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Diagnostics and management of infective endocarditis post-transcatheter aortic valve implantation - A systematic review

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Preface

In the process of finding a project for my master thesis, I was put in contact with Dr.Brage Håheim. We had a meeting where we discussed different clinical challenges within the field of infectious disease and cardiology. The decision was made to ask Dr.Vegard Skogen if he would be an additional supervisor on this thesis. Transcatheter aortic valve implantation (TAVI) and Infective endocarditis (IE) soon became the main topic of interest for us.

Considering the development in the field of cardiology as well as diagnostics, the interest was mainly on how we can diagnose and treat a TAVI IE patient, when there were so many contradicting factors involved in the process.

The process itself has been as educational, as the academic aspect of the thesis. I would like to address a special thanks to Dr. Håheim and Dr. Skogen for identifying records in the databases, help screening, discussing academics and patient cases, great support, encouragement and feedback. Furthermore, I would like to acknowledge and thank everyone who has helped us in the identification process and advisement. A final thanks to my family for all their help, support and encouragement.

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Abstract

Background: As transcatheter aortic valve implantation (TAVI) has expanded the treatment options to otherwise inoperable patients, it has become as prevalent as surgical aortic valve replacement. TAVI infective endocarditis (IE) has thereby become a feared complication. IE is heterogenous in its presentation, identifying characteristics and diagnostic criteria among these patients is crucial in diagnosing IE. Treatment entails a conventional approach with antibiotics or in combination with surgery. Treatment option for TAVI IE is highly debated in high-risk patients. The primary aim of this systematic review is to find knowledge on how TAVI IE patients are diagnosed and treated as stated in the literature.

Method: Records were searched in MEDLINE and EMBACE. The search strategy is based on how TAVI IE is diagnosed, clinical presentation, treatment, and outcome. EndNote, Rayyan and EPPI-REVIEWER were used in the process of screening and selecting studies. All studies were first assessed by titles and abstracts, then selected articles in full text against the inclusion criteria. All disagreements between the (three) researchers were discussed until agreement.

Results: Final selection process left us with 16 empirical retrospective/prospective/ observational studies and 51 case studies, between year 2005-2019.

Conclusion: Diagnosing TAVI IE is based on the new modified duke criteria's (MDC), where pathological findings and clinical judgement are the cornerstone. This review indicates a rise of enterococci as the causative microorganism for TAVI IE, while the common first symptoms recognized are fever, heart failure and systolic murmur. Treatment choice for TAVI IE should be a case-by-case decision based on clinical judgment and managed individually. Studies included in this review indicate that surgical option as a treatment to TAVI IE should be reserved for complicated and life-threatening cases. Unfortunately, there are not enough studies/data to determine whether surgery or AB is appropriate and when.

Abbreviation

- TAVI : Transcatheter aortic valve implantation
- IE: Infective endocarditis (IE)
- AS: Aortic stenosis
- SAVR: Surgical aortic valve replacement
- AB: Antibiotics
- STS: Society of Thoracic Surgeons
- CAD: Coronary artery disease
- COPD: Chronic obstructive pulmonary disease
- PCI: Percutaneous coronary intervention
- MI: Myocardial infarction
- CABG: Coronary artery bypass graft
- CoPS: Coagulase-positive staphylococcus
- CoNS: Coagulase-negative staphylococcus
- TEE: Transesophageal echocardiography
- TTE: Transthoracic echocardiography
- PVE: Prosthetic valve endocarditis
- LVEF: Left ventricular ejection fraction
- MDC: Modified Duke criteria
- ICE: Intracardiac echocardiography
- PET/CT: Positron emission tomography–computed tomography
- MRI: Magnetic resonance imaging
- RCT: Randomized control studies

1.0 Introduction

1.1 Endocarditis

IE is an inflammation of the endocardium and/or heart valves caused by the hematogenous spread of bacteria or fungi. Etiology, microbiology and epidemiological factors have changed over the years. Patients are increasingly subject to implantable devices as well as invasive procedures, which have a significant effect on the occurrence of IE. Microorganisms have the ability to adhere to a native/ prosthetic leaflet, depending on agent, the patient's course and extent of damage may vary (1).

IE is a rare and complicated disease. It affects 3-10/100,000, and studies show that the incidence is increasing due to better diagnostics and treatment (2). Whether this is to do with changes in microbiological agent, patient demographics or risk factors, is unsure (3).

1.2 TAVI

Aortic stenosis (AS) is the most common heart valve disease. Prognosis is low and mortality rate is considered high without treatment (4). Surgical aortic valve replacement (SAVR) procedures are well documented to improve life expectancy, cardiovascular symptoms and quality of life in patients with severe AS. It has been the gold standard for treatment since its introduction in 1962 (5). A challenge with surgical treatment is patient frailty and high surgical risk.

Early literature states that 1/3 of elderly patients over 75 year were excluded based on advanced age and comorbidities (6). At the turn of the millennia TAVI was developed to provide definitive treatment to this specific group. The technique inserts a prosthetic valve transvascular which expands on top of the old aortic valve. The typical TAVI patient was someone with AS who has considerable comorbidities that increase the surgical risk for SAVR (6, 7).

The PARTNER trial (Placement of AoRtic TraNscathetER Valves) compared TAVI and SAVR, in patients with high surgical risk and patients that were not considered to be appropriate for surgery. The studies shows that patients with high surgical risk had lower 30-day mortality as well mortality for 1 year and 2-year TAVