y] Paolo Olivares, MD,[z] Rosana Hernandez-Antolin, MD,[hh] John G. Webb, MD,[ii] Sandro Sponga, MD,[jj] Raj Makkar, MD,[kk] Annapoorna S. Kini, MD,[ll] Marouane Boukhris, MD,[qq] Philippe Gervais, MD,[a] Axel Linke, MD,[b,d] Lisa Crusius, MD,[b,d] David Holzhey, MD,[b] and Josep Rodés-Cabau, MD[a,nn]

[a]Québec Heart & Lung Institute, Laval University, Québec City, Québec, Canada; [b]Heart Center Leipzig at University of Leipzig, Leipzig, Germany; [c]Heart Centre, Segeberger Kliniken, Bad Segeberg, Germany; [d]Herzzentrum Dresden, Technische Universität Dresden, Germany; [e]Normandie Univ, UNIROUEN, U1096, CHU Rouen, Department of Cardiology, FHU CARNAVAL, F-76000 Rouen, France; [f]Righospitalet, Copenhagen, Denmark; [g]Bichat Hôpital, Paris, France; [h]Deutsches Herzzentrum München, Munich, Germany; [i]Ospedale San Raffaele, Milan, Italy; [j]Maria Cecilia Hospital, GVM Care and Research, Cotignola RA, Italy; [k]Medical University of Silesia, Katowice, Poland; [l]Univ Rennes, CHU Rennes, Inserm, LTSI - UMR1099, F 35000 Rennes, France; [m]Heart Centre Bonn, Bonn, Germany; [n]St Michaels Hospital, Toronto, Ontario, Canada; [o]Southlake Hospital, Newmarket, Ontario, Canada; [p]Cardiovascular Institute, Hospital Clínico San Carlos, IdISSC, Madrid, Spain; [q]Hôpital Européen Georges-Pompidou, Paris, France; [r]Hôpital Rangueil, Toulouse, France; [s]Hospital Universitario Virgen de la Victoria, Malaga, Spain; [t]Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [u]IRCCS Policlinico San Donato, Milan, Italy; [v]Kerckhoff Heart and Thorax Centre, Bad Nauheim, Germany; [w]Hospital Universitario Reina Sofia, Cordoba, Spain; [x]Hospital Universitario Central de Asturias, Oviedo, Spain; [y]Clinique Pasteur, Toulouse, France; [z]Centro Cardiologico Monzino, IRCCS and Department of Biomedical and Clinical Sciences "Luigi Sacco," University of Milan, Milan, Italy; [aa]Cleveland Clinic, Cleveland, Ohio, USA; [bb]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (on behalf of Swiss TAVI); [cc]CIBERCV, Hospital Clinico Universitario de Valladolid, Valladolid, Spain; [dd]Sunnybrook Health Science Centre, Toronto, Ontario, Canada; [ee]Emory University School of Medicine, Atlanta, Georgia, USA; [ff]Instituto de Investigación Universitaria Gregorio Marañón, Hospital Gregorio Marañón, Madrid, Spain; [gg]Hospital Vall d'Hebron, Barcelona, Spain; [hh]Hospital Universitario Ramón y Cajal, Madrid, Spain; [ii]St Paul's Hospital, Vancouver, British Columbia, Canada; [jj]University Hospital of Udine, Udine, Italy; [kk]Cedars-Sinai Heart Institute, Los Angeles, California, USA; [ll]Mount Sinai Hospital, New York, New York, USA; [mm]Hospital Germans Trias i Pujol, Badalona, Spain; [nn]Hospital Clinic, Barcelona, Spain; [oo]Hospital de Bellvitge, l'Hospitalet de Llobregat, Spain; [pp]AOU Policlinico Vittorio Emanuele, University of Catania, Catania, Italy; [qq]Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada; [rr]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [ss]ASST-Spedali Civili di Brescia, Brescia, Italy; [tt]Istituto Clinico Sant'Ambrogio, Milan, Italy; [uu]University Hospital Galway, Galway, Ireland; [vv]Columbia University Medical Center, New York, New York, USA; [ww]InCor, Heart Institute, University of São Paulo Medical School, Sao Paulo, Brazil; [xx]Hospital Samaritano Paulista, São Paulo, Brazil; [yy]Hospital Beneficencia Portuguesa, São Paulo, Brazil; [zz]Ospedali Mauriziano, Torino, Italy; [aaa]Azienda Ospedaliera Santa Cocre e Carle, Cuneo, Italy; [bbb]Hospital Naval Marcilio Dias, Rio de Janeiro, Brazil; [ccc]Hospital São Francisco-Santa Casa de Porto Alegre, Porto Alegre, Brazil; [ddd]Hospital Pró-cardíaco, Rio de Janeiro, Brazil; [eee]Hospital Madre Teresa, Belo Horizonte, Brazil; [fff]Hospital São Luiz, Sao Paulo, Brazil; [ggg]Clínica Sao Vicente, Rio de Janeiro, Brazil; [hhh]Hospital Universitario de La Princesa, Madrid, Spain; [iii]St-Johannes-Hospital, Dortmund, Germany; [jjj]Montefiore Medical Center, New York, New York, USA.

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3.1 RÉSUMÉ

Contexte : Staphylococcus aureus (SA) a fait l'objet de nombreuses études en tant qu'agent causal de l'endocardite infectieuse (EI) sur prothèse valvulaire. Cependant, il existe peu de données probantes sur l'EI causée par SA survenant après un remplacement valvulaire aortique percutané (TAVR).

Méthodologie : Les données provenaient de l'Infectious Endocarditis After TAVR International Registry et concernaient notamment des patients chez qui une EI caractérisée s'était déclarée après un TAVR dans 59 centres répartis dans 11 pays. Les patients ont été divisés en deux groupes selon l'étiologie microbiologique, à savoir : EI non causée par SA vs EI causée par SA.

Résultats : Une EI causée par SA a été recensée chez 141 patients sur 573 (24,6 %) ; dans la plupart des cas (115/141, 81,6 %), SA était sensible à la méthicilline. Chez les patients atteints d'EI précoce causée par SA, les dispositifs implantés étaient plus souvent des prothèses autodéployées que des prothèses déployées par ballonnet. Des saignements majeurs et un sepsis compliquant le TAVR, des symptômes neurologiques ou une embolie systémique à l'admission et des EI mettant en cause des dispositifs cardiaques (autres que des TAVR) étaient associés à l'EI causée par SA ($p < 0,05$ dans tous les cas). Chez les patients atteints d'EI après un TAVI, la probabilité d'EI causée par SA passait de 19 % en l'absence de ces facteurs de risque à 84,6 % si ≥ 3 facteurs de risque étaient présents. Les taux de mortalité hospitalière (47,8 % vs 26,9 % ; $p < 0,001$) et de mortalité à 2 ans (71,5 % vs 49,6 % ; $p < 0,001$) étaient plus élevés chez les patients atteints d'EI causée par SA que chez ceux atteints d'EI non causée par SA. La chirurgie lors de la survenue du cas index d'un épisode d'EI causée par SA était associée à une mortalité plus faible durant la période de suivi par rapport au traitement médical seul (rapport des risques instantanés corrigé : 0,46, IC à 95 % : 0,22-0,96 ; $p = 0,038$).

Conclusions : L'EI causée par SA représentait environ 25 % des cas d'EI qui se sont déclarés après un TAVR et était associée à des taux très élevés de mortalité hospitalière et de mortalité tardive. La présence de certaines caractéristiques déterminerait une probabilité plus élevée d'EI causée par SA et pourrait aider à orienter le choix de l'antibiothérapie. La chirurgie lors de la survenue du cas index d'EI causée par SA se trouvait associée à de meilleurs résultats, et son rôle devrait être évalué dans le cadre des études à venir.

3.2 ABSTRACT

Background: *Staphylococcus aureus* (SA) has been extensively studied as causative microorganism of surgical prosthetic-valve infective endocarditis (IE). However, scarce evidence exists on SA IE after transcatheter aortic valve replacement (TAVR).

Methods: Data were obtained from the Infectious Endocarditis After TAVR International Registry, including patients with definite IE after TAVR from 59 centers in 11 countries. Patients were divided into 2 groups according to microbiologic etiology: non-SA IE vs SA IE.

Results: SA IE was identified in 141 patients out of 573 (24.6%), methicillin-sensitive SA in most cases (115/141, 81.6%). Self-expanding valves were more common than balloon-expandable valves in patients presenting with early SA IE. Major bleeding and sepsis complicating TAVR, neurologic symptoms or systemic embolism at admission, and IE with cardiac device involvement (other than the TAVR prosthesis) were associated with SA IE ($P < 0.05$ for all). Among patients with IE after TAVR, the likelihood of SA IE increased from 19% in the absence of those risk factors to 84.6% if ≥3 risk factors were present. In-hospital (47.8% vs 26.9%; $P < 0.001$) and 2-year (71.5% vs 49.6%; $P < 0.001$) mortality rates were higher among patients with SA IE vs non-SA IE. Surgery at the time of index SA IE episode was associated with lower mortality at follow-up compared with medical therapy alone (adjusted hazard ratio: 0.46, 95% CI 0.22-0.96; $P = 0.038$).

Conclusions: SA IE represented approximately 25% of IE cases after TAVR and was associated with very high in-hospital and late mortality. The presence of some features determined a higher likelihood of SA IE and could help to orientate early antibiotic regimen selection. Surgery at index SA IE was associated with improved outcomes, and its role should be evaluated in future studies.

3.3 INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has revolutionised the management of severe symptomatic aortic stenosis. Infective endocarditis (IE) after TAVR is a rare but life-threatening complication associated with high in-hospital and long-term mortality rates.[156,165,181] Despite the evolution of the TAVR procedure (simplified and less invasive) along with device iterations, the overall incidence of IE after TAVR has remained stable over time.[199] In the near future, the number of TAVR procedures is expected to rise owing to its expansion to the treatment of younger and lower surgical risk patients. Therefore, the total number of patients at risk of developing this life-threatening complication may increase substantially.

Staphylococcus aureus (SA) remains the most frequent microorganism in both community-acquired and hospital-acquired bacteremia, with mortality rates ranging from 10% to 30%.[60,200,201] The increasing exposure to medical procedures along with the increasing number of patients with implantable medical devices (prosthetic heart valves, implantable cardiac devices, grafts) has translated into SA becoming the predominant causative microorganism of native or surgical prosthetic valve endocarditis in developed countries.[29,31,60] TAVR patients represent an elderly population with a high comorbidity burden and exposure to health care-associated procedures. Thus, these patients have a significant potential risk of bloodstream infections and IE due to SA. In the surgical field, several studies have suggested that prosthetic-valve IE (PVE) caused by SA is associated with worse clinical outcomes and high early mortality rates compared with other forms of IE.[202] Nevertheless, scarce data exist on SA IE in TAVR recipients, and fundamental features and prognosis of this particular group of patients remain unknown. The purpose of the present study was to evaluate the clinical characteristics, management, and in-hospital and late outcomes of patients with SA IE after TAVR.

3.4 METHODS

3.4.1 The Infectious Endocarditis After TAVR International Registry

Data from the Infectious Endocarditis After TAVR International Registry were used for this study. Briefly, the registry included data from 604 patients from 59 centers in 11 countries across Europe, North America, and South America from June 2005 to December 2020 with

definite IE, as determined by the modified Duke criteria, after TAVR (regardless of the structure involved). Informed consent was obtained from all patients before the procedure, and the individual anonymised data sharing was performed according to the ethics committee of each center, in compliance with the Declaration of Helsinki.

3.4.2 Patient selection and data collection

Each center retrospectively identified patients according to the modified Duke criteria. Only TAVR patients, regardless of the structure affected (native/prosthetic valve or implantable cardiac device), developing definite IE were included. Only the first episode of IE recorded for an individual patient was included in the analysis. A dedicated case report form was used at all sites for data collection that included baseline and periprocedural TAVR features, as well as IE characteristics, microbiological profile, management, and in-hospital and follow-up outcomes (191 variables). Based on the microbiological profile, the global cohort was divided into 2 groups of patients: patients with IE after TAVR caused by SA (SA IE), and patients with IE after TAVR caused by another microorganism (non-SA IE). Non-SA IE included enterococci (33.6%), coagulase-negative staphylococci (24.1%), oral streptococci (18.3%), *Streptococcus gallolyticus* (6.9%), other streptococci (5.3%), culture-negative IE (8.3%), and other pathogens (4.5%). A total of 573 patients with well documented data on IE etiology (94.9% of the entire cohort) were included in the analysis. After the index IE, the median follow-up was 15 (interquartile range [IQR] 5-33) months, and follow-up was complete in 96.7% of the patients (19 patients were lost to follow-up).

3.4.3 Definitions

Definite IE was based on the modified Duke criteria.[45] Perioperative mortality risk was defined according to the logistic EuroSCORE. Transcatheter aortic valve type was divided into 2 groups: balloon-expandable valves (BEVs) and self-expanding valves (SEVs) or mechanically expandable valves **(Supplemental Table 3.1)**. Clinical end points were defined according to the Valve Academic Research Consortium 2 criteria.[184] Periannular complications and other systemic embolisation were defined as previously reported.[156] Persistent bacteremia was defined as positive blood cultures despite appropriate antibiotic therapy for > 7 days. Health care-associated IE was defined with the Friedman criteria.[186] Early prosthetic valve

endocarditis was defined as occurring within 12 months from TAVR. The presumed source of entry was determined by each site investigator based on medical records.

3.4.4 Statistical analysis

Depending on the variable distribution, which was assessed by means of the Shapiro-Wilk test, continuous variables were expressed as mean ± SD or median (IQR). Categoric variables were expressed as n (%). Group comparisons between groups were analysed with the use of the Student *t* test or Wilcoxon rank-sum test for continuous variables and $\chi 2$ or Fisher exact test for categoric variables. For bivariable analysis, patients with missing data were excluded. A multivariable Cox proportional hazard model was performed to determine the factors independently associated with 2-year mortality among patients with SA IE. This model included all variables considered a priori to contribute to in-hospital mortality. A multivariable logistic model was also performed to determine the associated factors of SA IE. Likewise, all variables considered a priori to contribute to SA IE were included in the multivariable model. The variables with a P value < 0.10 in the bivariate analysis were included in the multivariable models. Both models were built by backward stepwise (likelihood ratio) selection, and IE with TAVR involvement and surgery during IE hospitalisation were forced to remain in the Cox model. We used the Kaplan-Meier method to provide survival estimates, assessed with the use of a log-rank test. Event times were measured from initial IE symptoms to the date of death or last follow-up. Differences in the incidence of mortality were determined by means of the log-rank test. A 2-sided P value < 0.05 was considered to be statistically significant. Data analyses were performed with the use of Stata (version 15.1; Stata Corp, College Station, TX) and Prism (GraphPad Software, San Diego, CA) software.

3.5 RESULTS

3.5.1 Baseline and TAVR procedural characteristics

Definite IE was diagnosed in 604 patients after TAVR, and 31 were excluded for the analysis due to missing data of post- TAVR IE microbiologic etiology. The flowchart of the study population is depicted in **Figure 3.1**. SA IE was detected in 141 patients out of the 573 (24.6%), and most of them were associated with methicillin-sensitive SA (115 patients, 81.6%). Baseline and procedural features of the study population grouped according to the microbiological profile (SA IE vs non-SA IE) are presented in **Table 3.1**. Underlying

comorbidities and surgical risk determined by the logistic EuroSCORE were well balanced in both groups, except for a higher median body mass index in non-SA IE patients (27.2 kg/m2 [IQR 24.4-30.9] vs 25.6 kg/m2 [IQR 23.4-28.9]; P = 0.001). Although there were no differences regarding the type of valve and IE etiology in the overall cohort, patients presenting early SA IE were more likely to have SEVs (59.4% vs 47.1% in patients with BEVs; P = 0.041). TAVR-related complications were more frequent in patients with SA IE compared with non-SA IE, including acute renal failure (19.2% vs 10.4%; P = 0.005), stroke (8.5% vs 3.2%; P = 0.008), and sepsis (16.3% vs 7.9%; P = 0.001). Although the median length of hospital stay was similar in both groups, patients with SA IE presented longer hospitalisations in an acute care facility after TAVR (2 days [IQR 1-5] vs 1.5 days [IQR 1-3]; P = 0.011).

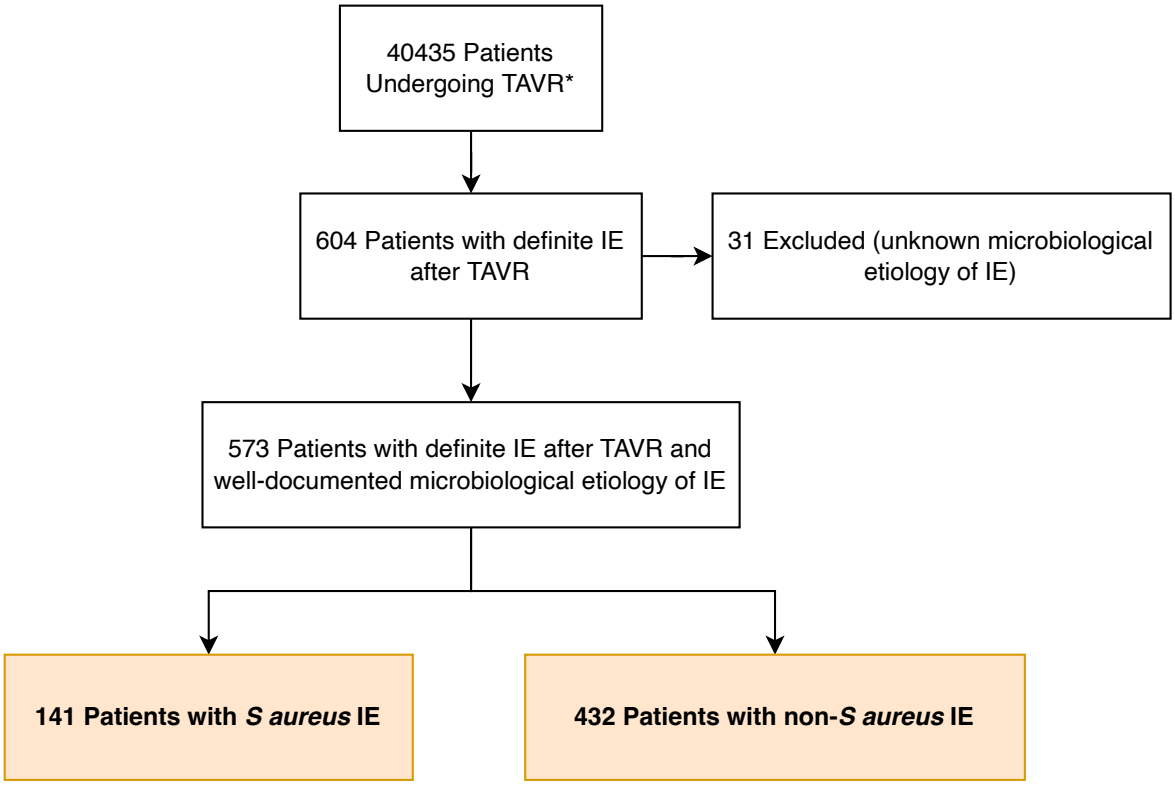


Figure 3.1. Flow-chart of study population of patients with infective endocarditis (IE) after transcatheter atrial valve replacement (TAVR).

*Forty-four centers reported data on the total number of TAVR procedures.

Table 3.1. Baseline characteristics, procedural details, and in-hospital TAVR outcomes, according to the causative microorganism (S. aureus vs non-S. aureus) of IE.

	Non-*S. Aureus* (n=432)	*S aureus* IE (n=141)	Unadjusted P value
Baseline characteristics			
Age, years	81 (75-84)	80 (75-84)	0.579
Female	154 (35.7)	58 (41.1)	0.241
Body mass index (kg/m2)	27.2 (24.4-30.9)	25.6 (23.4-28.9)	0.001
Diabetes mellitus	160 (37.0))	54 (38.3)	0.788
COPD	112 (25.9)	44 (31.2)	0.221
Atrial fibrillation	186 (43.1)	56 (39.7)	0.473
Chronic renal failure	173 (40.1)	67 (47.5)	0.162
Previous Stroke	61 (14.1)	15 (10.6)	0.290
Previous valve surgery	48 (11.1)	14 (9.9)	0.683
Previous infectious endocarditis	6 (1.4)	3 (2.1)	0.545
Logistic EuroSCORE, %	14.0 (8-23.4)	13.5 (8.7-21.4)	0.581
Left ventricular ejection fraction, %	54.3 (13.1)	51.5 (14.5)	0.067
Mean transaortic gradient, mmHg	46.0 (15.5)	41.7 (16.0)	0.005
Aortic valve area, cm2	0.73 (0.22)	0.72 (0.25)	0.532
Periprocedural characteristics			
Implantation site			
Catheterization laboratory	181 (41.9)	55 (39.0)	0.659
Operating or hybrid room	251 (58.1)	86 (61.0)	
Approach			
Transfemoral	380 (88.0)	128 (90.9)	0.360
Other	52 (12.0)	13 (9.2)	
Conscious sedation	213 (49.3)	76 (53.9)	0.272
Prosthesis type			
Balloon-expandable	225 (52.1)	73 (51.8)	0.233
Self-expandable	200 (46.3)	65 (46.1)	
Antibiotic prophylaxis			
B-Lactam alone	313 (79.0)	109 (87.2)	0.613
Vancomycin (alone or in combination)	17 (4.3)	4 (3.2)	
In-hospital Outcomes (TAVR)			
Acute renal failure	45 (10.4)	27 (19.2)	0.005
Stroke	14 (3.2)	12 (8.5)	0.008
Major vascular complication	25 (5.8)	14 (9.9)	0.082
Major bleeding	34 (7.9)	20 (14.2)	0.023
Sepsis	34 (7.9)	23 (16.3)	0.001

New pacemaker implantation	74 (17.1)	30 (21.3)	0.257
Residual aortic regurgitation >2 at discharge	63 (14.6)	19 (13.5)	0.839
Length of ICU stay, days	1.5 (1-3)	2 (1-5)	0.011
Length of hospital stay, days	8.5 (6-14)	9 (7-15)	0.060

Values are median (interquartile range), n (%), or mean ± SD. COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IE, infective endocarditis; *S. aureus, Staphylococcus aureus*; TAVR, transcatheter atrial valve replacement.

3.5.2 Characteristics and outcomes of the index IE episode after TAVR

The features, management, and outcomes of the index IE episode after TAVR, comparing SA IE and non-SA IE are detailed in **Table 3.2**. The median time between TAVR and IE diagnosis was lower in SA IE patients (4.7 months [IQR 1.2- 13.9] vs 6.3 months [IQR 2.1-14.9]; P = 0.032). Although fever was the most common presenting symptom in both groups, patients with SA IE showed higher rates of neurologic manifestations (27.0% vs 15.7%; P = 0.003) and systemic embolism (18.4% vs 10.7%; P = 0.014) at admission. Health care-associated IE was more frequent in the SA IE group (53.2% vs 40.7%; P = 0.010). IE episodes with TAVR prosthesis involvement were more likely in the non-SA IE group (63.4% vs 51.1%; P = 0.013), whereas the SA IE group presented a higher proportion of implantable cardiac device (other than TAVR prosthesis) infection (9.2% vs 2.6%; P = 0.001). The presence of vegetations as assessed by either transthoracic or transesophageal echocardiography was lower in the SA IE group (53.0% vs 66.3%; P = 0.006). Despite the high proportion of patients with unknown infection foci (SA IE 37.6% and non-SA IE 43.5%), SA IE episodes were more likely to be related to TAVR procedures (7.1% vs 3.2%; P = 0.047), skin/soft tissue infection (8.5% vs 1.9%; P < 0.001), and vascular access (9.2% vs 1.4%; P < 0.001), whereas gastrointestinal (SA IE 1.4% vs non-SA IE 8.3%; P = 0.004) and odontologic (SA IE 0.7% vs non-SA IE 5.3%; P = 0.015) foci were more frequent in the non-SA IE group.

Table 3.2. Main clinical characteristics, management, and outcomes of IE after TAVR, according to the causative microorganism (S. aureus vs non-S. aureus).

	Non-*S. Aureus* (n=432)	*S aureus* (n=141)	Unadjusted P value
Time from TAVR, months	6.3 (2.1-14.9)	4.7 (1.2-13.9)	0.032
Early IE	291 (67.4)	101 (71.6)	0.379
Late IE	139 (32.2)	40 (28.4)	
Initial symptoms			
Fever	326 (75.5)	116 (82.3)	0.058
New-onset heart failure	171 (39.6)	58 (41.1)	0.602
Neurological	68 (15.7)	38 (27.0)	0.003
Systemic embolism	46 (10.7)	26 (18.4)	0.014
Cutaneous	17 (3.9)	9 (6.4)	0.213
Health care-associated infection	176 (40.7)	75 (53.2)	0.010
Echocardiographic findings			
Vegetation	279 (66.3)	71 (53.0)	0.006
Vegetation size, mm	10 (6-15)	10 (7-17)	0.298
No TAVR platform affection	158 (36.6)	69 (48.9)	0.013
Periannular complication	83 (24.4)	22 (23.4)	0.840
New aortic regurgitation	54 (14.8)	6 (6.2)	0.025
New mitral regurgitation	63 (17.7)	12 (12.9)	0.274
Structure involved			
Isolated TAVR prosthesis	221 (51.2)	57 (40.4)	0.027
Mitral (native- or prosthetic valve)	65 (15.1)	21 (14.9)	0.965
Implantable cardiac device	11 (2.6)	13 (9.2)	0.001
Right-sided IE	8 (1.9)	0 (0.0)	0.210
Multi (2 localization at least)	127 (29.4)	50 (35.5)	0.176
Presumed source of entry			
Unknown	188 (43.5)	53 (37.6)	0.216
Procedural TAVR related	14 (3.2)	10 (7.1)	0.047
Urological	43 (10.0)	10 (7.1)	0.309
Odontological	23 (5.3)	1 (0.7)	0.018
Gastrointestinal	36 (8.3)	2 (1.4)	0.004
Pacemaker implantation	8 (1.9)	4 (2.8)	0.478
Skin/soft tissue infection	8 (1.9)	12 (8.5)	<0.001
Intravascular source	6 (1.4)	13 (9.2)	<0.001
Other	106 (24.5)	36 (25.5)	0.812
Complications during IE hospitalization			
Any complication	275 (66.1)	109 (80.7)	0.001

Heart failure	159 (38.2)	72 (53.3)	0.002
Acute renal failure	139 (35.7)	74 (58.7)	<0.001
Septic shock	92 (22.2)	58 (43.3)	<0.001
Stroke	41 (9.9)	16 (11.9)	0.508
Other systemic embolization	40 (9.6)	19 (14.2)	0.138
Persistent bacteremia	101 (26.9)	46 (41.8)	0.003
Surgery during IE hospitalization	82 (19.5)	29 (21.0)	0.694
Time to surgery, days	17 (7-37)	11.5 (5-22)	0.094
Isolated Aortic valve replacement	44/77 (57.1)	11/29 (37.9)	0.078
Isolated mitral valve replacement	1/77 (1.3)	2/29 (6.9)	0.121
Isolated cardiac device extraction	7/77 (9.1)	11/29 (37.9)	<0.001
Combined surgery	25/77 (32.5)	5/29 (17.2)	0.121
Follow-up outcomes			
Follow-up, months*	15.4 (4.8-35.6)	13.1 (3.7-24.3)	0.077
In-hospital mortality	113 (26.9)	66 (47.8)	<0.001
1-year mortality rate, (95% CI), %	43.7 (38.8-48.9)	62.1 (53.8-70.5)	<0.001†
2-year mortality rate, (95% CI), %	49.6 (44.5-55.1)	71.5 (62.9-79.7)	<0.001†
Recurrence of IE	41/307 (13.4)	7/72 (9.7)	0.312

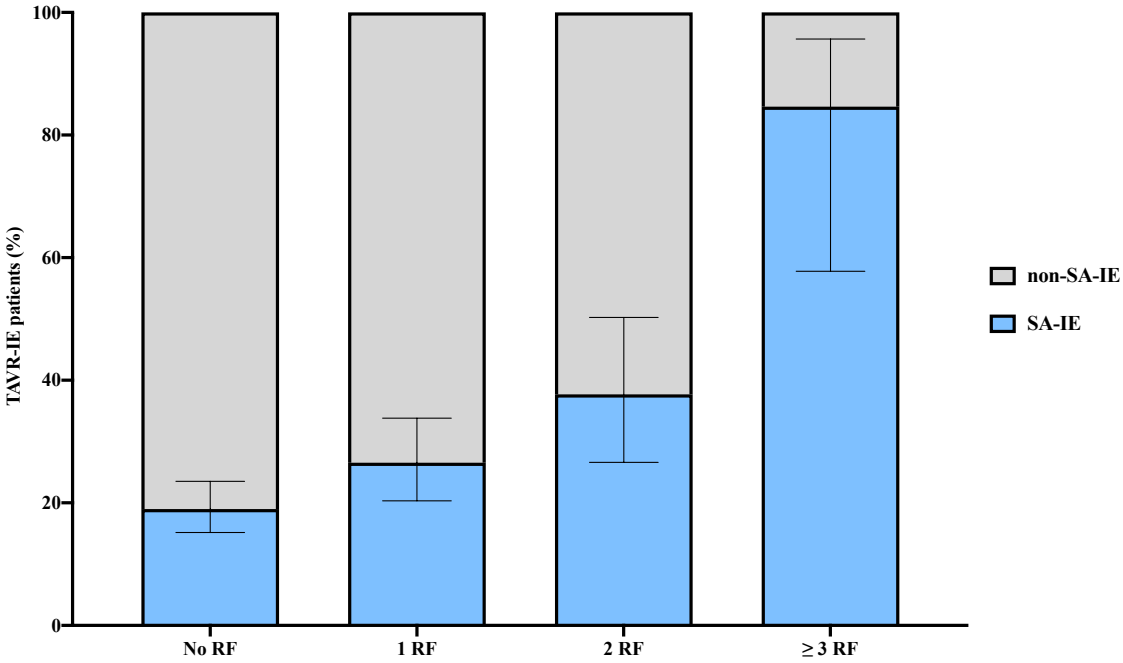
Values are median (interquartile range) or n (%) unless otherwise specified. CI, confidence interval; IE, infective endocarditis; S. aureus, Staphylococcus aureus; TAVR, transcatheter atrial valve replacement.
* Patients who survived the in-hospital period. † Log-rank test.

The rate of patients presenting at least 1 IE-related complication during index hospitalisation was higher in the SA IE group (80.7% vs 66.1%; P = 0.001). SA IE patients were complicated more frequently with new-onset heart failure (53.3% vs 38.2%; P = 0.002), acute renal failure (58.7% vs 35.7%; P < 0.001), persistent bacteremia (41.8% vs 26.9%; P = 0.003), and septic shock (43.3% vs 22.2%; P < 0.001). There was an important variability of antibiotic regimens in both groups, with more than 40 different drug combinations. β-Lactam antibiotics alone were less likely used in SA IE (11.5% vs 25.3%; P = 0.001), whereas the use of vancomycin alone or in combination with other antibiotics was similar (SA IE 35.1% vs non-SA IE 27.5%; P = 0.116).

There were no differences between groups in surgical management rates (SA IE 21.0% vs non-SA IE 19.5%; P = 0.694). In-hospital mortality was substantially higher in the SA IE group (47.8% vs 26.9%; P < 0.001).

3.5.3 Factors associated with SA IE

The univariate and multivariate-adjusted logistic models determining the factors associated with SA as a causative microorganism in patients with post-TAVR IE are presented in **Supplemental Table 3.2**. The factors independently associated with SA IE were TAVR-related complications such as major bleeding (adjusted odds ratio [ORadj] 2.82, 95% confidence interval [CI] 1.24-6.43; P = 0.013) and sepsis (ORadj: 2.31, 95% CI 1.13-4.72; P = 0.021), neurologic symptoms (ORadj: 2.16, 95% CI 1.19-3.92; P = 0.011), and systemic embolism (ORadj: 2.06, 95% CI 1.04-4.08; P = 0.038) at IE admission, as well as IE with implantable cardiac devices involvement (other than TAVR) (ORadj: 4.50, 95% CI 1.93-10.54; P = 0.001). The likelihood of IE due to SA in patients with none of the above-mentioned factors was 19.0% (95% CI 15.2%-23.5%), and it increased to 26.5% (95% CI 20.3%-33.8%), 37.7% (95% CI 26.6%-50.3%), and 84.6% (95% C, 57.8%-95.7%), in the presence of 1, 2 and ≥3 factors, respectively **(Figure 3.2)**.



Incidence (95% CI)	18.99% (15.16-23.52)	26.54% (20.34-33.83)	37.70% (26.61-50.25)	84.62% (57.77-95.67)
No. of patients				
non-SA-IE	273	119	38	2
SA-IE	64	43	23	11

Figure 3.2. Likelihood of *Staphylococcus aureus* (SA) infective endocarditis (IE) in patients with IE after transcatheter aortic valve replacement (TAVR) according to the presence of associated risk factors (RFs).

3.5.4 Follow-up outcomes

The Kaplan-Meier estimate survival curves at 2-year follow-up comparing patients with SA IE and non-SA IE are shown in **Figure 3.3**. The mortality rate was higher in the SA IE group (71.5% vs 49.6%; P < 0.001 by log-rank test). The multivariate-adjusted Cox model determining the independent factors associated with follow-up mortality according to microbiologic etiology (non-SA IE vs SA IE) is presented in **Figure 3.4** and **Supplemental Table 3.3**. A higher risk profile as determined by the logistic EuroSCORE, the lack of surgical management during the index IE hospitalisation, and IE-related complications such as septic shock and persistent bacteremia determined an increased risk of mortality in patients with SA IE.

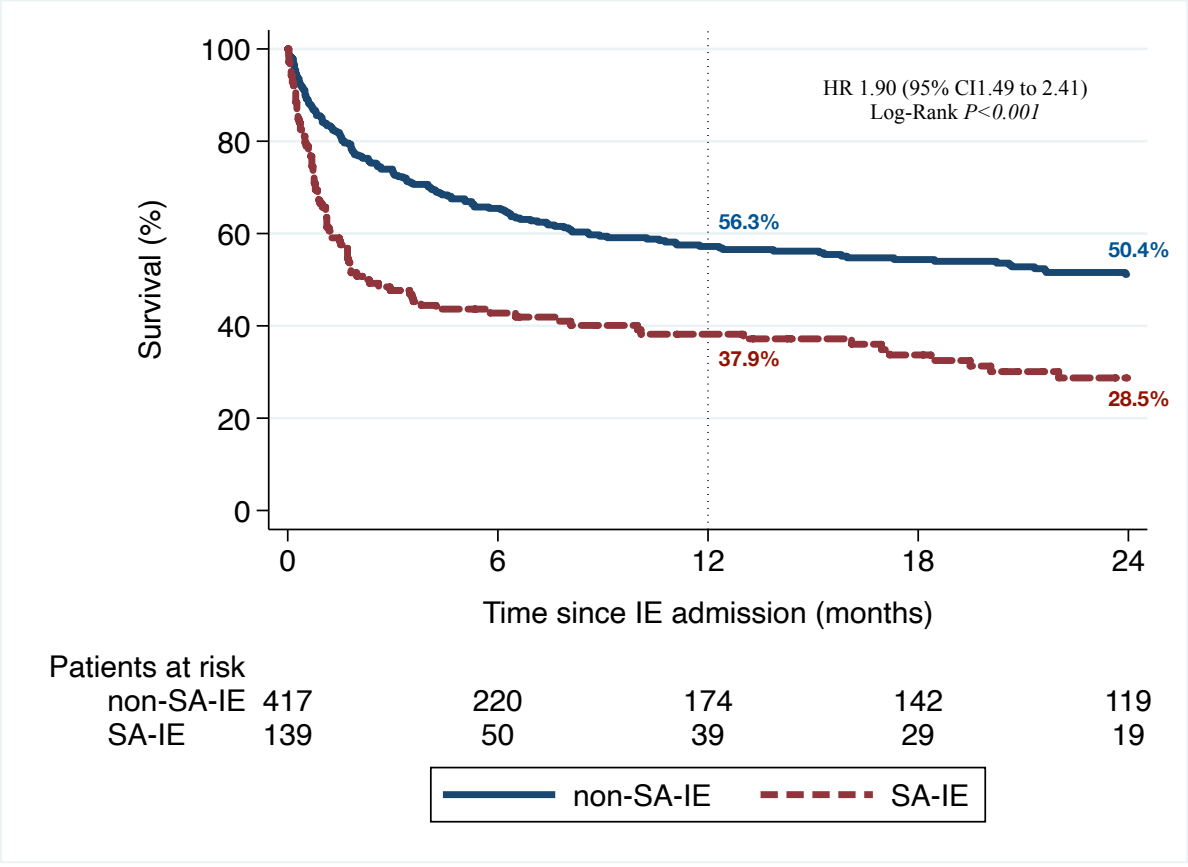


Figure 3.3. Kaplan-Meier estimated survival curve at 2-year follow-up comparing patients with and without Staphylococcus aureus infective endocarditis (SA IE).
CI, confidence interval; HR, hazard ratio

3.6 DISCUSSION

The main findings of this study can be summarised as follows: 1) About 25% of cases of IE after TAVR had SA as a causative microorganism; 2) patients with SA IE presented TAVR-related complications (acute renal failure, stroke, major bleeding and sepsis) more frequently and had longer intensive unit care hospitalisations after TAVR; 3) periprocedural TAVR major bleeding or sepsis, neurologic symptoms or systemic embolisms at admission and IE with signs of cardiac device involvement (other than the TAVR prosthesis) were associated with SA IE, and the presence of such factors (particularly in combination) at the index IE hospitalisation determined a high likelihood of SA IE (> 80% in patients with ≥ 3 factors); 4) SA IE was associated with a higher incidence of IE-related complications (compared with non-SA IE) and a very high in-hospital (close to 50%) and follow-up (> 70% at 2 years) mortality rates; 5) the lack of surgical management at index IE hospitalisation among SA IE patients determined an increased mortality risk.

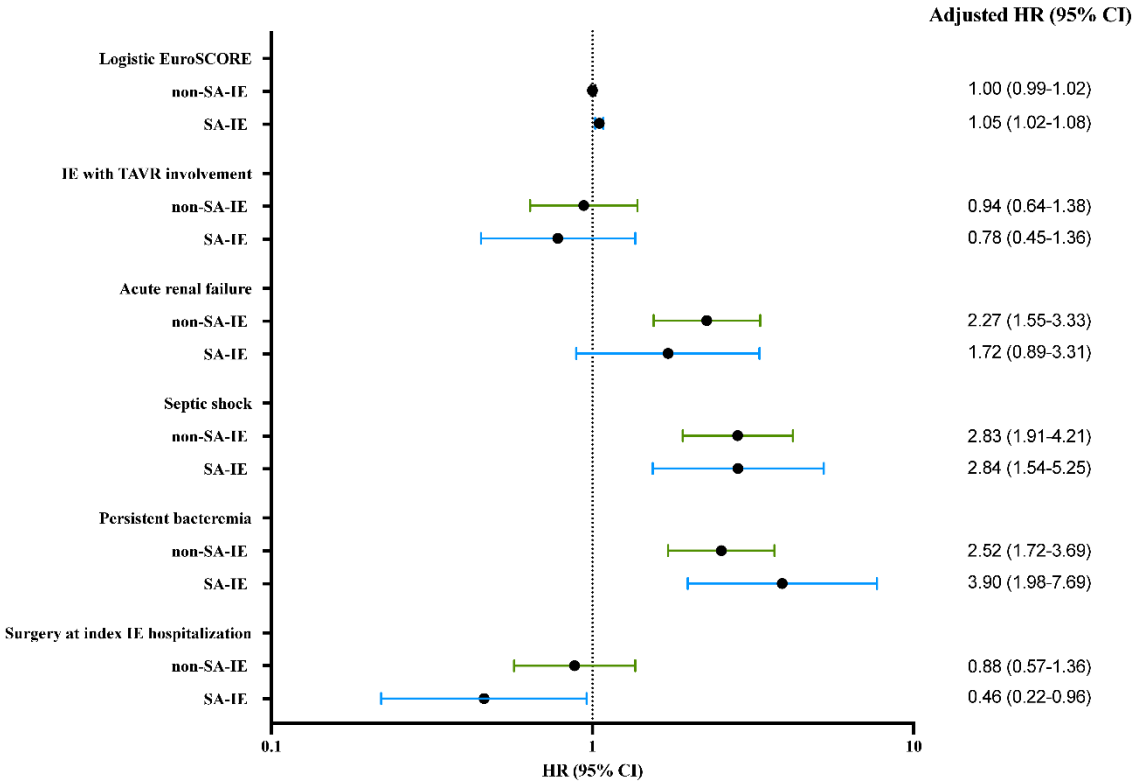


Figure 3.4. Factors associated with cumulative follow-up mortality in patients with infective endocarditis (IE) comparing *Staphylococcus aureus* (SA) IE and non-SA IE.

CI, confidence interval; HR, hazard ratio; TAVR, transcatheter atrial valve replacement.

PVE is the most severe subtype of IE, representing 10%-30% of all IE cases.[203] The incidence of post-TAVR IE has been previously reported as ranging from 0.6% to 3.4% per year.[154,156,165] Despite the evolution of TAVR over the years with simplified procedures and improved devices, the overall IE incidence remains stable.[200] There are scarce data comparing IE after surgical aortic valve replacement (SAVR) and TAVR. Although most studies reported similar incidence rates,[146,147] a recent study analysing a pooled cohort of 3 randomised clinical trials showed a lower incidence of IE after TAVR compared with SAVR.[150] Of note, the microbiological profile differs between SAVR-IE and TAVR-IE. While enterococci represent only ~10% of SAVR-IE, previous analyses using the same cohort of patients of the present study revealed this microorganism as the leading cause of TAVR-IE.[156,165,181,199] Our data showed that TAVR-IE was associated with SA in 1 out of 4 patients. These results are similar to those reported in SAVRIE registries. However, the proportion of patients presenting with late SA IE after TAVR was slightly higher than those with late SA IE after SAVR.[29] This finding may be related to the particular TAVR patients' profile, leading to more frequent diagnostic and therapeutic invasive procedures during the follow-up period.

The diagnosis of PVE is challenging, and early diagnosis is essential because delayed treatment is associated with worse clinical outcomes.[70–72] This issue is even more relevant in patients with suspected IE after TAVR. First, TAVR recipients represent a particular population with a high comorbidity burden, with patients commonly presenting with atypical symptoms. Previous studies suggest that the modified Duke criteria show a lower diagnostic accuracy for TAVR-IE than native-valve IE, mainly related to a higher incidence of negative blood cultures and inconclusive echocardiographic findings.[156,165] Second, IE after TAVR has been associated with a high incidence of severe IE-related complications and poor outcomes, with a mortality rate at 1-year follow-up close to 50%. To date, no factors associated with SA as a causative microorganism of post-TAVR IE has been identified. Our data show that TAVR complicated by major bleeding or sepsis, the presence of neurologic symptoms or systemic embolism at IE index admission, and signs of infection involving implantable cardiac devices other than the TAVR prosthesis were independently associated with SA IE in TAVR patients. These findings may have important clinical implications as the presence of such factors, particularly in combination, determined a very high likelihood of SA IE (> 80% in patients with ≥ 3 risk factors). Thus, in patients presenting with suspected IE after TAVR and exhibiting 2 or more risk factors for SA IE, treatment should be promptly initiated and oriented toward

appropriate antibiotic regimens to cover SA while waiting for blood culture results. Further studies are warranted to determine if this strategy translates into a lower rate of IE-related complications and improved clinical outcomes. Importantly, there was no association between the prosthesis type and the overall risk of IE. However, patients presenting early SA IE were more likely to have SEVs than BEVs. This finding may be partially explained by the higher proportion of patients receiving a permanent pacemaker after the TAVR procedure in the SEV group than in the BEV group (25.4% vs 10.4%), which might increase the risk of bacteremia and consequently the risk of SA IE.

IE after TAVR has been associated with a poor prognosis and high mortality rate. The present study results also highlight the virulence of SA IE. Patients developing SA IE presented a worse prognosis and higher in-hospital and late mortality rates than those in whom the IE was caused by other microorganisms (47.8% vs 26.9% in-hospital and 71.5% vs 49.6% late mortality). These mortality rates were also substantially higher than those reported in patients presenting surgical prosthetic-valve SA IE, with an in-hospital mortality rate around 35%.[204,205] This difference could be explained in part by the higher baseline risk of TAVR patients because of age and comorbidities, such that any complication would place them at greater risk of mortality than their surgical counterparts. The rate of acute renal failure, acute heart failure, and septic shock during the index hospitalisation in the SA IE group was twice that observed in the non-SA IE group. PVE management involves complex antibiotic regimens along with surgery (valve explantation) in selected patients. Previous studies reported that approximately half of the patients with native- or surgical prosthetic-valve IE secondary to SA undergo surgery during the IE index hospitalisation.[60–62] Current guidelines recommend combined and prolonged antibiotic regimens,[31,38] and the results of our study showed a wide variability of antibiotic regimens in patients with SA IE after TAVR. A possible explanation for this finding could be the noteworthy proportion of antimicrobial resistance, renal/hepatic toxicity, and drug interactions in the TAVR population, which could hamper the application of these recommendations in real-world situations. In addition, the rate of surgical intervention in patients with SA IE was particularly low. Although surgical treatment of PVE caused by SA should be considered (if there is a low likelihood of control with the use of antimicrobial therapy), the rate of surgery was similar to that of patients with non-SA IE. Previous studies have failed to demonstrate improved outcomes in patients with TAVR-IE undergoing surgery compared with those treated with antibiotics alone.[174] Importantly, our findings suggest that in

patients with SA IE after TAVR, surgery may have a protective effect when adjusting for perioperative mortality risk (logistic EuroSCORE) and severe IE-related complications (acute renal failure, septic shock, persistent bacteremia). Nevertheless, the role of surgical treatment in TAVR patients is still debated and these results should be interpreted with caution. Until recently, a significant proportion of TAVR recipients exhibited absolute contraindications for surgery. Therefore, universal recommendations of surgery in native- or prosthetic-valve IE could not be extrapolated to TAVR recipients. Nevertheless, the contemporary TAVR patient profile is rapidly changing, with an increasing proportion of low-surgical-risk patients, which could lead to an increased number of TAVR-IE patients undergoing surgery in the coming years. Dedicated studies are crucial to further substantiate our findings and establish surgery indications in TAVR-IE patients.

The population at risk of IE after TAVR is projected to rise exponentially owing to the expansion of this treatment to younger patients with a higher life expectancy. Consequently, strategies aimed at limiting the occurrence of IE and improving the clinical outcomes of this population become even more relevant, and prevention should be the cornerstone of this life-threatening disease. First, TAVR should keep moving forward to more simplified (and less invasive) procedures leading to an earlier patient's ambulation and shorter hospital stays. Second, evidence and specific recommendations regarding the most appropriate antimicrobial prophylaxis (in addition to aseptic measures) before some invasive procedures are urgently required. Also, the importance of limiting health care-associated procedures that could potentially trigger a bloodstream infection in this population should be highlighted. Third, novel strategies for SA bacteremia prevention and prosthetic infection would address an important unmet medical need. Device iterations with innovative antibacterial biomaterials that prevent bacteria adhesion to the prosthetic surfaces could become be important to reduce IE in case of bloodstream infection.

3.6.1 Study limitations

The present study has certain limitations. First, it is an observational, retrospective study, with the limitations and potential bias inherent to that design. Centres participated voluntarily and there was no external monitoring committee to assess the accuracy of data reported by each center. Second, this study included patients with definite IE after the TAVR procedure

regardless of the structure involved. Our cohort included approximately 60% of patients in whom the TAVR prosthesis involvement was clearly identified. The rest were subjects who had isolated cardiac devices IE (other than TAVR), mitral valve IE, or right-side IE or patients in whom TAVR involvement was not confirmed with the use of conventional imaging techniques. Unfortunately, we were unable to determine if some of these latter patients showed any undetected TAVR involvement. Third, detailed information concerning imaging assessment during the follow-up was not available in most patients.

3.7 CONCLUSION

SA IE after TAVR is a particular life-threatening complication among patients with post-TAVR IE, with a very high in-hospital (~50%, 2 times higher than non-SA IE) and long-term (> 70% at 2 years) mortality. The presence of some features (periprocedural TAVR complications such as major bleeding/sepsis, neurologic symptoms/embolism at index IE, and involvement of cardiac devices other than the TAVR valve) determined a higher likelihood of SA IE. In patients presenting with suspected IE after TAVR, the presence of 2 or more risk factors may prompt an early treatment oriented toward antibiotic regimens to cover SA while waiting for blood culture results. Although the role of surgery has not yet been established in TAVR-IE patients, the results of this study suggest that surgical treatment may have a protective effect in post-TAVR SA IE patients. Further studies are warranted.

3.8 ACKNOWLEDGEMENTS

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3.9 FUNDING SOURCES

The authors have no funding sources to declare.

3.10 DISCLOSURES

Dr Rodés-Cabau has received institutional research grants from Edwards Lifesciences, Medtronic, and Boston Scientific. Dr Tchetche has reported consulting fees from Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic. Dr Herrmann has received institutional research grants from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic and consulting fees from Edwards Lifesciences and Medtronic. Dr Webb has received consulting fees from Edwards Lifesciences and St Jude Medical. Dr Makkar has received research grants from Edwards Lifesciences, Medtronic, Abbott, Capricor, and St Jude Medical, has served as a proctor for Edwards Lifesciences, and has received consulting fees from Medtronic. Dr de Brito has received honoraria from Medtronic and Edwards Lifesciences for symposium speeches and proctoring cases. Dr Lerakis has received consulting fees from Edwards Lifesciences. Dr Le Breton has received lecture fees from Edwards Lifesciences, outside the submitted work. Dr Sinning has received speaker honoraria from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic and research grants from Boston Scientific, Edwards Lifesciences, and Medtronic, outside the submitted work. Dr Won-Keun has received personal fees from Boston Scientific, Edwards Lifesciences, Abbott, Medtronic, and Meril, outside the submitted work. Dr Stortecky reports grants to his institution from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott and has received personal fees from Boston Scientific, BTG, and Teleflex, outside the submitted work. Dr Husser has received personal fees from Boston Scientific and payments from Abbott. Dr Mangner has received personal fees from Edwards Lifesciences, Medtronic, Biotronik, Novartis, Sanofi Genzyme, AstraZeneca, Pfizer, and Bayer, outside the submitted work. Dr Linke has received personal fees from Medtronic, Abbott, Edwards Lifesciences, Boston Scientific, Astra Zeneca, Novartis, Pfizer, Abiomed, Bayer, and Boehringer, outside the submitted work. The other authors have no conflicts of interest to disclose.

3.11 SUPPLEMENTAL MATERIAL

Supplemental Table 3.1. Transcatheter aortic valve classification

Balloon-expandable prostheses	Self- or mechanically expandable prostheses
Edwards Sapien™ [Edwards Lifesciences, Irvine, CA, USA]	Medtronic CoreValve™ and Evolut R™ [Medtronic, Minneapolis, MN, USA]
Sapien XT™ [Edwards Lifesciences, Irvine, CA, USA]	Lotus™ Valve System [Boston Scientific, Marlborough, MA, USA]
Sapien 3™ [Edwards Lifesciences, Irvine, CA, USA]	Portico™ valve [Abbott Vascular, Abbott Park, IL, USA]
	Symetis Accurate™ [TA and neo] [Symetis SA, a Boston Scientific company, Ecublens, Switzerland]
	Direct flow™ [Direct Flow Medical Inc. Santa Rosa, CA, USA]
	JenaValve™ [JenaValve Technology Inc. Irvine, CA]
	Medtronic Engager™ [Medtronic, Minneapolis, MN, USA]
	Centera™ [Edwards Lifesciences, Irvine, CA, USA]

Supplemental Table 3.2. Factors associated with *S aureus* as causative microorganism in patients with IE post-TAVR.

	Univariate Analysis OR (95% CI)	Unadjusted p Value	Multivariate Analysis OR (95% CI)	Adjusted p Value
Baseline and TAVR features				
Antibiotic Prophylaxis				
B-Lactam alone	1.86 (1.05-3.29)	0.034	-	-
Other	1 [Reference]		-	-
In-hospital Outcomes (TAVR)				
Stroke	2.82 (1.27-6.25)	0.011	-	-
Major Bleeding	1.97 (1.09-3.55)	0.025	2.82 (1.24-6.43)	0.013
Major vascular complication	1.82 (0.92-3.61)	0.086	-	-
Acute renal failure	2.07 (1.23-3.50)	0.006	-	-
Sepsis	2.51 (1.41-4.45)	0.002	2.31 (1.13-4.72)	0.021
Healthcare-associated IE	1.65 (1.13-2.42)	0.010	-	-
Symptoms at IE admission			-	-
Fever	1.64 (0.98-2.76)	0.060	-	-
Neurological	2.00 (1.27-3.15)	0.003	2.16 (1.19-3.92)	0.011
Systemic embolism	1.91 (1.13-3.24)	0.015	2.06 (1.04-4.08)	0.038
Structure involved				
Vegetation	0.57 (0.39-0.85)	0.006	-	-
Isolated TAVR prosthesis	0.67 (0.44-1.04)	0.074	-	-
Cardiac device involvement	3.29 (1.65-6.59)	0.001	4.50 (1.93-10.54)	0.001

TAVR, transcatheter aortic valve replacement

Supplemental Table 3.3. Factors associated with cumulative follow-up mortality in patients with infective endocarditis caused by *S aureus* after TAVR.

	Univariate Analysis HR (95% CI)	Unadjusted p Value	Multivariate Analysis HR (95% CI)	Adjusted p Value
Baseline and TAVR features				
Logistic EuroSCORE[a]	1.03 (1.01-1.05)	0.008	1.05 (1.02-1.08)	0.001
Concomitant mitral regurgitation	1.52 (0.97-2.38)	0.070	-	-
Mean transaortic gradient	0.98 (0.97-1.00)	0.014	-	-
Approach				
Transfemoral	0.53 (0.26-1.11)	0.093	-	-
Other	1 [Reference]	-	-	-
In-hospital Outcomes (TAVR)				
Residual aortic regurgitation >2	1.67 (0.94-2.96)	0.094	-	-
Major Bleeding	1.89 (1.11-3.21)	0.019	-	-
Sepsis	1.71 (1.00-2.91)	0.048	-	-
Acute renal failure	1.74 (1.08-2.80)	0.022	-	-
IE clinical characteristics				
Heart failure at IE admission	1.49 (0.98-2.28)	0.065	-	-
IE with TAVR involvement[b]	0.89 (0.59-1.34)	0.578	0.78 (0.45-1.36)	0.387
Management				
Surgery at index IE hospitalization[b]	0.66 (0.38-1.15)	0.139	0.46 (0.22-0.96)	0.038
In-hospital complication				
Heart failure	2.19 (1.39-3.45)	0.001	-	-
Acute renal failure	3.25 (1.94-5.43)	<0.001	1.72 (0.89-3.31)	0.105
Septic shock	5.59 (3.50-8.92)	<0.001	2.84 (1.54-5.25)	0.001
Persistent bacteremia	3.97 (2.36-6.68)	<0.001	3.90 (1.98-7.69)	<0.001

HR, hazard ratio; TAVR, transcatheter aortic valve replacement.
[a] Per 1% increase.
[b] Variable was forced to remain in the final model.

CHAPTER 4: ^{18}F-Fluorodeoxyglucose Uptake Pattern in Noninfected Transcatheter Aortic Valves

David del Val, MD[1], Mikael Trottier, MD[2], Alberto Alperi, MD[1], Guillem Muntané-Carol, MD[1], Laurent Faroux, MD[1], Robert Delarochellière, MD[1], Jean-Michel Paradis, MD[1], Eric Dumont, MD[3], Dimitri Kalavrouziotis, MD[3], Siamak Mohammadi, MD[3], Michel Tessier, MD[2], Philippe Gervais, MD[4], Mélanie Côté, MSc[1], Josep Rodés-Cabau, MD[1]

[1]Department of Cardiology, Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada.
[2]Department of Nuclear Medicine, Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada.
[3]Department of Cardiac Surgery, Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada.
[4]Department of Infectious Diseases, Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada.

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4.1 RÉSUMÉ

Contexte : Une accumulation légère et homogène de ^{18}F-FDG entourant l'anneau prothétique a été décrite au niveau des prothèses valvulaires chirurgicales en l'absence d'infection active. La présence de ce phénomène niveau des valves aortiques implantées par cathéter non infectées est inconnue.

Objectifs : Cette étude visait à caractériser le modèle d'absorption du ^{18}F-FDG au niveau des valves aortiques implantées par cathéter non infectées et à évaluer s'il existait des différences dans le modèle d'absorption du ^{18}F-FDG entre différentes prothèses.

Méthodes : Étude prospective et observationnelle, incluant des patients présentant une sténose aortique sévère symptomatique traitée par remplacement de valve aortique percutané (TAVR) (valves Sapien 3 et Evolut R/PRO) et ayant bénéficié d'un TEP/TDM au ^{18}F-FDG 3 mois après le TAVR. Une exclusion de l'endocardite infectieuse a été effectuée avant le TEP/TDM au ^{18}F-FDG chez tous les patients.

Résultats : Au total, 22 patients ont bénéficié d'un TEP/TDM au ^{18}F-FDG (âge médian 82 ans [intervalle interquartile, 76-85], 50 % d'hommes, score STS moyen, 3,2±1,1 %). La plupart des procédures ont été réalisées par une voie transfémorale (68,2 %), et des valves Sapien 3 et Evolut R/PRO ont été implantées chez respectivement 16 et 6 patients. Le TEP/TDM au ^{18}F-FDG a été réalisé à une médiane de 92 (l'intervalle interquartile, 85-117) jours post-TAVR. Le score visuel qualitatif médian était de 1. Les analyses qualitatives et semi-quantitatives n'ont montré aucune différence significative en termes de captation de ^{18}F-FDG en comparant le Sapien 3 au THV Evolut R/PRO.

Conclusions : Les valves aortiques implantées par catheter non-infectées n'ont pas présenté un modèle caractéristique de captation du ^{18}F-FDG 3 mois après la procédure TAVR. Il n'y avait pas de différences en termes de captation du ^{18}F-FDG entre les valves Sapien 3 et Evolut R/PRO.

4.2 ABSTRACT

Background: A mild and homogeneous ^{18}F-FDG accumulation surrounding the prosthetic ring has been described in surgical prostheses in the absence of active infection. The presence of this phenomenon in noninfective transcatheter aortic valves is unknown. This study aimed to characterize the uptake pattern of ^{18}F-FDG in noninfected transcatheter aortic valves and to assess whether there were differences in the ^{18}F-FDG uptake pattern between different prostheses.

Methods: Prospective, observational study, including patients with symptomatic severe aortic stenosis treated with TAVR (Sapien 3 and Evolut R/PRO valves) who had a ^{18}F-FDG PET/CT performed 3 months after TAVR. A rule out of infective endocarditis was performed before the ^{18}F-FDG PET/CT in all the patients.

Results: A total of 22 patients underwent ^{18}F-FDG PET/CT (median age 82 years [IQR, 76-85], 50% men, mean STS score, 3.2±1.1%). Most procedures were performed through transfemoral approach (68.2%), and 16 and 6 patients received a Sapien 3 and Evolut R/PRO valves, respectively. The ^{18}F-FDG PET/CT was performed at a median of 92 (IQR, 85-117) days post-TAVR. The median qualitative visual score was 1. Both qualitative and semi-quantitative analyses showed no significant differences in terms of ^{18}F-FDG uptake comparing the Sapien 3 vs Evolut R/PRO THV.

Conclusions: Noninfected transcatheter aortic valves did not exhibit a characteristic ^{18}F-FDG uptake pattern 3 months after the TAVR procedure. There were no differences in terms of ^{18}F-FDG uptake between the Sapien 3 and Evolut R/PRO THV.

4.3 RESEARCH LETTER

Positron emission tomography with [^{18}F]-fluordeoxyglucose combined with computed tomography (^{18}F-FDG PET/CT) has demonstrated to improve the diagnostic accuracy of prosthetic-valve infective endocarditis.[39,206] In previous studies with surgical prostheses, a mild and homogeneous ^{18}F-FDG accumulation surrounding the prosthetic ring has been described in the absence of active infection and may be considered as a normal pattern.[207–209] To date, the presence of this phenomenon in transcatheter aortic valves remains unknown. The aims of this study were (1) to characterize the uptake pattern of ^{18}F-FDG in noninfected transcatheter aortic valves at 3 months following transcatheter aortic valve replacement (TAVR) and (2) to assess whether there are differences in the ^{18}F-FDG uptake pattern between the 2 most widespread prostheses.

Data that support the findings of this study are available from the corresponding author upon reasonable request. In this prospective, observational study, we included patients with symptomatic severe aortic stenosis treated with TAVR (Sapien 3 and Evolut R/PRO valves) who underwent a ^{18}F-FDG PET/CT 3 months after the procedure. The main exclusion criteria were (1) definite or possible infective endocarditis (IE) (according to the modified Duke criteria) at the time of ^{18}F-FDG PET/CT, (2) patients with any contraindication to ^{18}F-FDG PET/CT, and (3) patients undergoing transcatheter aortic valve-in-valve replacement. The study was approved by the local Ethics Committee and all patients gave written informed consent. Patients underwent ^{18}F-FDG PET/CT (GE Discovery RX 2009 PET and Lightspeed 16 CT, GE Healthcare, Chicago) following a minimum of 8 hours of fasting period and a preparatory low-carbohydrate, high-protein, and fat diet. After the capillary glucose was checked, a 5 MBq/kg dose of ^{18}F-FDG was administrated intravenously, and PET imaging acquisitions were performed 60 minutes after the radiolabeled tracer injection (3-minute acquisitions per bed position, 2 iterations, 21 subsets). Images were reconstructed from 3-dimensional data sets using the VUE Point algorithm (matrix size of 128x128) and a gaussian filter (full width at half maximum=6 mm). Both attenuation-corrected and nonattenuation-corrected images were analyzed. Nevertheless, given that a metal artifact reduction algorithm was not implemented, only the nonattenuation-corrected images (without scatter correction) were used for definite interpretation to avoid artifacts related to the overcorrection of attenuation induced by high-density material (eg, stent frame or calcium). The qualitative visual uptake was

scored: none (score=0), mild hypermetabolism (equal or less intense to pulmonary parenchyma; score=1), moderate hypermetabolism (more intense than pulmonary parenchyma; score=2), and severe hypermetabolism (very intense uptake; score=3). Areas of abnormal pulmonary parenchyma were excluded. The ^{18}F-FDG uptake pattern was classified as (1) absent, (2) homogeneous, (3) heterogeneous or patchy pattern. All cases were analyzed by an experienced nuclear medicine physician and a cardiologist on MIMvista software (MIM Software Inc, Cleveland). Continuous variables were expressed as mean SD or median (interquartile range [IQR]) according to variable distribution. Categorical variables were expressed as number (%). Data analyses were performed using the Stata software (version 15.1, Stata Corp, College Station).

A total of 22 patients without clinical signs of IE and negative blood cultures underwent ^{18}F-FDG PET/CT (median age 82 [IQR, 76–85] years; 50% women; mean STS score 3.2±1.1%). The most frequent underlying comorbidities were coronary artery disease (54.6%), chronic renal failure (36.4%), and diabetes mellitus (22.7%). A total of 5 (22.7%) patients had previous implantable cardiac devices. The majority of them, showed mild-to-moderate aortic valve calcification (median calcium score of 1727 [IQR, 1001–2641] AU). Most procedures (68.2%) were performed through transfemoral approach, with 16 and 6 patients receiving a Sapien 3 and Evolut R/Pro valve, respectively. The median TAVR time was 61.5 (IQR, 55–90) minutes, and preimplantation valvuloplasty and balloon postdilatation were performed in 13.6% and 22.7% of the patients, respectively. Patients underwent ^{18}F-FDG PET/CT at a median time of 92 (IQR, 85–117) days following TAVR. No patient received antibiotic treatment within 30 days before ^{18}F-FDG PET/CT. The images were acquired 62.6 (IQR, 60.7–65.8) minutes after the injection of a median of 7.8 (IQR, 6.2–8.7) mCi of ^{18}F-FDG (equivalent to 288.6 [IQR, 229.4–321.9] MBq). A mild homogeneous increase of ^{18}F-FDG uptake was frequently identified in the periprosthetic area on attenuation-corrected images, whereas this phenomenon was undetectable in all the cases on the nonattenuation-corrected images. The median qualitative visual score was 1, and there were no differences comparing the Sapien 3 and Evolut R/ PRO transcatheter heart valves **(Figure 4.1)**.

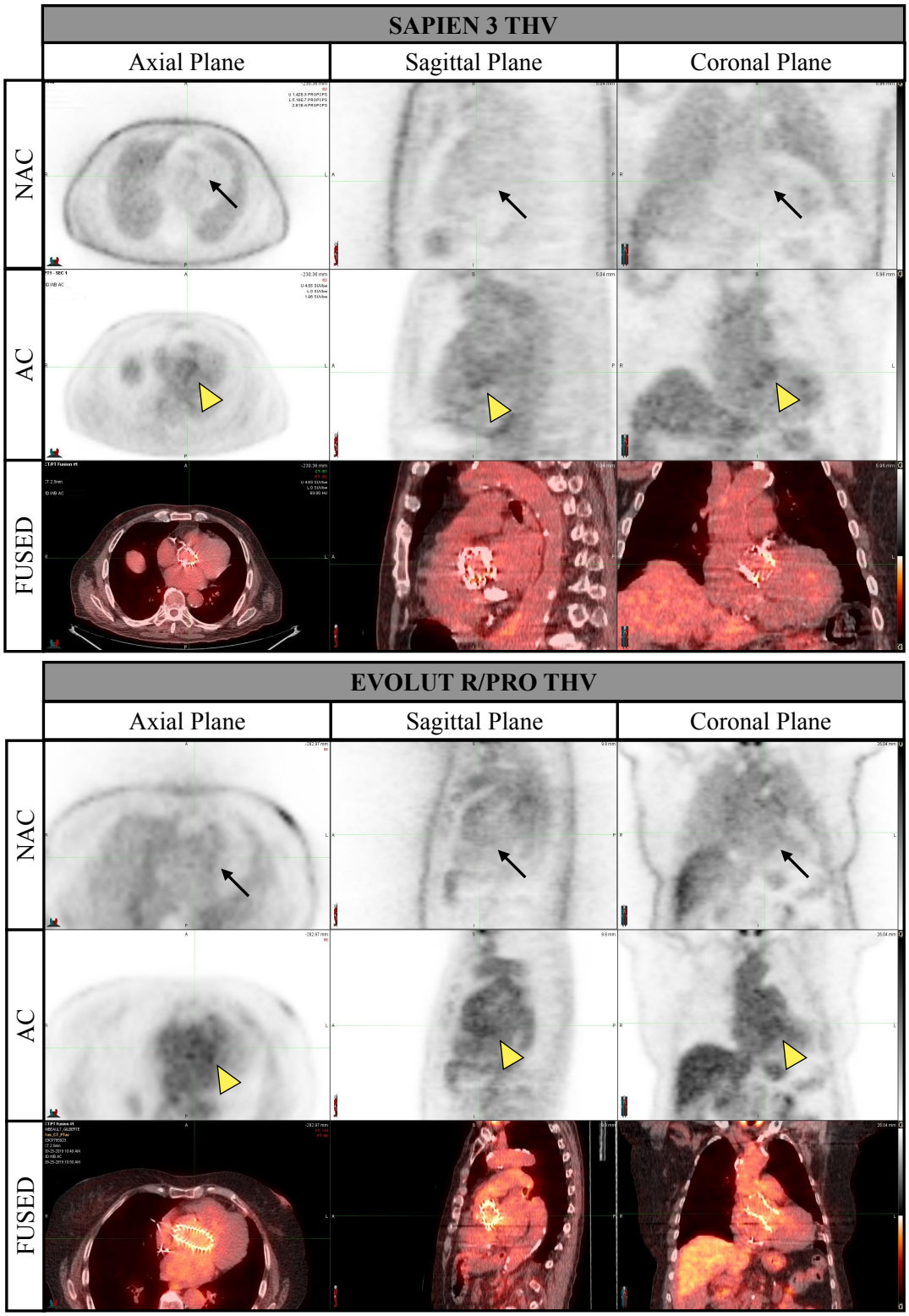

Figure 4.1. ^{18}F-Fluordeoxyglucose (^{18}F-FDG) uptake in patients with noninfected transcatheter aortic valves.

Examples of fused, attenuation-corrected (AC), and nonattenuation-corrected (NAC) images in patients treated with a Sapien 3 and Evolut R/PRO transcatheter heart valve (THV). An increased and homogenous ^{18}F-FDG uptake was visualized surrounding the prosthesis ring on AC images related to the high-density transcatheter aortic valve replacement stent frame and the absence of metal artifact reduction algorithm (yellow arrowheads). However, there was no evidence of increased ^{18}F-FDG uptake in the periprosthetic area on NAC images (black arrows).

The main limitation of this study was the lack of a comparative group including patients with definite IE. Also, patients undergoing TAVR <3 months were excluded from the study and, whether those patients present or not any characteristic ^{18}F-FDG uptake pattern remains unanswered.

In conclusion, in the studied population, noninfected transcatheter aortic valves did not exhibit a significant ^{18}F-FDG uptake pattern 3 months after the TAVR procedure with no differences between balloon- and self-expanding transcatheter valve systems. Thus, the visualization of a significant activity surrounding the prosthetic ring (more intense than the normal pulmonary parenchyma) on the nonattenuation-corrected images might be interpreted as highly suspect of TAVR-IE and managed accordingly.

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4.5 DISCLOSURES

None.

CHAPTER 5: Surgical Treatment of Patients With Infective Endocarditis After Transcatheter Aortic Valve Implantation

Norman Mangner, MD,[a],* David del Val, MD,[b],* Mohamed Abdel-Wahab, MD,[c,d] Lisa Crusius, MD,[a] Eric Durand, MD,[e] Nikolaj Ihlemann, MD,[f] Marina Urena, MD,[g] Costanza Pellegrini, MD,[h] Francesco Giannini, MD,[i,j] Tomasz Gasior, MD,[a] Wojtek Wojakowski, MD,[k] Martin Landt, MD,[d] Vincent Auffret, MD,[l] Jan Malte Sinning, MD,[m] Asim N. Cheema, MD,[n,o] Luis Nombela-Franco, MD,[p] Chekrallah Chamandi, MD,[q] Francisco Campelo-Parada, MD,[r] Erika Munoz-Garcia, MD,[s] Howard C. Herrmann, MD,[t] Luca Testa, MD,[u] Won-Keun Kim, MD,[v] Juan Carlos Castillo, MD,[w] Alberto Alperi, MD,[x] Didier Tchetche, MD,[y] Antonio L. Bartorelli, MD,[z] Samir Kapadia, MD,[aa] Stefan Stortecky, MD,[bb] Ignacio Amat-Santos, MD, PHD,[cc] Harindra C. Wijeysundera, MD,[dd] John Lisko, MD,[ee] Enrique Gutiérrez-Ibanes, MD,[ff] Vicenç Serra, MD,[gg] Luisa Salido, MD,[hh] Abdullah Alkhodair, MD,[ii] Ugolino Livi, MD,[jj] Tarun Chakravarty, MD,[kk] Stamatios Lerakis, MD,[ee,ll] Victoria Vilalta, MD,[mm] Ander Regueiro, MD,[nn] Rafael Romaguera, MD,[oo] Utz Kappert, MD,[a] Marco Barbanti, MD,[pp] Jean-Bernard Masson, MD,[qq] Frédéric Maes, MD,[rr] Claudia Fiorina, MD,[ss] Antonio Miceli, MD,[tt,uu] Susheel Kodali, MD,[vv] Henrique B. Ribeiro, MD,[ww,xx] Jose Armando Mangione, MD,[yy] Fabio Sandoli de Brito, JR, MD,[ww] Guglielmo Mario Actis Dato, MD,[zz] Francesco Rosato, MD,[aaa] Maria-Cristina Ferreira, MD,[bbb] Valter Correia de Lima, MD,[ccc] Alexandre Siciliano Colafranceschi, MD,[ddd] Alexandre Abizaid, MD,[ww] Marcos Antonio Marino, MD,[eee] Vinicius Esteves, MD,[fff] Julio Andrea, MD,[ggg] Roger R. Godinho, MD,[xx] Fernando Alfonso, MD,[hhh] Helene Eltchaninoff, MD,[e] Lars Søndergaard, MD,[f] Dominique Himbert, MD,[g] Oliver Husser, MD,[h,iii] Azeem Latib, MD,[i,jjj] Hervé Le Breton, MD,[l] Clement Servoz, MD,[r] Isaac Pascual, MD,[x] Saif Siddiqui, MD,[y] Paolo Olivares, MD,[z] Rosana Hernandez-Antolin, MD,[hh] John G. Webb, MD,[ii] Sandro Sponga, MD,[jj] Raj Makkar, MD,[kk] Annapoorna S. Kini, MD,[ll] Marouane Boukhris, MD,[qq] Philippe Gervais, MD,[b] Mélanie Côté, MSC,[b] David Holzhey, MD,[c] Axel Linke, MD,[a] Josep Rodés-Cabau, MD[b,nn]

[a]Herzzentrum Dresden, Technische Universität Dresden, Germany; [b]Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada; [c]Heart Center, Leipzig University, Leipzig, Germany; [d]Heart Center, Segeberger Kliniken, Bad Segeberg, Germany; [e]Normandie Univ, UNIROUEN, U1096, CHU Rouen, Department of Cardiology, FHU CARNAVAL, F-76000 Rouen, France; [f]Righospitalet, Copenhagen, Denmark; [g]Bichat Hôpital, Paris, France; [h]Deutsches Herzzentrum München, Munich, Germany; [i]Ospedale San Raffaele, Milan, Italy; [j]Maria Cecilia Hospital, GVM Care and Research, Cotignola RA, Italy; [k]Medical University of Silesia, Katowice, Poland; [l]Univ Rennes, CHU Rennes, Inserm, LTSI-UMR1099, F 35000 Rennes, France; [m]Heart Center Bonn, Bonn, Germany; [n]St. Michaels Hospital, Toronto, Ontario, Canada; [o]Southlake Hospital, Newmarket, Ontario, Canada; [p]Cardiovascular Institute, Hospital Clínico San Carlos, IdISSC, Madrid, Spain; [q]Hôpital Européen Georges-Pompidou, Paris, France; [r]Hôpital Rangueil, Toulouse, France; [s]Hospital Universitario Virgen de la Victoria, Malaga, Spain; [t]Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [u]IRCCS Pol. San Donato, Milan, Italy; [v]Kerckhoff Heart and Thorax Centre, Bad Nauheim, Germany; [w]Hospital Universitario Reina Sofia, Cordoba, Spain; [x]Hospital Universitario Central de Asturias, Oviedo, Spain; [y]Clinique Pasteur, Toulouse, France; [z]Centro Cardiologico Monzino, IRCCS and Department of Biomedical and Clinical Sciences "Luigi Sacco," University of Milan, Milan, Italy; [aa]Cleveland Clinic, Cleveland, Ohio, USA; [bb]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (on behalf of Swiss TAVI); [cc]CIBERCV, Hospital Clinico Universitario de Valladolid, Valladolid, Spain; [dd]Sunnybrook Health Science Center, Toronto, Ontario, Canada; [ee]Emory University School of Medicine, Atlanta, Georgia, USA; [ff]Instituto de Investigación Universitaria Gregorio Marañón, Hospital Gregorio Marañón, Madrid, Spain; [gg]Hospital Vall d'Hebron, Barcelona, Spain; [hh]Hospital Universitario Ramón y Cajal, Madrid, Spain; [ii]St. Paul's Hospital, Vancouver, British Columbia, Canada; [jj]University Hospital of Udine, Udine, Italy; [kk]Cedars-Sinai Heart Institute, Los Angeles, California, USA; [ll]Mount Sinai Hospital, New York, New York, USA; [mm]Hospital Germans Trias i Pujol, Badalona, Spain; [nn]Hospital Clinic Barcelona, Barcelona, Spain; [oo]Hospital de Bellvitge, L'Hospitalet de Llobregat, Spain; [pp]A.O.U. Policlinico Vittorio Emanuele, University of Catania, Catania, Italy; [qq]Centre Hospitalier de l'Université de Montreal, Montreal, Quebec, Canada; [rr]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [ss]ASST-Spedali Civili di Brescia, Brescia, Italy; [tt]Istituto Clinico Sant'Ambrogio, Milan, Italy; [uu]University Hospital Galway, Galway, Ireland; [vv]Columbia University Medical Center, New York, New York, USA; [ww]InCor, Heart Institute, University of São Paulo Medical School, Sao Paulo, Brazil; [xx]Hospital Samaritano Paulista, Sao Paulo, Brazil; [yy]Hospital Beneficencia Portuguesa, Sao Paulo, Brazil; [zz]Ospedale Mauriziano, Torino, Italy; [aaa]Azienda Ospedaliera S. Cocre e Carle, Cuneo, Italy; [bbb]Hospital Naval Marcilio Dias, Rio de Janeiro, Brazil; [ccc]Hospital São Francisco-Santa Casa de Porto Alegre, Porto Alegre, Brazil; [ddd]Hospital Pró-cardíaco, Rio de Janeiro, Brazil; [eee]Hospital Madre Teresa, Belo Horizonte, Brazil; [fff]Hospital São Luiz, Sao Paulo, Brazil; [ggg]Clínica São Vicente, Rio de Janeiro, Brazil; [hhh]Hospital Universitario de La Princesa, Madrid, Spain; [iii]St.-Johannes Hospital, Dortmund, Germany; and the [jjj]Montefiore Medical Center, New York, New York, USA.

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5.1 RÉSUMÉ

Contexte : Le traitement optimal des patients développant une endocardite infectieuse (EI) après un remplacement valvulaire aortique percutané (TAVI) est incertain.

Objectifs : L'objectif de cette étude était d'examiner les caractéristiques cliniques et le pronostic des patients présentant une EI après un TAVI traités par chirurgie cardiaque et antibiotiques (EI-CC) par rapport aux patients traités uniquement par antibiotiques (EI-AB).

Méthodes : Une analyse de la probabilité pondérée brute et inverse de recevoir le traitement (IPTW) a été effectuée pour étudier l'effet de la chirurgie cardiaque par rapport au traitement médical seul sur la mortalité toutes causes confondues à un an chez les patients atteints d'une endocardite infectieuse après remplacement valvulaire aortique percutanée (TAVI-EI) certaine. L'étude s'est basée les données du registre international Infectious Endocarditis after TAVI.

Résultats : Parmi 584 patients, 111 patients (19 %) ont été traités par EI-CC et 473 patients (81 %) par EI-AB. Au sein de la cohorte brute, les patients traités par EI-CC avaient un risque de décès hospitalier et à un an similaire à celui des patients traités par EI-AB (respectivement HRunadj : 0,85 ; IC à 95% : 0,58-1,25 et HRunadj : 0,88 ; IC à 95% : 0,64-1,22). Après ajustement pour tenir compte du biais de sélection et du biais lié au temps immortel, les patients traités par EI-CC conservaient un risque de décès hospitalier et à un an similaire à celui des patients traités par EI-AB (respectivement HRadj : 0,92 ; IC à 95% : 0,80-1,05 et HRadj : 0,95 ; IC à 95% : 0,84-1,07). Les résultats restaient identiques lorsque les patients avec et sans atteinte de la prothèse TAVI ont été analysés séparément. Les facteurs prédictifs de la mortalité pendant l'hospitalisation et à un an comprenaient l'EuroSCORE I logistique, l'implication d'un *Staphylococcus aureus*, une insuffisance rénale aiguë, une bactériémie persistante et un choc septique.

Conclusions : Dans ce registre, la majorité des patients ayant présenté une TAVI-EI ont été traités uniquement par antibiotiques. La chirurgie cardiaque n'était pas associée à une amélioration de la mortalité hospitalière ou à un an toutes causes confondues. La mortalité élevée des patients atteints de TAVI-EI était fortement liée aux caractéristiques des patients, à l'agent pathogène et aux complications liées à l'EI.

5.2 ABSTRACT

Background: The optimal treatment of patients developing infective endocarditis (IE) after transcatheter aortic valve implantation (TAVI) is uncertain.

Objectives: The goal of this study was to investigate the clinical characteristics and outcomes of patients with TAVI-IE treated with cardiac surgery and antibiotics (IE-CS) compared with patients treated with antibiotics alone (IE-AB).

Methods: Crude and inverse probability of treatment weighting analyses were applied for the treatment effect of cardiac surgery vs medical therapy on 1-year all-cause mortality in patients with definite TAVI-IE. The study used data from the Infectious Endocarditis after TAVI International Registry.

Results: Among 584 patients, 111 patients (19%) were treated with IE-CS and 473 patients (81%) with IE-AB. Compared with IE-AB, IE-CS was not associated with a lower in-hospital mortality (HRunadj: 0.85; 95% CI: 0.58-1.25) and 1-year all-cause mortality (HRunadj: 0.88; 95% CI: 0.64-1.22) in the crude cohort. After adjusting for selection and immortal time bias, IE-CS compared with IE-AB was also not associated with lower mortality rates for in-hospital mortality (HRadj: 0.92; 95% CI: 0.80-1.05) and 1-year all-cause mortality (HRadj: 0.95; 95% CI: 0.84-1.07). Results remained similar when patients with and without TAVI prosthesis involvement were analyzed separately. Predictors for in-hospital and 1-year all-cause mortality included logistic EuroSCORE I, *Staphylococcus aureus*, acute renal failure, persistent bacteremia, and septic shock.

Conclusions: In this registry, the majority of patients with TAVI-IE were treated with antibiotics alone. Cardiac surgery was not associated with an improved all-cause in-hospital or 1-year mortality. The high mortality of patients with TAVI-IE was strongly linked to patients' characteristics, pathogen, and IE-related complications.

5.3 INTRODUCTION

The incidence of infective endocarditis (IE) after transcatheter aortic valve implantation (TAVI) ranges between 0.7% and 3.4% per patient-year,[156–158,163,210–212] similar to IE rates after surgical aortic valve replacement.[146,155] TAVI-IE is associated with high in-hospital mortality,[156] and the prognosis of patients surviving the initial IE episode is poor.[181] Data from historical and contemporary TAVI cohorts showed similar IE rates but temporal improvements regarding the incidence of early IE and clinical outcomes, with lower in-hospital and 1-year mortality in recent times.[199]

The optimal treatment of prosthetic valve endocarditis (PVE) is uncertain. In IE episodes after surgical valve replacement, surgery is performed in roughly 50% of cases,[29] which is in contrast to the 12.0% surgical valve explantation rate observed in TAVI-IE.[156] Studies on the treatment effect of cardiac surgery (CS) in native valve IE and PVE revealed inconsistent results, with those showing improved survival after early valve replacement[61] and those indicating no benefit of CS compared with medical treatment after adjustment for differences in clinical characteristics and immortal time bias.[65] In TAVI-IE, smaller studies suggested that CS compared with medical therapy failed to reduce in-hospital and 1-year mortality.[156,174]

The aim of the current analysis derived from the Infectious Endocarditis after TAVI International Registry was to evaluate the characteristics and outcome of patients with TAVI-IE treated with cardiac surgery and antibiotics (IE-CS) compared with patients treated with antibiotics alone (IE-AB), applying an appropriate propensity score–based method to provide adjusted estimates of the treatment effect for in-hospital and 1-year all-cause mortality.

5.4 METHODS

5.4.1 The Infectious Endocarditis after TAVI International Registry

The data underlying this paper will be shared upon reasonable request to the corresponding author and authors of each participating center. Details regarding the design of the observational, multicenter, international Infectious Endocarditis after TAVI

International Registry have been published previously.[156] Briefly, the registry collected data from 604 patients with definite IE according to the modified Duke criteria after TAVI from 59 TAVI centers in 11 countries across Europe, North America, and South America between June 2005 and November 2020. Informed consent was obtained from all patients before the procedure, and the individual anonymized data sharing was performed according to the local ethics committee of each center.

5.4.2 Patient selection and data collection

Patients were retrospectively and prospectively identified by each center according to the modified Duke criteria. TAVI patients with definite IE were included irrespective of the structure affected (prosthetic/native valve and/or implantable cardiac device). Only the first IE episode recorded for an individual patient was included in the analysis, thereby avoiding duplicates. At each site, a dedicated case report form was used for data collection. Based on the received treatment, the global cohort was divided into IE-CS and IE-AB. The decision to perform CS was made on an individual basis at the discretion of the local IE team at the participating centers. CS included TAVI platform explantation (e.g., aortic valve replacement), surgery of other affected valves (either native or prosthetic), reconstruction of destroyed anatomic structures, implantable cardiac device removal, and concomitant procedures such as coronary artery bypass grafting or ascending aorta replacement.

5.4.3 Definitions

The definition of definite IE was based on the modified Duke criteria.[45] Clinical endpoints were defined according to the Valve Academic Research Consortium-2 criteria.[184] Perioperative mortality risk was defined according to the logistic EuroSCORE I.[185] Transcatheter aortic valve type was divided into 2 groups: balloon-expandable and self-expandable or mechanically expandable valves **(Supplemental Table 5.1)**. IE with TAVI platform involvement was defined as any IE episode involving the TAVI prosthesis (leaflet and/or stent frame) assessed by conventional imaging techniques. Early IE was defined as occurring within 1 year, and late IE as >1 year after TAVI.[38] Health care–associated infection was defined as IE diagnosed within 48 hours of admission in an outpatient with extensive health care contact as previously described.[29] Periannular

complications, persistent bacteremia, and systemic embolization were defined as previously reported.[156]

5.4.4 Outcome measures

The 1-year all-cause mortality after symptom onset was the primary outcome measure. In-hospital and 2-year mortality were secondary outcome measures. Long-term follow-up was complete in 98.4% of patients (15 patients were lost to follow-up at 1 year, 4 [3.6%] and 11 [2.3%] in IE-CS and IE-AB, respectively). Complications during IE treatment were collected and included heart failure, acute renal failure, stroke, septic shock, systemic embolization, persistent bacteremia, and the composite of those complications.

5.4.5 Statistical analysis

Categorical variables are expressed as number (%). Continuous variables are expressed as mean ± SD or median (IQR) depending on the variable distribution, which was assessed by the Shapiro-Wilk test. Between-group comparisons were analyzed by using the Student's *t*-test or Wilcoxon rank sum test for continuous variables and the chi-square or Fisher exact test for categorical variables. Unadjusted HRs were computed by using a univariate Cox proportional hazards model. Missing data were assumed to be missing at random and were dealt with multivariable imputation by using chained equations. Predictive mean matching by stratifying on treatment group was used for continuous variables, imputing stratum-specific means. Missing values of binary variables were imputed by using logistic regressions. The variables used to predict missing values were selected on a clinical basis, and missing values were imputed by stratifying on treatment group. Ten imputed data sets were created. Missing values for the primary outcome and variables containing >25% missing values were not imputed.

To calculate the inverse probability of treatment weights, we estimated each patient's propensity to undergo CS using a logistic regression model. This model included baseline, procedural, and outcome TAVI variables along with variables related to the IE episode considered a priori by the investigator to contribute to the outcome (1-year

mortality) and/or the treatment decision **(Supplemental Table 5.2)**. IE-CS was assigned a weight of 1/propensity score and IE-AB a weight of 1/1-propensity score. To avoid extreme weights, stabilized weights were used, with trimming of 2.5% of tails.[213] Balance among covariates was assessed by using absolute standardized mean differences (ASD), and effect sizes below 0.2 were considered to be small.[214,215]

To evaluate the factors associated with mortality among patients with TAVI-IE, Cox proportional hazards models were fit for in-hospital mortality and all-cause 1-year mortality. These models included all the variables considered a priori to contribute to mortality and those with a significant imbalance (ASD >0.20) after inverse probability treatment weighting (IPTW) (doubly robust method). CS was included as a time-varying covariate in these models to control for immortal time bias. The proportional hazards assumption was tested by assessing log-minus-log survival plots and scaled Schoenfeld residuals. The Kaplan-Meier method was used to provide survival estimates with differences assessed by the log-rank test in the crude cohort. Event times were measured from the date of initial IE symptoms to the date of death or last follow-up. One-year all-cause mortality for IE-AB versus IE-CS was also evaluated across propensity quintiles; for sensitivity analyses, the cohort was divided into patients with and without TAVI prosthesis involvement.

A 2-sided *P* value <0.05 was considered statistically significant. Data analyses were performed by using Stata software version 15.1 (Stata Corp) and SAS version 9.3 (SAS Institute, Inc).

5.5 RESULTS

5.5.1 Baseline and TAVI characteristics of the crude cohort

Among 604 patients with TAVI-IE, 584 (96.7%) had information available on their treatment status. Among these, 111 patients (19%) were treated with CS (and antibiotics) (i.e., IE-CS) and 473 patients (81%) were treated with antibiotics alone (i.e., IE-AB). Rates of CS were stable over different periods of time **(Supplemental Figure 5.1)**.

Table 5.1. Baseline characteristics, procedural details, and in-hospital TAVI outcomes, overall and according to the treatment strategy.

	Overall (n=584)	IE-AB (n=473)	IE-CS (n=111)	Unadjusted P value[a]	Unadjusted OR/HR (95%CI)
Baseline characteristics					
Age, years	80.7 (75.4-84.7)	81.0 (75.9-85.5)	77.8 (73.5-81.8)	<0.001	0.95 (0.92-0.98)
Female	219 (37.5)	185 (39.1)	34 (30.6)	0.097	0.69 (0.44-1.07)
Body mass index, (kg/m^2)	26.9 (24.1-30.7)	26.7 (23.9-30.3)	27.3 (24.5-32.6)	0.034	1.04 (1.01-1.07)
Diabetes mellitus	216 (37.0)	181 (38.3)	35 (31.5)	0.186	0.74 (0.48-1.15)
COPD	158 (27.1)	126 (26.7)	32 (28.8)	0.640	1.12 (0.71-1.76)
Atrial fibrillation	247 (42.3)	203 (42.9)	44 (39.6)	0.529	0.87 (0.57-1.33)
Chronic renal failure	252 (43.2)	213 (45.0)	39 (35.1)	0.058	0.66 (0.43-1.02)
Previous Stroke	77 (13.2)	58 (12.3)	19 (17.1)	0.174	1.48 (0.84-2.60)
Previous heart surgery	132 (22.6)	108 (22.8)	24 (21.6)	0.784	0.93 (0.57-1.54)
Previous valve surgery	65 (11.1)	49 (10.4)	16 (14.4)	0.222	1.46 (0.79-2.67)
Previous infectious endocarditis	9 (1.5)	7 (1.5)	2 (1.8)	0.682	1.22 (0.25-5.96)
Logistic EuroSCORE I, %	14.2 (8.6-22.5)	14.7 (9.0-23.4)	11.5 (6.4-18.6)	0.003	0.98 (0.96-1.00)
Left ventricular ejection fraction, %	57 (46-62)	57 (47-62)	58 (45-62)	0.684	0.99 (0.98-1.01)
Mean transaortic gradient, mmHg	44 (35-54)	44 (34-54)	43 (36-53)	0.367	0.99 (0.98-1.01)
Aortic valve area, cm^2	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.7 (0.6-0.9)	0.078	1.76 (0.73-4.26)
Periprocedural characteristics					
Implantation site					
Catheterization laboratory	234 (40.1)	201 (42.5)	33 (29.7)	0.014	1.75 (1.12-2.73)[b]
Operating or hybrid room	350 (59.9)	272 (57.5)	78 (70.3)		

Approach					
Transfemoral	514 (88.0)	417 (88.1)	97 (87.4)	0.821	0.93 (0.50-1.74)[c]
Other	70 (12.0)	56 (11.8)	14 (12.6)		
Endotracheal intubation	290 (49.7)	242 (51.2)	48 (43.2)	0.133	0.73 (0.48-1.10)
Prosthesis type					
Balloon-expandable	307 (52.6)	244 (51.6)	63 (56.8)	0.326	1.23 (0.81-1.87)[d]
Self-expanding	277 (47.4)	229 (48.4)	48 (43.2)		
Antibiotic prophylaxis					
B-Lactam alone	548 (93.8)	444 (93.9)	104 (93.7)	0.945	0.97 (0.41-2.28)[e]
Other	36 (6.2)	29 (6.1)	7 (6.3)		
In-hospital Outcomes (TAVI)					
Acute renal failure	70 (12.0)	61 (12.9)	9 (8.1)	0.162	0.60 (0.29-1.24)
Stroke	26 (4.5)	22 (4.7)	4 (3.6)	0.800	0.77 (0.26-2.27)
Major vascular complication	38 (6.5)	33 (7.0)	5 (4.5)	0.342	0.63 (0.24-1.65)
Major bleeding	52 (8.9)	46 (9.7)	6 (5.4)	0.150	0.53 (0.22-1.28)
New pacemaker implantation	104 (17.8)	80 (16.9)	24 (21.6)	0.243	1.36 (0.81-2.26)
Length of hospital stay, median (IQR), days	9 (6-14)	9 (6-15)	9 (6-13)	0.363	0.99 (0.97-1.00)

Values are median (IQR) or n (%). [a]P values are results of comparing IE-AB vs IE-CS. [b]Catheterization laboratory as reference. [c]Other approach as reference. [d]Self-expanding valve as reference. [e]Other antibiotic prophylaxis as reference.
COPD = chronic obstructive pulmonary disease; IE-AB = infective endocarditis treated with antibiotics only; IE-CS = infective endocarditis treated with cardiac surgery (and antibiotics); TAVI = transcatheter aortic valve implantation.

Baseline and procedural TAVI characteristics comparing IE-CS with IE-AB in the crude cohort are shown in **Table 5.1**. IE-CS patients were younger, had a higher body mass index, and a numerically lower rate of chronic renal failure leading to a lower logistic EuroSCORE I. In IE-CS, TAVI procedures had been more often performed in a hybrid/operating room. Procedural factors and the rate of TAVI-related complications were similar between groups.

5.5.2 Characteristics and complications of IE after TAVI

The main clinical, echocardiographic, and microbiological findings, as well as complications during IE treatment of the crude cohort, are depicted in **Table 5.2**. Early and late IE occurred in roughly two-third and one-third of the patients, respectively. The median time from TAVI to IE symptom onset was 5.7 months (IQR: 1.7-14.4 months) with no significant difference between groups. Initial IE symptoms were comparable between IE-CS and IE-AB except for a significantly lower rate of neurologic symptoms in IE-CS. Based on echocardiography, IE-CS more often had evidence of typical IE vegetation and higher rates of both TAVI platform involvement and periannular complications. Vegetation size was slightly larger in IE-CS compared with IE-AB; however, rates of new aortic and mitral regurgitation were comparable between groups. The most commonly detected microorganisms were enterococci, *Staphylococcus aureus*, and coagulase-negative staphylococci, with higher rates of coagulase-negative staphylococci in IE-CS and comparable rates of the remaining ones. Despite the high proportion of patients with unknown infection foci, presumed entry sources were comparable between groups, and health care–associated infection occurred in 44.2% with no significant differences between IE-AB and IE-CS.

The rate of any complication during IE treatment was higher in IE-CS compared with IE-AB (ORunadj: 2.16; 95% CI: 1.27-3.68), primarily driven by higher rates of heart failure, systemic embolization excluding stroke, and persistent bacteremia.

Table 5.2. Main clinical characteristics of IE after TAVI, overall and according to the treatment strategy.

	Overall (n=584)	IE-AB (n=473)	IE-CS (n=111)	Unadjusted P value[a]	Unadjusted OR/HR (95%CI)
Time from TAVI, months	5.7 (1.7-14.4)	5.7 (1.5-14.2)	7.4 (2.3-15.4)	0.146	1.01 (0.99-1.02)
Early IE (within 1 year)	402 (68.8)	330 (69.8)	72 (64.9)	0.316	1.25 (0.81-1.93)[b]
Late IE (>1 year)	182 (31.2)	143 (30.2)	39 (35.1)		
Initial symptoms					
Fever	460 (78.8)	375 (79.3)	85 (76.6)	0.531	0.85 (0.52-1.40)
New-onset heart failure	243 (41.6)	194 (41.0)	49 (44.1)	0.547	1.14 (0.75-1.72)
Neurological	109 (18.7)	99 (20.9)	10 (9.0)	0.004	0.37 (0.19-0.74)
Systemic embolism	73 (12.5)	57 (12.1)	16 (14.4)	0.498	1.23 (0.68-2.23)
Cutaneous	26 (4.5)	20 (4.2)	6 (5.4)	0.588	1.29 (0.51-3.30)
Health care–associated infection	258 (44.2)	208 (44.0)	50 (45.1)	0.838	1.04 (0.69-1.58)
Echocardiographic findings					
Vegetation	371 (63.5)	287 (60.7)	84 (75.7)	0.003	2.02 (1.26-3.23)
Vegetation size, mm	10 (6-15)	10 (6-15)	11 (8-20)	0.016	1.04 (1.01-1.07)
TAVI platform involvement	350 (59.9)	268 (56.7)	82 (73.9)	0.001	2.16 (1.36-3.43)
Periannular complication	117 (20)	78 (16.5)	39 (35.1)	<0.001	2.74 (1.73-4.34)
New aortic regurgitation	63 (10.8)	47 (9.9)	16 (14.4)	0.335	1.35 (0.73-2.51)
New mitral regurgitation	76 (13.0)	61 (12.9)	15 (13.5)	0.967	0.99 (0.53-1.83)
Valves involved					
Isolated TAVI prosthesis	284 (48.6)	222 (46.9)	62 (55.9)	<0.001	0.96 (0.85-1.08)[c]
Mitral (native-/prosthetic valve)	86 (14.7)	80 (16.9)	6 (5.4)		

Cardiac device	23 (3.9)	8 (1.7)	15 (13.5)		
Right-sided IE	8 (1.4)	6 (1.3)	2 (1.8)		
Other[d]	183 (31.3)	157 (33.2)	26 (23.4)		
Causative microorganisms					
Staphylococcus aureus	138 (23.6)	109 (23.0)	29 (26.1)	0.492	1.18 (0.73-1.90)
Methicillin Sensitive	114/138 (82.6)	88/109 (80.7)	26/29 (89.7)	0.231	2.19 (0.61-7.91)[e]
Methicillin Resistant	24/138 (17.4)	21/109 (19.3)	3/29 (10.3)		
Coagulase-negative Staphylococci	104 (17.8)	74 (15.6)	30 (27.0)	0.005	2.00 (1.23-3.25)
Methicillin Sensitive	69/104 (71.1)	49/74 (70.0)	20/30 (74.1)	0.692	1.22 (0.45-3.33)[e]
Methicillin Resistant	28/104 (28.9)	21/74 (30.0)	7/30 (25.9)		
Enterococci	145 (24.8)	123 (26.0)	22 (19.8)	0.175	0.70 (0.42-1.17)
Streptococci					
Oral streptococci	78 (13.4)	68 (14.4)	10 (9.0)	0.135	0.59 (0.29-1.19)
S. gallolyticus (S. bovis)	27 (4.6)	23 (4.9)	4 (3.6)	0.570	1.00 (0.99-1.00)
Culture negative	35 (6.0)	25 (5.3)	10 (9.0)	0.137	1.77 (0.83-3.81)
Presumed source of entry					
Unknown	278 (47.6)	226 (47.8)	52 (46.9)	0.761	1.02 (0.93-1.11)[f]
Procedural TAVI related	24 (4.1)	20 (4.2)	4 (3.6)		
Urological	52 (8.9)	41 (8.7)	11 (9.9)		
Odontological	24 (4.1)	22 (4.7)	2 (1.8)		
Pacemaker implantation	12 (2.1)	8 (1.7)	4 (3.6)		
Skin infection	20 (3.4)	15 (3.2)	5 (4.5)		
Vascular access	19 (3.3)	15 (3.2)	4 (3.6)		
Other	155 (26.5)	126 (26.6)	29 (26.1)		

IE complication					
Any complication	419 (71.8)	327 (69.1)	92 (82.9)	0.004	2.16 (1.27-3.68)
Heart failure	243 (41.6)	180 (38.1)	63 (56.8)	<0.001	2.14 (1.41-3.25)
Acute renal failure	238 (40.8)	186 (39.3)	52 (46.9)	0.147	1.36 (0.90-2.06)
Stroke	57 (9.8)	44 (9.3)	13 (11.7)	0.441	1.29 (0.67-2.49)
Septic shock	159 (27.2)	128 (27.1)	31 (27.9)	0.854	1.04 (0.66-1.66)
Other systemic embolization	59 (10.1)	38 (8.0)	21 (18.9)	<0.001	2.67 (1.50-4.77)
Persistent bacteremia	171 (29.3)	122 (25.8)	49 (44.1)	<0.001	2.27 (1.48-3.49)

Values are median (IQR), n (%), or n/N (%). [a]P values are results of comparing IE-AB vs IE-CS. [b]Early infective endocarditis (within 1 year) as reference. [c]TAVI as reference. [d]2 localization at least. [e]Methicillin-sensitive as reference. [f]Procedural TAVI related as reference.
Abbreviations as in Table 5.1.

5.5.3 Predictors for performing cardiac surgery in TAVI-IE

The ORs used to determine the propensity score for CS **(Supplemental Table 5.2)** indicate that CS was less likely performed in older patients (OR: 0.95; 95% CI: 0.92-0.98) and those with neurologic symptoms on admission (OR: 0.37; 95% CI: 0.19- 0.74). In contrast, patients with TAVI platform involvement (OR: 2.16; 95% CI: 1.36-3.43), vegetation size >10 mm (OR: 2.35; 95% CI: 1.54-3.59), periannular complications (OR: 2.74; 95% CI: 1.73-4.34), and IE-related complications, including heart failure (OR: 2.14; 95% CI: 1.41-3.25), other systemic embolization (OR: 2.67; 95% CI: 1.50-4.77), and persistent bacteremia (OR: 2.27; 95% CI: 1.48-3.49), were more likely to receive CS.

5.5.4 Management and outcome of IE

The management and outcomes are detailed in **Table 5.3**. Median time from initial symptoms to CS was 17.5 days (IQR: 6-41 days) in the crude cohort. Isolated aortic valve replacement (TAVI prosthesis explantation) was performed in 51.9% of all surgically treated patients. Aortic root replacement was performed in 10 patients (9.4%) with no difference between self-expanding and balloon-expandable prostheses (6 [5.7%] vs 4 [3.8%]; P = 0.238). Isolated mitral valve replacement and isolated device extraction were performed in 2.8% and 17%, respectively. A total of 23 patients (21.7%) received combined procedures detailed in **Table 5.3**.

The median follow-up of patients who survived the index hospitalization was 14.3 months (IQR: 4.6- 32.4 months), with no significant differences between IE-CS and IE-AB. The in-hospital mortality of the entire crude cohort was 31.9% with no significant differences between IE-CS (29.1%) and IE-AB (32.6%) (HRunadj: 0.85; 95% CI: 0.58-1.25). The main causes of in-hospital mortality are shown in **Supplemental Table 5.3**. The 1-year all-cause mortality of the entire crude cohort was 47.9% and was not significantly different between IE-CS (47.1%) and IE-AB (48.2%) (HRunadj: 0.88; 95% CI: 0.64-1.22) **(Table 5.3, Figure 5.1A)**. The 2-year all-cause mortality was also similar in IECS and IE-AB. Patients surviving the initial IE treatment episode were evaluated in a landmark analysis. Similar to the overall results, there was no difference in mortality between IE-CS and IE-AB in patients who have been discharged home **(Figure 5.1B)**.

Table 5.3. Outcomes of IE after TAVI during index hospitalization, overall and according to the treatment strategy.

	Overall (n=584)	IE-AB (n=473)	IE-CS (n=111)	Unadjusted P value[a]	Unadjusted OR/HR (95%CI)
Surgery during IE hospitalization					
Time to surgery, median (IQR), days	17.5 (6-41)		17.5 (6-41)	-	-
Isolated AVR, n (%)	55/106 (51.9)	-	55/106 (51.9)		
Isolated MVR, n (%)	3/106 (2.8)	-	3/106 (2.8)		
Isolated device extraction, n (%)	18/106 (17.0)	-	18/106 (17.0)		
Combined procedures					
AVR+CABG, n (%)	5/106 (4.7)	-	5/106 (4.7)	-	-
AVR+MV repair/replacement, n (%)	13/106 (12.3)	-	13/106 (12.3)		
AVR+MVR+TV repair, n (%)	2/106 (1.9)	-	2/106 (1.9)		
AVR+ device extraction, n (%)	3/106 (2.8)	-	3/106 (2.8)		
Other, n (%)	7/106 (6.6)	-	7/106 (6.6)		
Follow-up outcomes					
Follow-up, median (IQR), months[b]	14.3 (4.6-32.4)	14.6 (4.8-34.6)	12.9 (3.2-24.1)	0.143	1.00 (0.98-1.01)
In-hospital mortality, n (%)	183/573 (31.9)	151/463 (32.6)	32/110 (29.1)	0.420	0.85 (0.58-1.25)c
1-year mortality rate, % (95% CI)[d]	47.9 (43.7-52.3)	48.2 (43.5-53.1)	47.1 (37.4-57.9)	0.448[e]	0.88 (0.64-1.22)[c]
2-year mortality rate, % (95% CI)[d]	55.1 (50.6-59.7)	55.0 (50.1-60.0)	56.3 (45.5-67.8)	0.535[e]	0.91 (0.67-1.23)[c]
IE recurrence, n (%)[b]	49/401 (12.2)	42/322 (13.0)	7/79 (8.9)	0.312	0.65 (0.28-1.50)[c]

Values are median (IQR) or n/N (%) unless otherwise indicated. [a]P values are results of comparing IE-AB vs IE-CS. [b]Patients who survived in-hospital period. [c]HR (95% CI). [d]Kaplan-Meier estimated rates. [e]Log-rank test.

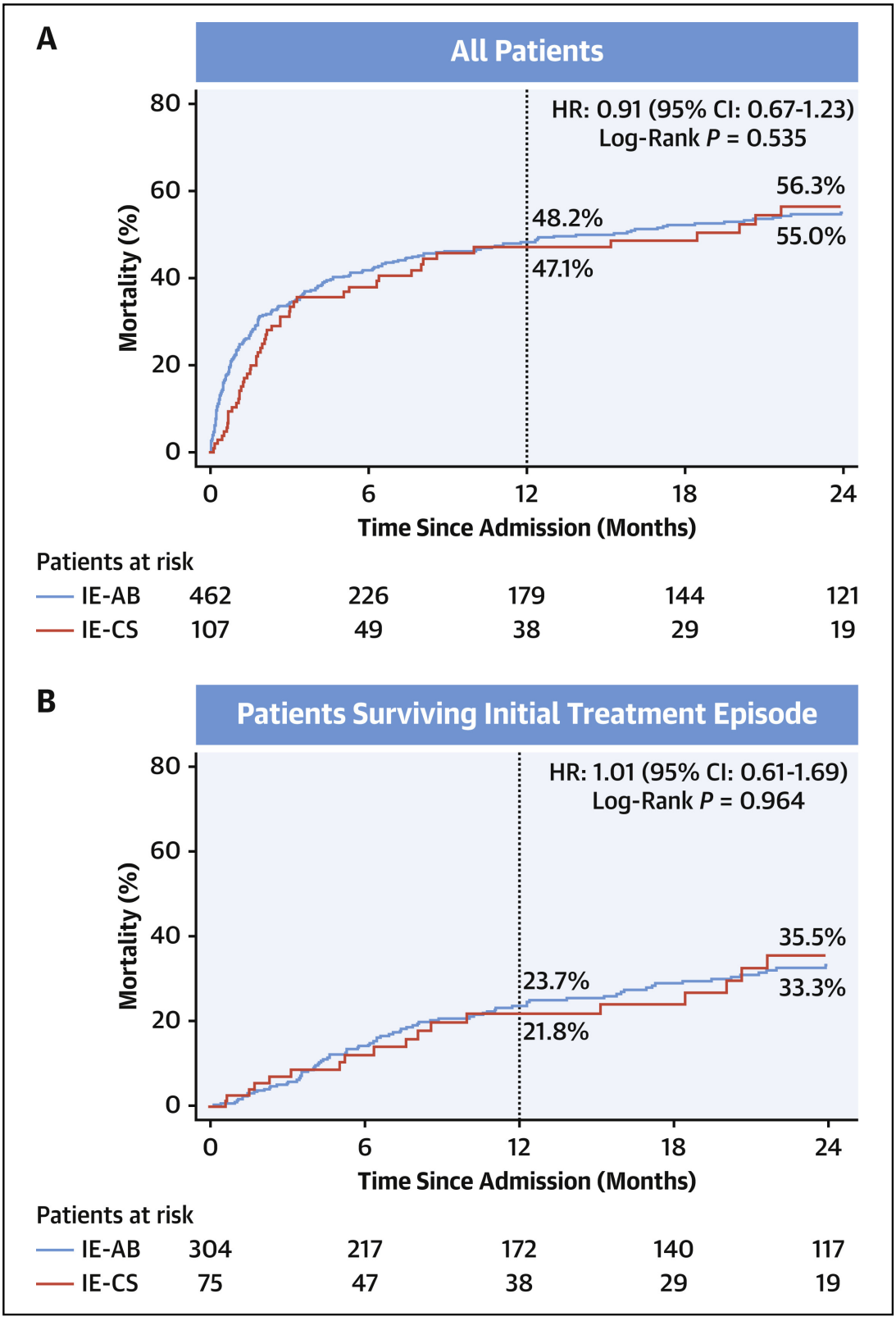

Figure 5.1. Unadjusted All-Cause Mortality According to Treatment

(A) Unadjusted all-cause mortality was comparable between IE-CS and IE-AB. (B) In a landmark analysis, unadjusted long-term mortality of patients surviving the initial IE treatment episode was also not different between IE-CS and IE-AB. HRs and corresponding 95% CIs are for 2-year all-cause mortality.

To control for treatment selection bias, the probability of surgery according to propensity score was calculated for each patient **(Supplemental Table 5.2)**. The resulting values and absolute standardized mean differences are provided in **Supplemental Tables 5.4 and 5.5**. To account for immortal time bias, IE-CS was introduced as a time-varying covariate into the model that also included variables with a significant imbalance (ASD >0.20) after IPTW. The full model is shown in **Supplemental Table 5.6**. This adjusted analysis revealed that IE-CS was not associated with reduced in-hospital mortality (HRadj: 0.92; 95% CI: 0.80-1.05) and 1-year all-cause mortality (HRadj: 0.95; 95% CI: 0.84-1.07) **(Figure 5.2)**. Predictors of in-hospital and 1-year all-cause mortality in this model included logistic EuroSCORE I, *S aureus*, acute renal failure, persistent bacteremia, and septic shock, whereas TAVI platform involvement was not independently associated with those outcomes **(Figure 5.3, Supplemental Table 5.6)**.

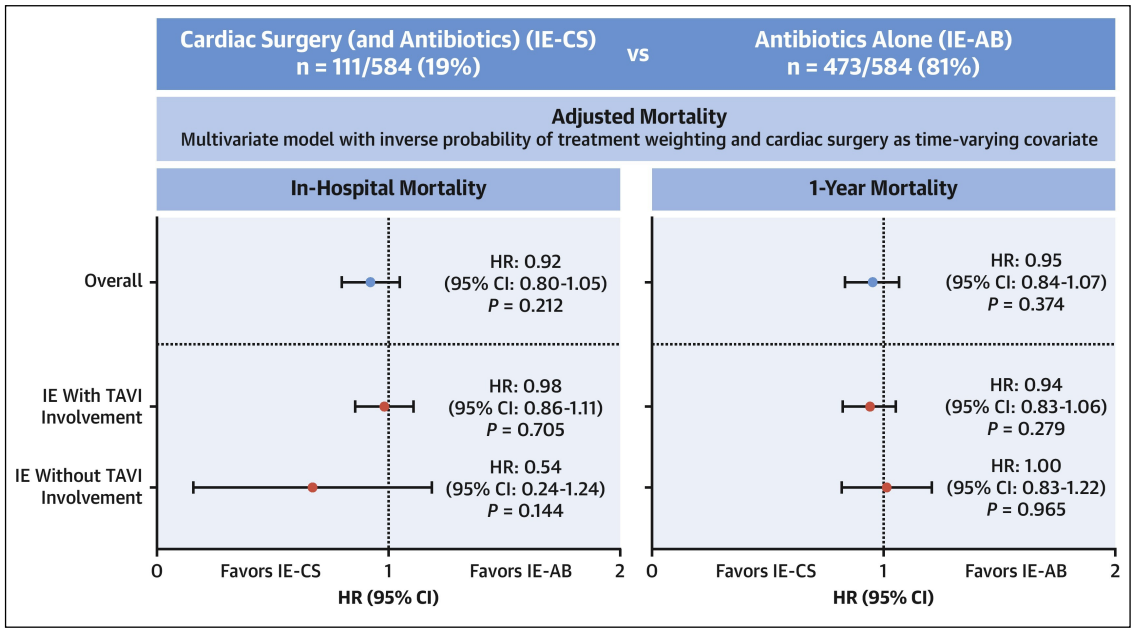

Figure 5.2: Surgical Treatment of Patients With Infective Endocarditis After Transcatheter Aortic Valve Implantation

In patients experiencing infective endocarditis (IE) after transcatheter aortic valve implantation (TAVI), 19% were treated with cardiac surgery and antibiotics (IE-CS) and 81% with antibiotics alone (IE-AB). No significant difference for in-hospital and 1-year all-cause mortality was detectable between IE-CS and IE-AB after adjusting for treatment selection by inverse probability of treatment weighting and immortal time bias by including cardiac surgery as a time-varying covariate in the overall cohort as well as in patients with and without TAVI platform involvement.

The division into quintiles according to the predicted probability of CS led to 117 patients per quintile who were comparable in clinical characteristics and probability of CS but differed by the treatment received. We analyzed the 1-year all-cause mortality within each quintile considering CS as a time-varying covariate. No significant mortality benefit was found for IE-CS in any quintile, although the analysis was limited by the low IE-CS numbers in the first 3 quintiles **(Supplemental Figure 5.2)**.

The IE recurrence rate was 12.2%, with no significant difference between IE-CS and IE-AB (ORunadj: 0.65; 95% CI: 0.28-1.50) **(Table 5.3)**.

5.5.5 Sensitivity analysis in patients with and without TAVI involvement.

Because the TAVI platform involvement was not associated with outcome, and to further evaluate the effect of CS in patients with (n = 350) and without (n = 234) TAVI involvement, the adjusted analyses were repeated in patients restricted to those conditions. There were no differences between IE-CS and IE-AB in patients with TAVI involvement (in-hospital mortality HRadj: 0.98 [95% CI: 0.86-1.11]; 1-year all-cause mortality HRadj: 0.94 [95% CI: 0.83-1.06]) and in patients without TAVI involvement (in-hospital mortality HRadj: 0.54 [95% CI: 0.24-1.24]; 1-year all-cause mortality HRadj: 1.00 [95% CI: 0.83-1.22]) **(Figure 5.2)**. Factors associated with in-hospital and 1-year all-cause mortality in these cohorts are provided in **Supplemental Table 5.7**.

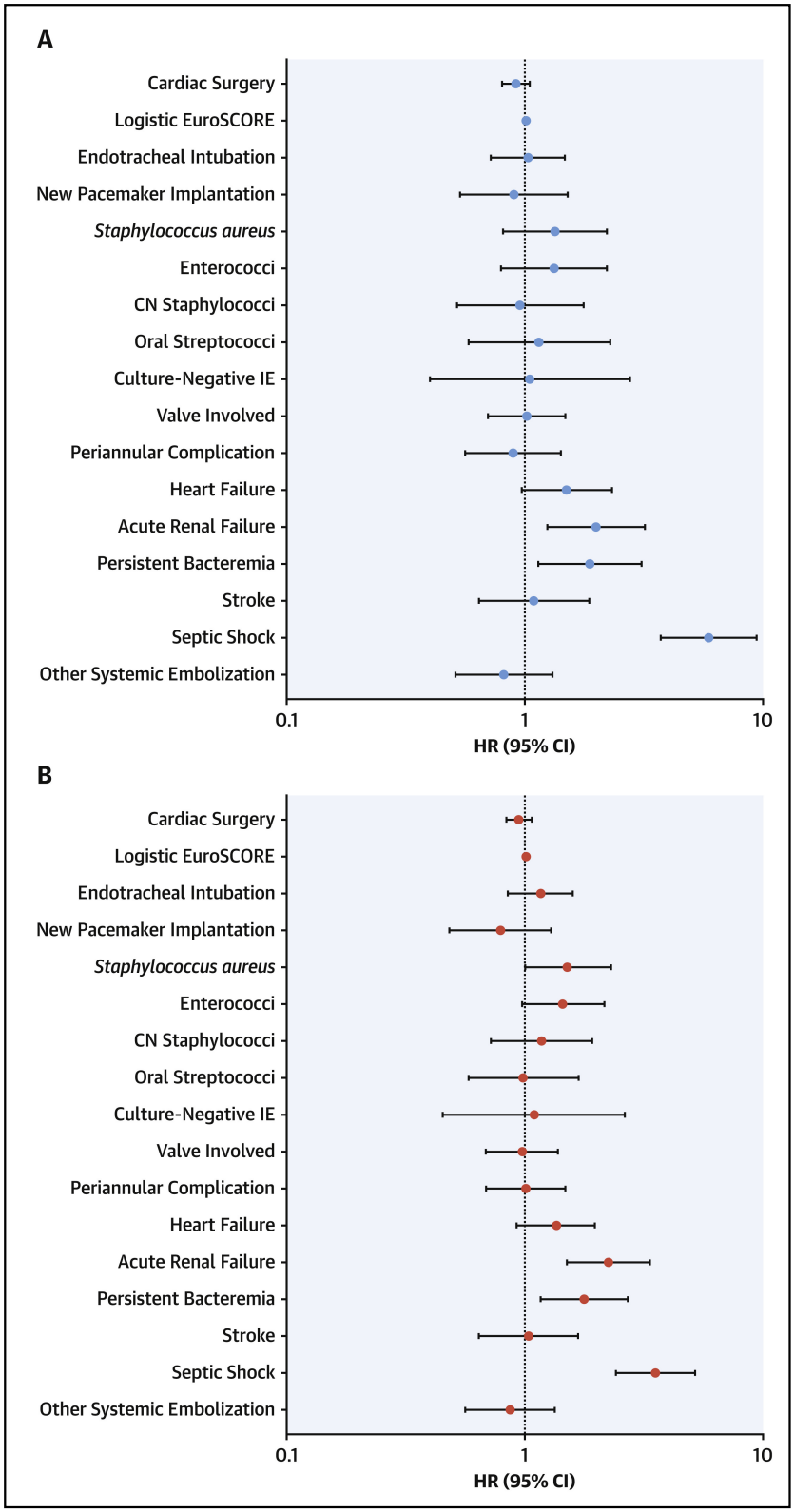

Figure 5.3: Factors Associated With In-Hospital and 1-Year All-Cause Mortality in TAVI-IE

Cox proportional hazards model for in-hospital (A) and 1-year all-cause (B) mortality. HRs and corresponding 95% CIs are shown. The HR for the Logistic EuroSCORE is per 1% increase. The reference for "Valve involved" is no transcatheter aortic valve implantation (TAVI) platform involvement.

5.6 DISCUSSION

This study evaluated the effect of 2 clinically relevant treatment options in patients developing TAVI-IE. The 5 main findings of this analysis were: 1) ~1 of 5 patients developing IE after TAVI received surgical treatment in an international, multicenter setting; 2) older age and more severe initial IE symptoms (e.g., neurologic symptoms) reduced the probability of undergoing CS, whereas TAVI platform involvement, vegetation size, and IE-related complications increased the likelihood of receiving surgical treatment; 3) in-hospital and 1-year all-cause mortality was high, with ~50% of the patients dying within 1 year after symptom onset; 4) the mortality rates for IE-CS and IE-AB were not significantly different in the crude cohort; a finding that was confirmed in an appropriate multivariate model adjusting for treatment selection and immortal time bias; and 5) mortality was predicted by patients' characteristics, pathogens, and in particular IE-related complications, including acute renal failure, persistent bacteremia, and septic shock.

5.6.1 Choice of treatment and its predictors

CS is performed in ~50% of patients with PVE after surgical valve replacement during the index hospitalization, most commonly due to acute heart failure caused by valvular destruction.[29,65] This is in contrast to the observed 19% in the current analysis and to the 14.8% surgical treatment rate in TAVI-IE patients described in the first report of the Infectious Endocarditis after TAVI International Registry.[156] This low rate of surgical interventions remained stable over time in a contemporary cohort compared with a historical one despite a decreasing baseline risk profile, whereas the percentage of patients with a formal indication for surgical treatment remained stable in both groups (~80%).[199] This finding suggests that factors other than the global surgical risk may influence the decision on whether to perform CS. Most of the patients treated thus far by TAVI (and developing IE afterward) are not only at increased surgical risk, they are particularly older. In the International Collaboration on Endocarditis–Prospective Cohort Study,[65] patients with PVE were ~60 years of age, which is roughly 20 years younger than in our analysis. In addition, IE-CS patients were 2 years younger than IE-AB patients in the crude cohort, indicating that age might be an important determinant for treatment decision as indicated by the OR for age calculated from the logistic regression model used to determine the propensity score for CS and inverse probability of treatment weighting.

More severe IE-related symptoms at presentation were associated with a lower probability of receiving surgical treatment, which is in line with studies comparing CS with medical therapy in PVE of surgically implanted valves.[65] However, a clearly visible involvement of the TAVI prosthesis and the surrounding tissue increased the likelihood of being treated with CS. It is distressing that patients with negative echocardiographic imaging less often received CS, as the prognosis of patients with affirmed continuous bacteremia after TAVI is not different between those with positive compared with negative imaging by echocardiography.[157] The reduced sensitivity of echocardiography is well known in PVE,[38,147] and other imaging techniques, such as multislice computed tomography and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography imaging, are useful in the setting of suspected PVE[216] and have already been included in recent guidelines.[38,217] The question remains if those imaging modalities (and their combination) can lead to earlier diagnosis and treatment with improved outcomes, in particular in the setting of TAVI-IE with the value of this multimodality approach not determined.[218]

IE-related complications, including heart failure, persistent bacteremia, and systemic embolization other than stroke, were also associated with a higher likelihood of performing CS. This reflects the indication for CS provided by current guidelines and suggests that those criteria at least partially have been implemented in TAVI-IE.[38,217]

5.6.2 Surgical considerations

The median time from diagnosis to CS was 17.5 days. This prolonged time period is most likely caused by multiple factors, including difficult decision-making by both the patient and the treating physicians, transfer from another hospital, and treatment failure of the initial approach. The latter factor might explain the increased rate of IE-related complications in IE-CS, thereby generating the indication for CS. This delay might have diminished the positive effects of CS. However, controversy exists regarding the optimal time point of CS in IE.[38,217] One randomized trial including patients with native valve IE and relevant valve dysfunction found that early surgery compared with conventional treatment (with 77% of patients receiving surgery beyond 48 hours) reduced the risk of the composite endpoint embolic events and in-hospital mortality within 6 weeks, with no

difference in all-cause mortality after 6 months.[64] No randomized clinical trial evaluating the role and timing of CS in PVE has been performed.

Surgical treatment of TAVI-IE is challenging[219]; in particular, adhesion of large stent frames of self-expanding devices with the ascending aorta may lead to complex surgical procedures.[220] However, the distribution of self-expanding vs balloon-expandable devices was not different in this analysis, and aortic root replacement was performed equally in self-expanding and balloon-expandable devices. The rate of CS was also similar in a study comparing these 2 principal types of TAVI prostheses.[159] About one-fifth of IE-CS received combination procedures due to extensive infection or concomitant diseases; an example is coronary artery disease, which might have had an effect on mortality because of additional procedures (e.g., coronary artery bypass grafting) may prolong operation time and have been associated with early mortality in IE treated with CS.[221]

5.6.3 Outcome

TAVI-IE is associated with a poor prognosis,[156,157,181] with one-third of the patients experiencing in-hospital death and a mortality rate of roughly 50% after 1 year in this analysis. This is in line with other published data,[147] although lower mortality has been documented in more recent patients compared with a historical cohort.[199] Compared with patients with PVE after surgical valve replacement, both in-hospital and 1-year mortality rates are higher in TAVI-IE.[65] Several patient- and disease-related factors may contribute to this finding, including older age, a higher burden of comorbidities, and a high rate of nosocomial/health care–associated IE, with enterococci and staphylococci as the main causative microorganism.[43]

The current study showed that in-hospital and 1-year all-cause mortality was not significantly different between IE-CS and IE-AB in the crude cohort, confirming the results of a small study showing that CS provided no significant mortality benefit compared with medical therapy.[174] The first analysis of the Infectious Endocarditis after TAVI International Registry[156] showed that surgery during IE hospitalization was also

not associated with a reduced risk of in-hospital death. However, these analyses lacked appropriate statistical methods to evaluate the treatment effect.

To account for selection bias, we applied the method of IPTW that is favored in observational studies comparing treatment effects due to no substantial reduction in sample size and, at least in simulation studies, its superior performance in controlling for selection bias compared with stratification or propensity matching.[222] Immortal time bias is an important issue in observational studies. The probability of receiving CS is influenced by longer survival, leading to the problem that patients who die early during hospitalization are considered as deaths associated with medical therapy despite potentially developing or already having an indication for CS. To reduce this bias, surgery was included as a time-varying covariate in the multivariate model adjusted by IPTW. This analysis revealed no significant differences between IE-CS and IE-AB regarding in-hospital and 1-year all-cause mortality. In contrast, patient characteristics, pathogen, and IE-related complications, including acute renal failure, persistent bacteremia, and septic shock, were independently associated with 1-year all-cause mortality. This is similar to observations made in native valve IE and PVE,[29,61,65] partially reflecting the indications for CS suggested by current guidelines.[38,217] Hypothetically, patients having those factors (e.g., IE caused by *S aureus*) might benefit from early CS before other complications (e.g., septic shock) occur.

It is noteworthy that TAVI platform involvement (vs no involvement)) was not independently associated with mortality. Moreover, restricting the analysis to patients with definite TAVI platform involvement did not change the results, indicating that the overall cohort was not diluted by inclusion of patients having no TAVI platform involvement.

5.6.4 Study limitations

First, although this was an international, multicenter registry, it was voluntary, observational, and nonrandomized in nature, with the limitations and potential bias on data collection and analysis inherent to this design. Second, there was no external

monitoring to verify the accuracy of data reported by each center. Third, the fact that that our model did not account for institutional characteristics, and the local IE team decided on an individual basis to perform CS, is a potential bias because personal judgment and readiness to assume risk may differ between IE teams. Moreover, the availability of structural requirements and surgical expertise may lead to different treatment decisions across participating centers. In addition, the reasons not to perform CS were not documented in our registry. Fifth, most of the patients were already at high surgical risk before TAVI, and the operative risk was even higher after they developed IE. Therefore, projecting the future expansion of TAVI to younger, lower risk patients, these results may not be transferable, and surgery could be an excellent option in those patients.

5.7 CONCLUSIONS

The majority of patients with TAVI-IE were treated with antibiotics alone. Approximately one-half of the patients had died within 1 year, with mortality strongly associated with each patient's characteristics, pathogen, and IE-related complications. The mortality rates for IE-CS and IE-AB were not significantly different in the crude cohort, which was confirmed by an appropriate multivariate model adjusting for treatment selection and immortal time bias indicating that individual decision-making by a specialized IE team is mandatory to offer TAVI-IE the optimal treatment. Moreover, because both treatment options are associated with an equal worse outcome, prevention and early diagnosis of infective endocarditis are of utmost importance.

5.8 PERSPECTIVES

Competency in patient care and procedural skills: IE after TAVI is associated with high in-hospital and mid-term mortality irrespective of whether management includes antibiotics alone or is combined with CS intervention.

Translational outlook: Systematic collection and analysis of data by multidisciplinary teams are needed to develop standards for clinical assessment and management of patients with IE after TAVI.

5.9 ACKNOWLEDGMENTS

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5.11 SUPPLEMENTAL MATERIAL

Supplemental Table 5.1. Specific TAVI valve types implanted in patients developing infective Endocarditis.

Balloon-expandable prostheses	Self- or mechanically expandable prostheses
Edwards Sapien™ [Edwards Lifesciences, Irvine, CA, USA]	Medtronic CoreValve™ and Evolut R™ [Medtronic, Minneapolis, MN, USA]
Sapien XT™ [Edwards Lifesciences, Irvine, CA, USA]	Lotus™ Valve System [Boston Scientific, Marlborough, MA, USA]
Sapien 3™ [Edwards Lifesciences, Irvine, CA, USA]	Portico™ valve [Abbott Vascular, Abbott Park, IL, USA]
	Symetis Accurate™ [TA and neo] [Symetis SA, a Boston Scientific company, Ecublens, Switzerland]
	Direct flow™ [Direct Flow Medical Inc. Santa Rosa, CA, USA]
	JenaValve™ [JenaValve Technology Inc. Irvine, CA]
	Medtronic Engager™ [Medtronic, Minneapolis, MN, USA]
	Centera™ [Edwards Lifesciences, Irvine, CA, USA]

Supplemental Table 5.2. Odds ratio and 95%-Confidence Interval calculated from the logistic regression model used to determine the propensity score for surgery and inverse probability of treatment weighting.

	OR (95% CI) (for surgery)
Baseline and TAVI features	
Age*	0.95 (0.92-0.98)
Female Gender	0.69 (0.44-1.07)
Diabetes mellitus	0.74 (0.48-1.15)
COPD	1.12 (0.71-1.76)
Chronic renal failure	0.66 (0.43-1.02)
Previous Stroke	1.48 (0.84-2.60)
Previous heart surgery	0.93 (0.57-1.54)
LV-EF (<50% vs ≥50%)	0.97 (0.58-1.62)
Presenting features	
Early vs Late IE	1.25 (0.81-1.93)
Neurological symptoms	0.37 (0.19-0.74)
Echocardiographic findings	
Vegetation >10 mm	2.35 (1.54-3.59)
Periannular complication	2.74 (1.73-4.34)
TAVI platform affection†	2.16 (1.36-3.43)
Microorganism	
Staphylococcus aureus	1.18 (0.73-1.90)
Coagulase-negative Staphylococci	2.00 (1.23-3.25)
Enterococci	0.70 (0.42-1.17)
IE complications	
Heart failure	2.14 (1.41-3.25)
Acute renal failure	1.36 (0.90-2.06)
Stroke	1.29 (0.67-2.49)
Septic shock	1.04 (0.66-1.66)
Other systemic embolization	2.67 (1.50-4.77)
Persistent bacteremia	2.27 (1.48-3.49)

TAVI indicates transcatheter aortic valve implantation; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; IE, infective endocarditis.
* Per 1-year increase. † No TAVI platform involvement as reference

Supplemental Table 5.3. Main causes for in-hospital mortality.

	Overall (n=183)	IE-AB (n=151)	IE-CS (n=32)
Septic Shock/Multiorgan failure	112 (61.2)	93 (61.6)	19 (59.4)
Heart failure/Cardiogenic shock	21 (11.5)	17 (11.3)	4 (12.5)
Sudden death	10 (5.5)	9 (6.0)	1 (3.1)
Systemic embolism (including stroke)	14 (7.7)	10 (6.6)	4 (12.5)
Major bleeding	8 (4.4)	6 (4.0)	2 (6.3)
Other	3 (1.6)	3 (2.0)	0 (0)
Unknown	15 (8.2)	12 (8.6)	3 (6.3)

Values are n (%). IE-AB indicates infective endocarditis treated with antibiotics only; IE-CS, infective endocarditis treated with cardiac surgery (and antibiotics)

Supplemental Table 5.4. Baseline characteristics, procedural details, and in-hospital TAVI outcomes after IPTW.

	After IPTW		
	IE-AB	**IE-CS**	**ASD**
Baseline characteristics			
Age, years	79.5	78.2	0.19
Female	37.2	32.7	0.10
Body mass index, kg/m^2	27.7	28.8	0.19
Diabetes mellitus	36.3	32.4	0.08
COPD	27.4	28.7	0.03
Atrial fibrillation	42.8	40.0	0.06
Chronic renal failure	42.9	40.2	0.05
Previous Stroke	13.2	14.4	0.04
Previous heart surgery	10.1	15.7	0.17
Previous valve surgery	22.7	22.1	0.01
Previous infectious endocarditis	1.4	2.1	0.05
Logistic EuroSCORE, %	17.1	15.2	0.15
Left ventricular ejection fraction, %	53.8	52.9	0.07
Mean transaortic gradient, mmHg	44.9	44.5	0.03
Aortic valve area, cm2	72.6	75.6	0.12
Periprocedural characteristics			
Implantation site			
Operating or hybrid room	58.0	65.6	0.16
Approach			
Transfemoral	87.4	90.4	0.09
Endotracheal intubation	53.2	39.8	0.27
Prosthesis type			
Balloon-expandable	52.0	57.1	0.10
Antibiotic prophylaxis			
B-Lactam alone	93.5	94.2	0.03
In-hospital Outcomes (TAVI)			
Acute renal failure	13.3	9.2	0.13
Stroke	4.6	3.1	0.08
Major vascular complication	7.1	7.4	0.01
Major bleeding	10.9	5.5	0.20
New pacemaker implantation	16.2	28.2	0.29
Length of hospital stay, days	13.7	11.4	0.18

Values are relative frequencies (%) or mean. IE-AB indicates infective endocarditis treated with antibiotics only; IE-CS, infective endocarditis treated with cardiac surgery (and antibiotics); COPD, chronic obstructive pulmonary disease; TAVI, transcatheter aortic valve implantation; ASD, absolute standardized mean difference.

Supplemental Table 5.5. Main clinical characteristics of IE after TAVI after IPTW.

	After IPTW		
	IE-AB	**IE-CS**	**ASD**
Early IE (within 1 year)	30.64	35.8	0.11
Initial symptoms			
Fever	76.71	71.7	0.12
New-onset heart failure	42.97	39.4	0.07
Neurological	17.31	16.7	0.02
Systemic embolism	12.14	17.8	0.16
Cutaneous	4.93	4.9	0.00
Health care–associated infection	42.9	47.2	0.09
Echocardiographic findings			
Vegetation	67.48	73.5	0.13
Vegetation >10 mm	36.71	45.6	0.18
TAVR involvement	61.33	70.1	0.19
Periannular complication	22.55	26.3	0.09
New aortic regurgitation	12.47	15.1	0.08
New mitral regurgitation	16.98	17.3	0.01
Valves involved			
Isolated TAVR prosthesis	48.7	50.3	0.03
Mitral (native- or prosthetic valve)	16.6	7.2	0.29
Cardiac device	1.7	20.6	0.63
Right-sided IE	1.2	1.6	0.03
Other*	31.9	20.3	0.27
Causative microorganisms			
Staphylococcus aureus	22.01	26.0	0.09
Coagulase-negative Staphylococci	20.3	25.0	0.11
Enterococci	24.38	17.9	0.16
Streptococci			
Oral streptococci	15.95	6.5	0.30
S. gallolyticus (S. bovis)	5.21	6.6	0.06
Culture negative	5.23	12.7	0.26
IE complications			
Any complication	74.8	83.9	0.23
Heart failure	43.01	52.0	0.18
Acute renal failure	39.64	44.9	0.11
Stroke	11.07	12.9	0.06
Septic shock	23.39	28.1	0.11
Other systemic embolization	12.89	17.2	0.12

Persistent bacteremia	28.88	35.9	0.15

*2 localization at least
Values are relative frequencies (%).
IE-AB indicates infective endocarditis treated with antibiotics only; IE-CS, infective endocarditis treated with cardiac surgery (and antibiotics); IE, infective endocarditis; ASD, absolute standardized mean difference.

Supplemental Table 5.6. Predictors of in-hospital and 1-year Mortality in Patients with Infective Endocarditis after TAVI. Cox Proportional Hazards Model Weighted by the Inverse Probability of Surgery.

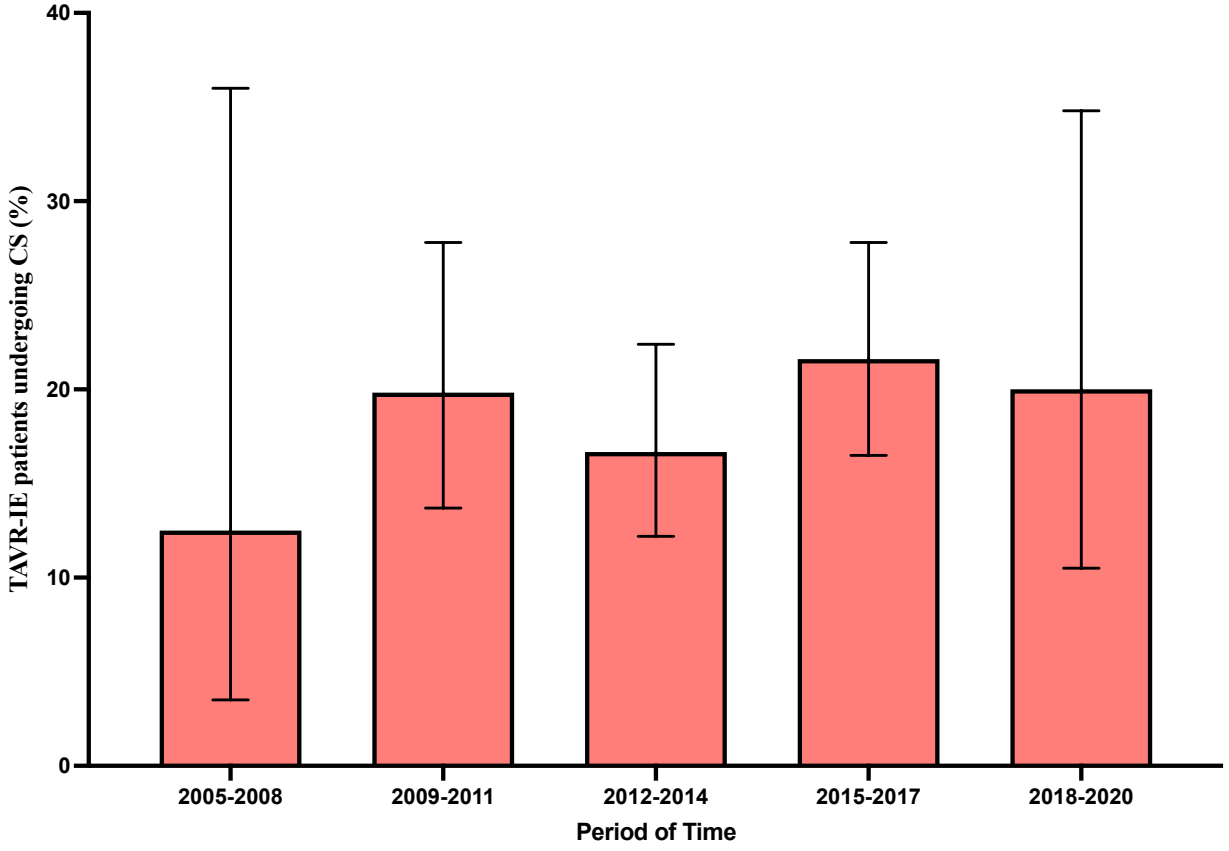
	In-Hospital Mortality Hazard Ratio (95% CI)	Adjusted P Value	1-year Mortality Hazard Ratio (95% CI)	Adjusted P Value
Cardiac Surgery vs. ABx only*	0.92 (0.80-1.05)	0.004	0.95 (0.84-1.07)	0.374
Logistic EuroSCORE†	1.01 (1.00-1.03)	0.055	1.02 (1.01-1.03)	0.005
Endotracheal intubation	1.03 (0.72-1.48)	0.866	1.17 (0.85-1.60)	0.342
New pacemaker implantation (after TAVI)	0.90 (0.53-1.51)	0.685	0.79 (0.49-1.29)	0.353
Staphylococcus aureus	1.34 (0.81-2.20)	0.254	1.51 (1.00-2.29)	0.049
Enterococci	1.33 (0.80-2.21)	0.277	1.45 (0.97-2.15)	0.070
Coagulase-negative Staphylococci	0.96 (0.52-1.77)	0.892	1.18 (0.72-1.92)	0.511
Oral streptococci	1.15 (0.58-2.28)	0.686	0.99 (0.58-1.69)	0.962
Culture-negative IE	1.05 (0.40-2.76)	0.918	1.09 (0.45-2.62)	0.847
Valves involved‡	1.02 (0.70-1.48)	0.921	0.97 (0.69-1.37)	0.870
Periannular complication	0.89 (0.56-1.41)	0.621	1.01 (0.69-1.49)	0.943
Heart failure	1.50 (0.97-2.32)	0.069	1.36 (0.93-1-98)	0.117
Acute renal failure	1.99 (1.24-3.19)	0.004	2.25 (1.51-3.35)	<0.001
Persistent bacteremia	1.88 (1.14-3.10)	0.014	1.78 (1.17-2.70)	0.008
Stroke	1.10 (0.64-1.86)	0.738	1.04 (0.64-1.67)	0.884
Septic shock	5.93 (3.72-9.44)	<0.001	3.54 (2.42-5.17)	<0.001
Other systemic embolization	0.82 (0.51-1-31)	0.400	0.87 (0.56-1.34)	0.523

TAVI, transcatheter aortic valve implantation
*Cardiac surgery included as a time-varying covariate. †Per 1% increase. ‡ No TAVI platform involvement as reference.

Supplemental Table 5.7. Predictors of in-hospital and 1-year Mortality in Patients with Infective Endocarditis after TAVI with and without TAVI involvement. Cox Proportional Hazards Model Weighted by the Inverse Probability of Surgery in patients with and without TAVI involvement.

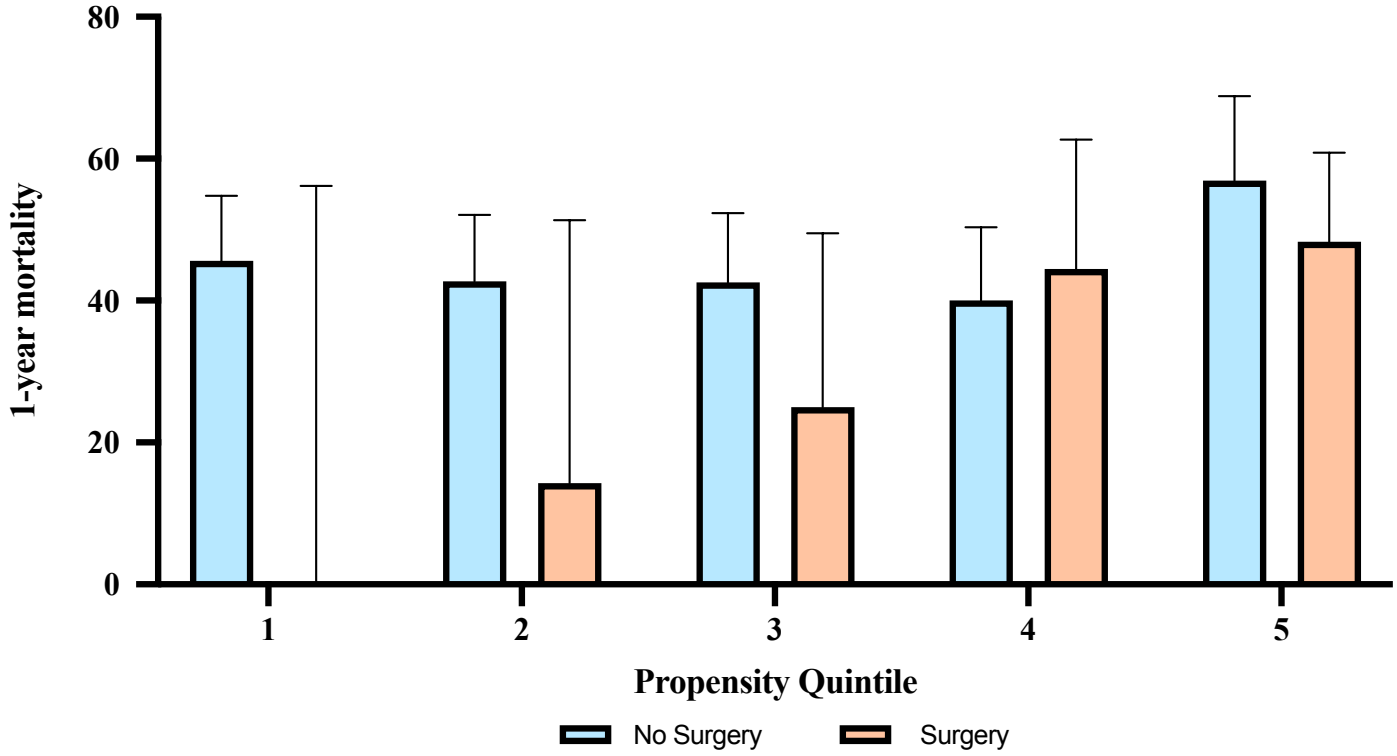
	IE with TAVI involvement (HR, 95% CI)		IE with no TAVI involvement (HR, 95% CI)	
	In-Hospital Mortality	**1-year Mortality**	**In-Hospital Mortality**	**1-year Mortality**
Cardiac Surgery vs. ABx only*	0.98 (0.86-1.11)	0.94 (0.83-1.06)	0.54 (0.24-1.24)	1.00 (0.83-1.22)
Logistic EuroSCORE†	1.01 (0.99-1.02)	1.00 (0.99-1.02)	1.02 (1.00-1.04)	1.04 (1.02-1.06)
Endotracheal intubation	1.03 (0.65-1.66)	1.10 (0.74-1.63)	1.14 (0.68-1.92)	1.60 (0.98-2.60)
New pacemaker implantation (after TAVI)	0.87 (0.42-1.84)	1.02 (0.55-1.90)	0.95 (0.49-1.84)	0.55 (0.30-1.01)
Staphylococcus aureus	1.55 (0.87-2.74)	1.36 (0.83-2.23)	1.45 (0.60-3.50)	1.94 (0.94-4.00)
Enterococci	1.42 (0.76-2.67)	1.50 (0.89-2.53)	1.09 (0.45-2.63)	1.30 (0.60-2.78)
Coagulase-negative Staphylococci	1.35 (0.69-2.64)	1.51 (0.87-2.62)	0.44 (0.13-1.50)	0.59 (0.22-1.56)
Oral streptococci	1.17 (0.51-2.67)	0.97 (0.49-1.95)	1.23 (0.46-3.30)	1.08 (0.40-2.95)
Culture-negative IE	1.22 (0.43-3.45)	0.99 (0.39-2.54)	1.46 (0.45-4.67)	4.07 (1.41-11.73)
Periannular complication	0.95 (0.58-1.56)	1.04 (0.69-1.58)	0.79 (0.30-2.06)	1.14 (0.49-2.68)
Heart failure	1.25 (0.71-2.19)	1.29 (0.82-2.03)	2.17 (1.16-4.03)	1.80 (1.05-3.08)
Acute renal failure	2.32 (1.30-4.12)	2.52 (1.56-4.05)	1.17 (0.60-2.32)	1.27 (0.69-2.32)
Persistent bacteremia	2.01 (1.12-3.62)	1.67 (1.06-2.64)	2.24 (0.90-5.58)	2.43 (1.27-4.66)
Stroke	1.10 (0.61-1.99)	1.26 (0.75-2.12)	1.69 (0.61-4.64)	1.04 (0.49-2.20)
Septic shock	4.55 (2.53-8.18)	3.45 (2.15-5.53)	12.09 (5.96-24.54)	4.54 (2.43-8.48)
Other systemic embolization	1.18 (0.72-1.93)	1.16 (0.73-1.83)	0.20 (0.06-0.68)	0.35 (0.13-0.93)

TAVI, transcatheter aortic valve implantation. *Cardiac surgery included as a time-varying covariate.
†Per 1% increase.



	12.5% (3.5-36.0)	19.8% (13.7-27.8)	16.7% (12.2-22.4)	21.6% (16.5-27.8)	20.0% (10.5-34.8)
No. of patients					
IE-AB	14	97	170	156	32
IE-CS	2	24	34	43	8

Supplemental Figure 5.1: Rates of cardiac surgery (CS) over different periods of time.



Propensity, mean (range)	0.031 (0.004-0.051)	0.074 (0.052-0.100)	0.135 (0.100-0.175)	0.232 (0.175-0.308)	0.476 (0.316-0.843)
No. of patients					
IE-AB	114	110	101	90	58
IE-CS	3	7	16	27	58

Supplemental Figure 5.2: 1-year all-cause mortality for IE-AB (no surgery) vs IE-CS (surgery) across propensity quintiles.

CHAPTER 6: Long-Term Outcomes After Infective Endocarditis After Transcatheter Aortic Valve Replacement

David del Val, MD[1], Axel Linke, MD[2,3], Mohammed Abdel-Wahab, MD[2,4], Azeem Latib, MD[5,6], Nikolaj Ihlemann, MD[7], Marina Urena, MD[8], Kim Won-Keun, MD MD[9], Oliver Husser, MD[10,11], Howard C Herrmann, MD[12], Luis Nombela-Franco, MD[13], Asim Cheema, MD[14,15], Hervé Le Breton, MD[16], Stefan Stortecky, MD[17], Antonio Bartorelli, MD[18], Jan Malte Sinning, MD[19], Ignacio Amat-Santos, MD, PhD[20], Antonio Munoz-Garcia, MD[21], Stamatios Lerakis, MD[22,23], Enrique Gutiérrez-Ibanez, MD[24], Martin Landt, MD[4], Didier Tchetche, MD[25], Luca Testa, MD[26], Helene Eltchaninoff, MD[27], Ugolino Livi, MD[28], Juan Carlos Castillo, MD[29], Tarun Chakravarty, MD[30], John G Webb, MD[31], Marco Barbanti, MD[32], Susheel Kodali, MD[33], Fabio Sandoli de Brito Jr, MD[34], Henrique Ribeiro, MD[35], Antonio Miceli, MD[36], Claudia Fiorina, MD[37], Guglielmo Mario Actis Dato, MD[38], Francesco Rosato, MD[39], Vicenç Serra, MD[40], Jean-Bernard Masson, MD[41], Harindra C Wijeysundera, MD[42], Jose Armando Mangione, MD[43], Maria-Cristina Ferreira, MD[44], Valter Correa Lima, MD[45], Alexandre Siciliano Colafranceschi, MD[46], Alexandre Abizaid, MD[47], Marcos Antonio Marino, MD[48], Vinicius Esteves, MD[49], Julio Andrea, MD[50], Dominique Himbert, MD[8], Costanza Pellegrini, MD[10], Vincent Auffret, MD[16], Paolo Olivares, MD[18], Fabian Nietlispach, MD[51], Thomas Pilgrim, MD[17], Eric Durand, MD[27], John Lisko, MD[22], Raj Makkar, MD[30], Abdullah Alkhodair, MD[31], Lars Søndergaard, MD[7], Mangner Norman, MD[2,3], Lisa Crusius, MD[2], David Holzhey, MD[2], Ander Regueiro, MD[1,52], Josep Rodés-Cabau, MD[1]

[1] Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada; [2] Heart Center, Leipzig University, Leipzig, Germany; [3]University Hospital Dresden, Dresden, Germany; [4]Heart Center, Segeberger Kliniken, Bad Segeberg, Germany; [5]Ospedale San Raffaele, Milan, Italy; [6]Montefiore Medical Center, New York, NY, USA; [7]Righospitalet, Copenhagen, Denmark; [8]Bichat Hôpital, Paris, France; [9]Kerckhoff Klinik, Bad Nauheim, Germany; [10]Deutsches Herzzentrum, München, Germany; [11]St.-Johannes-Hospital Dortmund; [12]Hospital of the University of Pennsilvania, Philadelphia, USA; [13]Hospital Universitario Clinico San Carlos, Madrid, Spain; [14]St Michaels Hospital, Toronto, Canada; [15]Southlake Regional Health Centre, Newmarket, ON, Canada; [16]Centre Hospitalier Universitaire de Rennes, Rennes, France; [17] Bern University Hospital (on behalf of Swiss Registry Centres), Bern, Switzerland; [18]Centro Cardiologico Monzino, Milan, Italy; [19]Heart Center Bonn, Bonn, Germany; [20]Hospital Clinico Universitario de Valladolid, Valladolid, Spain; [21]Hospital Universitario Virgen de la Victoria, Malaga, Spain; [22]Emory University School of Medicine, Atlanta, USA; [23]Mount Sinai Hospital, New York, NY, USA; [24]Hospital Gregorio Maranon, Madrid, Spain; [25]Clinique Pasteur, Toulouse, France; [26]IRCCS Pol. San Donato, Milan, Italy; [27]Hôpital Charles Nicolle, University of Rouen, Rouen, France; [28]AOU Santa Maria della Misericordia, Udine, Italy; [29]Hospital Universitario Reina Sofia, Cordoba, Spain; [30]Cedars-Sinai Heart Institute, Los Angeles, USA; [31]St Paul's Hospital, Vancouver, Canada; [32]Ferrarotto Hospital, Catania, Italy; [33]Columbia University Medical Center, New York, USA; [34]Hospital Israelita Albert Einstein, Sao Paulo, Brazil; [35]Instituto Nacional Cardiovascular (INCOR), Sao Paulo, Brazil; [36]Fondazione Toscana G. Monasterio, Massa, Italy; [37]Ospedali Civili di Brescia, Brescia, Italy; [38]Ospedali Mauriziano, Torino, Italy; [39]S. Cocre e Carle Cuneo, Cuneo, Italy; [40]Hospital Vall d'Hebron, Barcelona, Spain; [41]Centre Hospitalier de l'Universite de Montreal, Montreal, Canada; [42]Sunnybrook Health Science Center, Toronto, Canada; [43]Hospital Beneficencia Portuguesa, Sao Paulo, Brazil; [44] Hospital Naval Marcilio Dias, Rio de Janeiro, Brazil; [45]Hospital Sao Francisco-Santa Clara, Porto Alegre, Brazil; [46]Hospital Pró-cardíaco, Rio de Janeiro, Brazil; [47]Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil; [48]Hospital Madre Teresa, Belo Horizonte, Brazil; [49]Hospital Sao Luiz, Sao Paulo, Brazil; [50]Clínica Sao Vicente, Rio de Janeiro, Brazil; [51]University Hospital Zurich, Zurich, Switzerland; [52]Hospital Clinic de Barcelona, Barcelona, Spain.

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6.1 RÉSUMÉ

Contexte : Il existe peu de données sur le pronostic à long terme des patients atteints d'endocardite infectieuse (EI) après un remplacement percutané de valve aortique (TAVR).

Objectifs : Nous avons cherché à déterminer les facteurs pronostiques et le devenir à long terme des patients présentant EI certaine après un TAVR qui ont survécu à l'hospitalisation initiale.

Méthodes : Le registre international Infectious Endocarditis after TAVR a inclus des patients atteints d'une EI certaine après un TAVR provenant de 47 sites en Europe, en Amérique du Nord et en Amérique du Sud. Pour cette étude, les données sur le suivi à long terme des patients qui ont quitté l'hôpital (indemnes de mortalité hospitalière) après l'épisode initial d'EI ont été recueillies rétrospectivement entre octobre 2018 et octobre 2019.

Résultats : Un total de 155 patients ayant survécu à un épisode initial d'EI après un TAVR ont été inclus. Le taux de mortalité à 5 ans était de 62,5 % (IC à 95 % : 53,1 % à 71,9 %), et les taux de récidive d'EI et de chirurgie pendant le suivi étaient respectivement de 12,5 % (IC à 95 % : 7,4 % à 17,6 %) et de 3,8 % (IC à 95 % : 0,8 % à 6,7 %). La mortalité toutes causes confondues était associée de façon indépendante à l'insuffisance rénale chronique basale (HRadj : 2,20 ; IC à 95 %, 1,36 à 3,57, P=0,001), l'absence de fièvre comme symptôme initial (HRadj : 2,58 ; IC à 95 %, 1,50 à 4,44, P=0,001), l'absence d'atteinte de la prothèse TAVR (HRadj : 2,12 ; IC à 95 %, 1,28 à 3,51, P=0,004), une première poussée d'insuffisance cardiaque (HRadj : 1,91 ; IC à 95%, 1,15 à 3,17, P=0,013), une insuffisance rénale aiguë pendant l'hospitalisation pour EI (HRadj : 1,90 ; IC à 95%, 1,15 à 3,14 ; P=0,012) et une bactériémie persistante (HRadj : 2,21 ; IC à 95%, 1,21 à 4,03, P=0,010). Le taux de mortalité à 5 ans parmi les patients présentant plus de 2 facteurs de risque était de 100 %.

Conclusions : Les patients ayant survécu à un épisode initial d'EI après le TAVR présentaient un taux de mortalité très élevé lors du suivi à 5 ans. L'insuffisance rénale chronique, l'absence de fièvre ou d'affection de la prothèse TAVR lors de l'épisode initial

d'EI, et les complications liées à l'EI étaient associés à un pronostic sombre. D'autres études sont nécessaires pour prévenir et améliorer les résultats de l'EI après le TAVR.

6.2 ABSTRACT

Background: Limited data exist on long-term outcomes of patients with infective endocarditis (IE) after transcatheter aortic valve replacement (TAVR). We aimed to determinate the prognostic factors and long-term outcomes in patients with definite IE following TAVR who survived the index hospitalization.

Methods: The Infectious Endocarditis after TAVR International Registry included patients with definite IE after TAVR from 47 sites across Europe, North America, and South America. For this study, data on long-term follow-up of patients who were discharged (no in-hospital mortality) after the initial episode of IE were retrospectively collected between October 2018 and October 2019.

Results: A total of 155 patients who survived an initial IE episode after TAVR were included. The 5-year mortality rate was 62.5% (95% CI: 53.1% to 71.9%), and the rates of IE recurrence and surgery during follow-up were 12.5% (95% CI: 7.4% to 17.6%) and 3.8% (95% CI: 0.8% to 6.7%), respectively. All-cause mortality was independently associated with baseline chronic renal failure (HRadj: 2.20; 95% CI, 1.36 to 3.57, P=0.001), absence of fever as initial symptom (HRadj: 2.58; 95% CI, 1.50 to 4.44, P=0.001), no TAVR platform affection (HRadj: 2.12; 95% CI, 1.28 to 3.51, P=0.004), new-onset heart failure (HRadj: 1.91; 95% CI, 1.15 to 3.17, P=0.013), acute renal failure during IE hospitalization (HRadj: 1.90; 95% CI, 1.15 to 3.14; P=0.012), and persistent bacteremia (HRadj: 2.21; 95% CI, 1.21 to 4.03, P=0.010). The 5-year mortality rate among those patients with >2 risk factors was 100%.

Conclusions: Patients who survived an initial IE episode after TAVR had a very high mortality rate at 5-years follow-up. Chronic renal failure, absence of fever or transcatheter valve affection at index IE episode, and IE-related complications determined a dismal prognosis. Further studies are needed to both prevent and improve the outcomes of IE post-TAVR.

6.3 RESEARCH LETTER

Infective endocarditis (IE) after transcatheter aortic valve replacement (TAVR) is a rare but life-threatening complication associated with a high rate of severe complications and in-hospital death.[156,157,179] The high comorbidity burden of TAVR recipients along with an increased exposure to health care–associated procedures may explain, in part, the poorer clinical outcomes of this population. To date, most data on outcomes of IE after TAVR have been limited to short-term or midterm (1-year) follow-up.[165] In this study, we sought to evaluate the long-term (>2 year) outcomes and prognostic factors in patients developing definite IE after TAVR who survived the index hospitalization.

The Infective Endocarditis after TAVR International Registry collected data from 250 cases of definite IE (regardless of the structure involved) after TAVR (out of 20,006 patients undergoing TAVR; incidence: 1.1% per person-year) from 47 sites in Europe, North America, and South America between June 2005 and October 2015. The details and definitions of this registry have been previously reported.[156] The incidence of in-hospital mortality was 36% (90 patients). The present study analyzed the patients who survived the index IE episode. Data on long-term outcomes were updated by each center between October 2018 and October 2019. The follow-up was complete in all patients but 5 (98%). All patients provided signed informed consent for the procedures, and the study was performed in accordance with the local ethics committee of each center. A multivariable Cox proportional hazards model was performed to determine the factors independently associated with mortality. The variables considered to be associated with late mortality and with a P value of <0.10 in the univariable analysis were included in the multivariable model. The proportional hazards assumption was tested by assessing log-minus-log survival plots and scaled Schoenfeld residuals. Survival at the 5-year follow-up was presented as Kaplan-Meier curves, and the Kaplan-Meier method was used to estimate the 5-year mortality incidence. Event times were measured from the date of initial IE symptoms to the date of death or last follow-up. Differences in the incidence of mortality were determined using the log-rank test. A 2-sided P value of <0.05 was considered statistically significant; 95% CIs were reported in square brackets.

A total of 155 patients who survived an initial IE episode after TAVR were included (mean age: 79.4±7.8 years; 65.8% men; 11.6% with previous valve surgery; median Society of Thoracic Surgeons score: 6.7% [interquartile range, 3.9%–12%]). Most of these patients (85.8%) underwent TAVR through a transfemoral approach, with balloon- and self-expanding valves implanted in 49% and 51% of patients, respectively. The IE episode occurred after a median of 5.2 (interquartile range, 1.5–12.2) months after TAVR. One hundred six patients (68.4%) had IE affecting the TAVR prosthesis (55.6% with isolated TAVR-IE), 10.8% had native or prosthetic mitral valve IE, 3.2% had implantable cardiac device IE, 1.6% had tricuspid IE, and 28.8% had any other structure combination. *Enterococcus species* were the most common microorganism (30.6%). A total of 84 patients (54.2%) died at a median follow-up of 24 (interquartile range, 6–46) months after the initial IE episode. The Kaplan-Meier estimate of all-cause mortality incidence at 5 years was 62.5% [53.1%–71.9%] **(Figure 6.1)**. The main causes of death during follow-up were cardiovascular events (22.6% [13.7–31.6]), infectious diseases unrelated to the IE episode (16.7% [8.7%–24.6%]), complications or sequels related to the index IE episode (9.5% [3.2%–15.8%]), and cancer (7.1% [1.6%–12.7%]). Recurrence of IE occurred in 20 cases (12.5% [7.4%–17.6%]), and late surgery was performed in 6 patients (3.8% [0.8%–6.7%]). The independent predictors of mortality in the multivariable analysis were baseline chronic renal failure (adjusted hazard ratio [HRadj], 2.20 [1.36–3.57]; P=0.001), absence of fever as initial symptom (HRadj, 2.58 [1.50–4.44]; P=0.001), no involvement of TAVR prosthesis (HRadj, 2.12 [1.28– 3.51]; P=0.004), new-onset heart failure (HRadj, 1.91 [1.15–3.17]; P=0.013), acute renal failure during IE hospitalization (HRadj, 1.90 [1.15–3.14]; P=0.012), and persistent bacteremia despite appropriate antibiotic therapy for >7 days (HRadj, 2.21 [1.21–4.03]; P=0.010). The Kaplan-Meier survival curves at 5-year follow-up for the global cohort and according to the presence of risk factors of late mortality are shown in the **Figure 6.1**. The presence of >2 risk factors was associated with a dreadful prognosis (mortality of 100% at 5 years).

The main limitations of this study are the potential bias on data collection inherent to retrospective studies and the lack of an independent event adjudication committee.

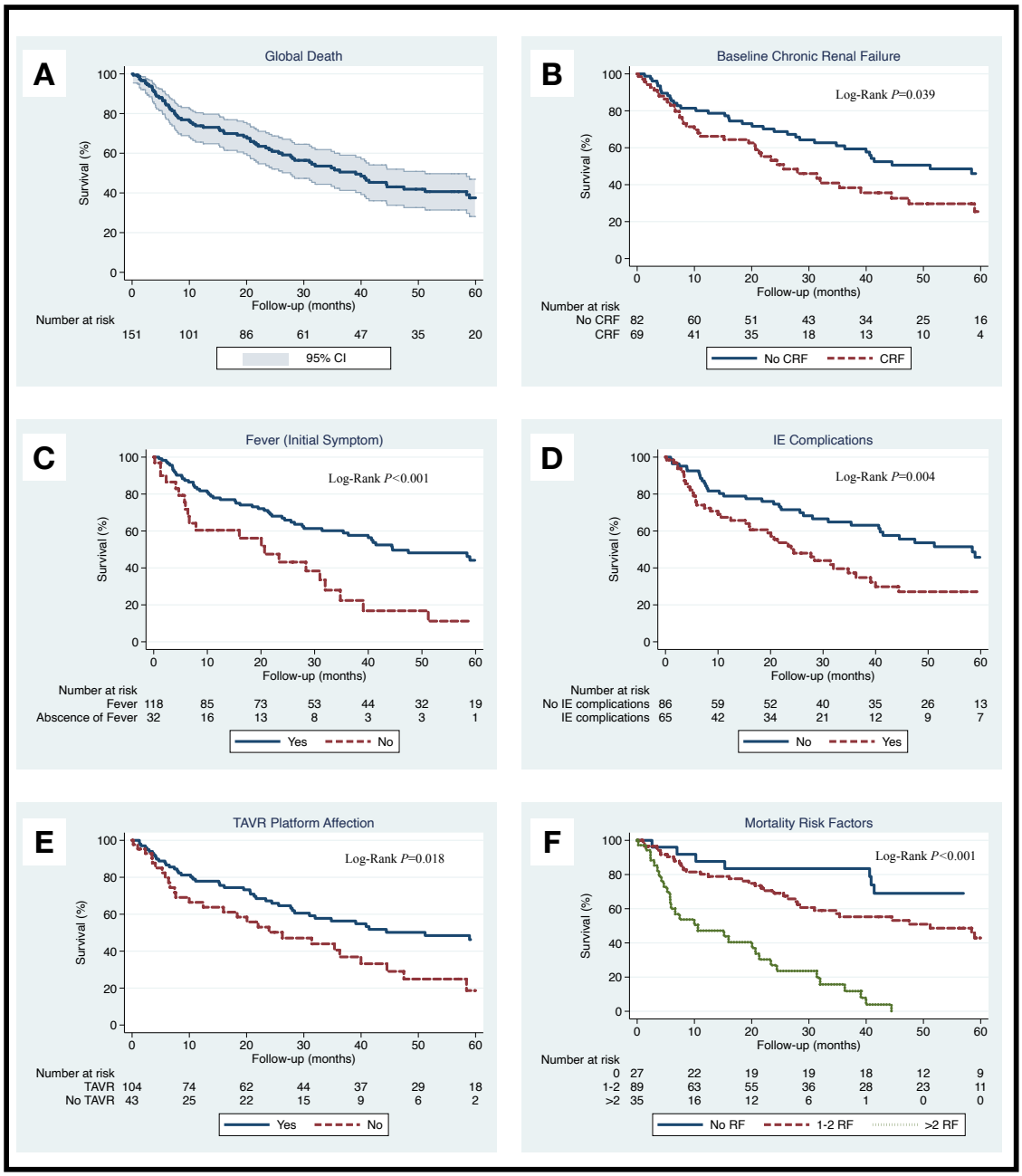

Figure 6.1. Kaplan-Meier estimate survival curves at 5-year follow-up of patients who survived the index IE hospitalization.

(A), Kaplan-Meier estimate survival curve at the 5-year follow-up of patients with IE after TAVR who survived the initial IE hospitalization. Kaplan-Meier estimate survival curve at the 5-year follow-up comparing patients with and without baseline chronic renal failure (B), fever as the initial symptom (C), IE-related complications (acute heart or renal failure and persistent bacteremia) (D), involvement of TAVR prosthesis (E), and the presence of factors associated with long-term mortality (F). These risk factors included chronic renal failure at TAVR baseline, the absence of fever as initial symptom, new-onset heart or renal failure during IE hospitalization, persistent bacteremia, and IE without TAVR platform involvement. Time 0 represents the time of IE diagnosis. CRF indicates chronic renal failure; IE, infective endocarditis; RF, risk factors; and TAVR, transcatheter aortic valve replacement.

In conclusion, patients who survived an initial IE episode after TAVR exhibited a poor prognosis, and about two-thirds of them had died at the 5-year follow-up. Chronic renal failure, IE characteristics (absence of fever, no TAVR prosthesis involvement), and the occurrence of IE-related complications determined an increased risk of late mortality. Late surgery during follow-up was low (<5%).

6.4 SOURCES OF FUNDING

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6.5 DISCLOSURES

There was no specific funding for this work. Dr Rodés-Cabau has receive institutional research grants from Edwards Lifesciences, Medtronic, and Boston Scientific. Dr Tchetche has received consulting fees from Abbott Vascular, Boston Scientific, Edwards Lifesciencies, and Medtronic. Dr Webb has received consulting fees from Edwards Lifesciences and St. Jude Medical. Dr Makkar has received research grants from Edwards Lifesciences, Medtronic, Abbott, Capricor, and St. Jude Medical; has served as a proctor for Edwards Lifesciences; and has received consulting fees from Medtronic. Dr de Brito has received honoraria from Medtronic and Edwards Lifesciences for symposium speeches and proctoring cases. Dr Lerakis has received consulting fees from Edwards Lifesciences. Dr Nietlispach has received speaker and proctor fees from Abbott Vascular, Edwards Lifesciences, and Medtronic. The other authors report no conflicts.

DISCUSSION, CLINICAL PERSPECTIVES AND CONCLUSIONS

7.1 DISCUSSION AND CLINICAL IMPLICATIONS

7.1.1 Incidence and temporal trends concerning infective endocarditis after transcatheter aortic valve replacement

Some studies have reliably evaluated the incidence of IE after TAVR, varying from 0.3 to 2.0 per 100 person-years.[146,148–150,152,154,155,157,158,162–164,170,175,176,179,223,224] These estimates are mainly based on large observational registries, non-dedicated randomized clinical trials, or analyses using nationwide administrative databases, with the limitations and bias inherent to these methodologies. It is worth noting that most of these studies include highly heterogeneous populations, ranging from elderly and inoperable patients treated with first-generation TAVR devices to younger patients with lower risk profiles undergoing minimalist procedures with the latest-generation TAVR devices. Hence, this variation in incidence rates is not particularly surprising and can be explained by the diversity of study designs and the heterogeneity of patient profiles.

Because of a great deal of interest in performing TAVR with a simplified and less invasive approach, the TAVR procedure has evolved substantially over the last few years. At present, this minimalist approach is considered the gold standard in most high-volume centers. The first study included in this PhD project aimed to elucidate whether this new TAVR era translated into a reduction in the incidence of IE, by comparing a historical cohort and a contemporary cohort. We found no significant temporal variation regarding the overall incidence of IE, although a slight downward trend was observed. Nevertheless, the incidence of early IE (within 60 days after TAVR), essentially related to the TAVR procedure and very early follow-up, was significantly lower in the contemporary cohort (2.3 vs. 4.9 per 1000 patient-years). This decline in early IE incidence may be explained by patient-related factors and procedure-related innovations. First, the profile of TAVR patients has shifted toward lower-risk patients with fewer serious comorbidities. These patients are typically less exposed to invasive medical procedures, and they are therefore at a lower risk of developing IE. Second, devices' iterations combined with procedural innovations, such as conscious sedation, left ventricular guidewire for rapid pacing, and transradial secondary access, have contributed to reducing major complications and shortening hospital stays, thus decreasing the risk of nosocomial infections.[182,183,225,226] Even though there is a paucity of studies assessing temporal trends in IE, recent data from a large study using a US administrative database showed a declining trend in overall IE

incidence between 2012 and 2017.[154] However, it is unknown whether this tendency reflects a decline in early IE or late IE, or both.

The downward trend in the early IE incidence observed in our study is noteworthy since the risk of IE appears to be greater in the first few months after TAVR. In the Swiss TAVR registry, including 7,203 consecutive patients undergoing TAVR, the highest risk of IE was observed during the early peri-procedural period (<100 days), with a 6-fold higher risk than more than 1 year after the procedure.[152] Furthermore, very early IE, closely related to the TAVR procedure, has been associated with dismal outcomes.[227] Although our findings have yet to be confirmed by further studies in contemporary TAVR populations, efforts to minimize the risk of peri-procedural infections with simplified interventions should continue. However, it is important to highlight that the shift to TAVR implementation in younger patients with longer life expectancy will lead to an exponential increase in the time at risk of developing this complication. Therefore, it would not be surprising if the incidence of IE, especially late IE, increases in the coming years.

7.1.2 Role of novel imaging techniques in the diagnosis of TAVR-IE

The diagnosis of PVE requires a high level of expertise and can be particularly challenging in patients with TAVR-IE. In the absence of specific recommendations in this subset of patients, current clinical guidelines suggest applying the modified Duke criteria or the ESC 2015 modified criteria.[31,38] However, the greater proportion of TAVR-IE patients presenting atypical symptoms and the lower sensitivity of TTE and TEE (especially at the early stages of the disease) led to a lower diagnostic accuracy for these criteria.[228] All these aspects result in diagnosis and treatment initiation delays, which in turn may lead to a major negative clinical impact. Thus, the integration of novel diagnostic tools for a more sensitive and accurate diagnosis in the setting of IE post-TAVR is strongly warranted. ^{18}F-FDG PET/CT, based on metabolic tissue activity, has been extensively used to improve the diagnostic accuracy of NVE and PVE.[216,229,230] The potential advantages of this imaging modality include the ability to detect intracardiac and systemic involvement of IE, even before structural damage is established.

Nevertheless, to date, scarce evidence is available on the use of ^{18}F-FDG PET/CT in IE post-TAVR.[231,232]

The fourth study of this PhD project evaluated the value of ^{18}F-FDG PET/CT in the diagnostic work-up of IE after TAVR. In this study, we found that noninfected transcatheter aortic valves did not exhibit a physiological ^{18}F-FDG uptake pattern three months after the TAVR procedure. Contrastingly, prior studies in surgical counterparts revealed that noninfective surgical prostheses frequently present a homogeneous ^{18}F-FDG uptake surrounding the prosthetic annular ring.[151,209,233] This characteristic pattern, related to sterile chronic inflammation, may remain steady over time and should be taken into account when evaluating patients with suspected PVE.[231,233] There are some plausible explanations for this distinction in physiological reaction between TAVR and surgical prostheses. First, SAVR typically involves the resection of native aortic leaflets, which could trigger a greater inflammatory healing response. In contrast, TAVR is considered less invasive and traumatic compared with contemporary surgical techniques. Second, the presence of sutures in most SAVR protheses may stimulate a chronic inflammatory response surrounding the prosthetic ring.[234] Third, surgical adhesives (which are not used in TAVR) have been identified as a confounding factor and predictor of false-positive ^{18}F-FDG-PET/CT.[208,235]

Certain distinctive differences in transcatheter aortic valves design and procedure-related features may potentially impact the host reaction after TAVR. For example, the much longer stent frame of the Evolut R/PRO valve compared with the low frame height of the SAPIEN 3 may be associated with greater local foreign-body reaction and, consequently, higher perivalvular ^{18}F-FDG uptake. Likewise, the balloon-expansion technique may induce a greater local injury and scarring, translating into an increase in ^{18}F-FDG uptake. However, we found no significant differences between the two prostheses in the qualitative analyses (attenuation- and nonattenuation-corrected images). Even in the patients on whom more aggressive strategies (pre- and post-balloon dilatation) were used, no significant ^{18}F-FDG uptake was observed surrounding the TAVR prosthesis at three months.

These findings may have meaningful clinical implications. In contrast with surgical patients, the presence of a significant ^{18}F-FDG uptake (more intense than the normal pulmonary parenchyma) surrounding the TAVR prosthesis should be interpreted as highly suspect of TAVR-IE and managed accordingly, regardless of the time since the procedure and valve type.

7.1.3 Infective endocarditis after transcatheter aortic valve replacement in patients with severe clinical presentations

Staphylococcus aureus is by far the most common microorganism causing IE in high-income countries, accounting for up to 40% of the infections. This contrasts with the unique microbiological profile of IE in TAVR patients, in which enterococci and *Staphylococcus aureus* are virtually tied in the ranking of causative microorganisms (~25% for each).[155,156] Several studies have recognized *Staphylococcus aureus* as an important prognostic marker in NVE and PVE.[203,236,237]

Although not surprising, the third study of this thesis highlighted the remarkable virulence of this pathogen in patients with IE post-TAVR. In this article, the authors identified for the first time the factors associated with *Staphylococcus aureus* IE in TAVR patients. TAVR complicated by major bleeding or sepsis, the presence of neurologic symptoms or systemic embolisms at IE index admission, and signs of infection involving implantable cardiac devices (other than the TAVR prosthesis) were independently associated with *Staphylococcus aureus* IE. Notably, the presence of these factors at admission, especially in combination, determined a very high likelihood of SA IE (> 80% in patients with ≥ 3 risk factors). This pre-blood cultures' probability estimate may have direct implications for improving clinical outcomes in such patients. It is well-known that delayed treatment initiation in IE is strongly associated with worse clinical outcomes,[70,71] and therefore, empirical therapy should be promptly initiated. Consequently, in patients presenting a very high probability of *Staphylococcus aureus* IE, empirical treatment should be oriented to cover *Staphylococcus aureus* properly, and the patients may be prioritized for further investigations. Additional studies are needed to determine whether this strategy translates into improved outcomes.

The second study included in this PhD project provides important data on the incidence, risk factors, and outcomes of patients with stroke complicating IE after TAVR. This serious complication occurred in about ~10% of the patients during the index hospitalization. This incidence was similar to that reported in other TAVR-IE observational studies,[154,170] but substantially lower (18%) than that described in the International Collaboration on Endocarditis-Prospective Cohort Study, including patients with PVE.[29] However, it should be noted that our study only included patients with clinically relevant strokes, although subclinical cerebrovascular embolisms can be detected in up to half of IE patients using advanced imaging techniques.[196] In addition, the complexity of stroke diagnosis in elderly patients with comorbid conditions, often presenting with nonspecific symptoms, is a recognized cause of misdiagnosis.[195] All these factors may have led to an underestimated incidence of stroke in TAVR-IE patients in our analysis.

Importantly, this study identifies the predictors of stroke in TAVR-IE patients for the first time in the literature. An increased risk of stroke was determined based on the following factors: a previous stroke (either at baseline or at the periprocedural period), residual AR ≥ moderate after TAVR, balloon-expandable valves, IE within 30 days after TAVR, and vegetation size > 8mm. The incidence of this life-threatening complication increased exponentially with the presence of the aforementioned factors, and in patients with more than three risk factors, the likelihood of stroke increased up to 60% during the index hospitalization. This proposed risk stratification may be useful in clinical decision-making as patients at a higher risk of stroke may benefit from early and, eventually, more aggressive therapies. Nevertheless, these findings need to be interpreted with caution and should be externally validated in other TAVR-IE cohorts.

7.1.4 Management of infective endocarditis after transcatheter aortic valve replacement

A large body of evidence supports the benefit of surgery in NVE and PVE.[61,66,188,238–240] Indeed, early intervention has been associated with improved outcomes compared with medical therapy in some clinical scenarios.[64,66,240] However, the optimal management of patients with TAVR-IE is uncertain. Conservative treatment with

antibiotic therapy alone, even in the presence of severe complications, is by far the most frequently used strategy across different studies.[156,157,163] The first and fifth articles included in this PhD project provide valuable insights into surgery in patients with TAVR-IE regarding its use and outcomes.

The proportion of patients with PVE undergoing surgery during the index hospitalization has increased over time, accounting for ~50% in contemporary studies.[12,62,237] This is in contrast with the consistently low rates of interventions observed in the first and fifth studies of this thesis (<20%).[223] Moreover, despite the expansion of TAVR to lower surgical risk patients in recent years, the first study revealed that low surgery rates remain stable with no significant temporal changes in trend. Notably, we found that despite a formal indication for surgery in more than 8 out of 10 patients, only those with lower risk underwent surgery, irrespective of the underlying IE-related complications. Several factors may explain these findings. First, our cohort represented an elderly population with a median age roughly 20 years higher than that of patients with PVE included in prior observational studies.[29,237] In the same way, Ragnarsson et al. observed that younger patients were more likely to undergo surgery than elderly patients, even though this treatment was associated with lower mortality irrespective of age in IE patients.[241] Second, the surgical recommendations by clinical practice guidelines for patients with PVE are not always applicable to TAVR-IE patients, who frequently present multiple underlying severe comorbidities and a high surgical risk. To date, no specific recommendations have been established for surgery in this population, and indications are usually individualized based on local experience. Moreover, certain patients are frequently deemed ineligible for surgery based on of classical surgical risk scores, but their use and accuracy could be questionable in the setting of IE.[242–244] Nevertheless, the role of surgery in TAVR-IE is subject to debate, and specific studies are crucial to further establish surgical indications in TAVR-IE patients.

The fifth article of this PhD project evaluated the benefit of cardiac surgery in TAVR-IE patients by applying a propensity score based method. In this study, cardiac surgery compared with medical therapy alone was not associated with improved in-hospital mortality or all-cause mortality at 1 year. Accordingly, previous studies have

failed to demonstrate improved outcomes in TAVR-IE patients undergoing surgery.[174,223] One study, including high-risk patients, observed no benefit of cardiac surgery compared with medical therapy regarding in-hospital and 1-year mortality.[174] Similarly, a recent analysis based on the US Nationwide Readmission Database reported no significant differences in terms of in-hospital mortality (9.9% vs. 12.4%) and 30-day readmissions comparing surgical intervention vs. medical management alone.[245] Furthermore, we noted that this lack of benefit persisted when restricting the analysis to patients with definite TAVR platform involvement (excluding patients with isolated cardiac device infections). However, it is important to emphasize that our study included a heterogeneous, high-risk patient population undergoing surgery according to local standards. Therefore, the outcomes of surgery in selected low-risk populations remain an unexplored issue to be addressed by future investigations.

7.1.5 Outcomes of infective endocarditis following transcatheter aortic valve replacement

Articles 1, 2, 3, 5 and 6 included in this PhD project provide important information on TAVR-IE outcomes and confirm the dismal prognosis associated with this complication. We found that the development of IE following TAVR was associated with a very high rate (~70%) of overall IE-related complications, including heart failure, acute renal failure, systemic embolisms, and uncontrolled infection. Importantly, new-onset heart failure, acute renal failure, and stroke were independent predictors of mortality during the index hospitalization, as stated in the first paper.

Our data showed that about one-third of the patients died during the index hospitalization and that mortality was much higher in patients with severe clinical presentations. As described in the second and third studies, in-hospital mortality concerning TAVR-IE caused by *Staphylococcus aureus* or complicated by stroke increased up to ~50%. This is in contrast with prior studies on PVE reporting in-hospital mortality rates of about 20%.[29,203] The causes of such high mortality are probably multifactorial and closely related to the characteristic profile of TAVR patients, as noted above. Nevertheless, encouraging results were observed in the first study, showing a

decreasing mortality rate over time for in-hospital and 1-year mortality and a significant absolute mortality reduction in the contemporary (vs. historical) cohort.

Finally, we reported for the first time in literature the long-term (> 2 years) outcomes and prognostic factors of patients who survived the index hospitalization. Few studies have evaluated the long-term prognosis of patients with definite NVE or PVE, reporting a 5-year mortality rate of ~40%.[169,246,247] This rate contrasts with the substantially higher long-term mortality rate observed in the sixth article included in this thesis. As previously mentioned, one-third of the patients died during the index hospitalization, but it is worth noting that our results extend the poor prognosis to those patients who survived the IE episode, with a mortality rate of >60% at 5 years. The high-risk profile of TAVR recipients combined with a high rate of IE complications may partially explain such results. The presence of at least one IE-related complication (including acute heart failure, acute renal failure, and persistent bacteremia) increased as much as twice the risk of death in the years following the IE episode. These results are in accordance with prior studies suggesting an association between IE complications and poorer in-hospital and late outcomes.[61] However, some aspects deserve special attention. Fever as a presenting symptom of IE appeared to be a protective factor in TAVR-IE patients, likely due to an earlier diagnosis and treatment in such cases, avoiding potential sequels. This highlights the importance of early diagnosis and the clinical management of this population for improving long-term survival. Also, the absence of fever may reflect an impaired immunological response, contributing to increased mortality. Notably, patients with IE involving the TAVR prosthesis exhibited a lower risk of mortality at long-term follow-up. While no clear explanation exists for this finding, the higher rate of pacemaker infections in IE patients without TAVR prosthesis (50% vs. 14.2%), usually involving more aggressive microorganisms, may have contributed to the poorer prognosis in this group.

7.2 FUTURE PERSPECTIVES

The studies included in this PhD research project provide important insights into IE after TAVR. Nevertheless, several questions remain unanswered, and a detailed understanding of this condition will be essential to improve outcomes. To date, only one

well-designed randomized clinical trial has been conducted in the field of IE.[64] This highlights the complexity of carrying out such studies on TAVR-IE, essentially owing to its low incidence. Consequently, evidence from randomized clinical trials is not expected in the next few years, and comprehensive observational studies will be necessary to address knowledge gaps.

TAVR has transformed the treatment of AS and is now being expanded to less complex and younger patients with lower surgical risk. The number of TAVR procedures is projected to grow exponentially in the future years, increasing the number of patients at risk of suffering from this life-threatening complication. As a result, despite the relatively low incidence of IE following TAVR, this complication may have a clinically meaningful impact in the future. TAVR will undoubtedly continue to evolve toward more simplified (and less invasive) procedures, enabling earlier patient recovery and shorter hospital stays. Consequently, in the upcoming years, we may witness a decline in early IE incidence (closely related to the TAVR procedure) and probably a slight increase in late IE incidence (longer time at risk due to greater life expectancy). Additionally, specific recommendations for surgery in TAVR-IE patients are urgently needed. To this end, further studies, including a wide representation of the whole spectrum of surgical risk, are required to determine the benefit of surgery in some subsets of patients.[151]

Prevention will be a cornerstone, given the poor prognosis and the lack of evidence supporting life-saving therapies in TAVR-IE patients. Current clinical guidelines recommend perioperative antibiotic prophylaxis in patients undergoing TAVR.[31,38] Along with antiseptic measures, antimicrobial prophylaxis should be initiated before TAVR and discontinued 48 hours after. Antibiotic prophylaxis with cephalosporin monotherapy is the most commonly used regimen for TAVR. However, it should be noted that, according to a large observational study, up to ~50% of the patients with periprocedural TAVR-IE had a microorganism not susceptible to the most frequently used periprocedural antibiotic prophylaxis.[152] For this *reason*, antibiotic prophylaxis regimens should be adapted to this unique clinical scenario. A recent review of recommendations for preventing TAVR-IE advocates switching from cephalosporin to amoxicillin/clavulanic acid, given its greater efficacy against enterococci.[248] Further studies are needed to assess whether new

antibiotic prophylaxis regimens would result in a lower incidence of periprocedural TAVR-IE.[151]

A major concern is the increasing incidence of health care-associated IE in TAVR patients, frequently associated with multidrug-resistant microorganisms. Approximately half of the TAVR-IE cases could be considered health care-associated IE[156,163], more than twice as many as those observed among their surgical counterparts.[29] The increased exposure to health-care interventions, strongly related to the risk of bacteremia, may play a fundamental role in causing this high incidence in the TAVR-IE population. Of note, patients with health care-associated IE showed lower 1-year survival rates compared with those presenting community-acquired IE. This highlights the need for practice-changing interventions and specific strategies to reduce this complication in TAVR patients. Also, the importance of limiting health care-associated procedures that could potentially trigger a bloodstream infection in this population should be emphasize. Contrary to dental procedures, antibiotic prophylaxis for patients undergoing invasive procedures (respiratory, gastrointestinal, urogenital tract, or skin procedures) is widely questioned and no longer recommended. Nevertheless, it is still unknown whether the widespread use of antibiotic prophylaxis during certain healthcare interventions may have an impact on reducing IE in TAVR patients.[151]

Finally, some promising strategies for the prevention of bacteremia and prosthesis infection may address a critical unmet medical need. Iterations of devices with novel antibacterial biomaterials that prevent microorganisms' adhesion to prosthetic surfaces may be relevant in reducing the likelihood of IE in case of bloodstream infection. In the same way, several efforts have been made to develop a vaccine providing protection against the majority of *Staphylococcus aureus* strains. Unfortunately, despite numerous preclinical trials reporting encouraging results, vaccines for preventing *Staphylococcus aureus* infections have failed to reduce IE incidence after cardiothoracic surgery significantly.[249,250] Further studies in this exciting field will be needed in the coming years.[151]

CONCLUSIONS

IE is a rare but life-threatening complication after TAVR associated with a high mortality rate. IE occurring after TAVR should be considered a distinct condition among patients with PVE, given its unique microbiological profile, the high incidence of IE-related complications, the uncertain role of cardiac surgery, and the dismal prognosis. The main findings of the present PhD research project can be summarized as follows:

1) The overall incidence of IE after TAVR remains stable, but early IE incidence showed a significant downward trend in recent years. The microbiological profile, high rate of complications, and low rate of surgical treatment remain unchanged. In-hospital and 1-year mortality rates were high, but they progressively decreased over time.

2) Stroke occurred in 1 out of 10 patients presenting with IE post-TAVR. A history of stroke, developing IE within 30 days after TAVR, vegetation size >8 mm, balloon-expandable valves, and residual aortic regurgitation ≥ moderate after TAVR determined an increased risk of stroke. The occurrence of stroke was associated with higher in-hospital and 1-year mortality rates, and surgical treatment failed to improve clinical outcomes.

3) IE following TAVR caused by *Staphylococcus aureus* accounted for ~25% of the cases and linked to with very high in-hospital (47.8%) and 2-year mortality rates (71.5%). The presence of some factors (major bleeding and sepsis complicating TAVR, neurologic symptoms or systemic embolism at admission, and IE with cardiac device involvement) determined a higher likelihood of *Staphylococcus aureus* infection and may guide empirical antibiotic treatment.

4) Only 19% of patients with TAVR-IE underwent cardiac surgery despite the high proportion of patients with formal indication for surgery (~80%) according to current clinical guidelines. Cardiac surgery was not associated with an improved in-hospital or 1-year all-cause mortality in unselected TAVR-IE patients.

5) Noninfective transcatheter aortic valves did not exhibit a significant ^{18}F-FDG uptake pattern three months after the TAVR procedure, showing no differences between balloon- and self-expanding transcatheter valve systems.

6) Patients who survived an initial IE episode after TAVR exhibited a poor prognosis, and about two-thirds of them died at 5-year follow-up. Chronic renal failure, IE-related characteristics (absence of fever and no TAVR prosthesis involvement), and the occurrence of IE-related complications determined an increased risk of late mortality.

In conclusion, IE is a serious complication following TAVR and the number of patients at risk of developing this condition is growing exponentially. Although the overall incidence rates remain stable, the incidence of early IE showed a significant downward trend in the past years, and the in-hospital and 1-year mortality rates progressively decreased over time. The occurrence of stroke during the index hospitalization was associated with higher rates of in-hospital and 1-year mortality, and when Staphylococcus aureus was involved (~25%) the outcomes of these patients was even worse, with very high in-hospital and 2-year mortality rates. The poor prognosis linked with this condition also extended to patients who survived the index hospitalization, with roughly two-thirds of them died at 5-year follow-up. Nearly 2 out of 10 patients with TAVR-IE underwent cardiac surgery, and this treatment was not associated with an improved in-hospital or 1-year all-cause mortality. However, further studies are needed to determine the outcomes of surgery in selected intermediate- and low-risk populations.

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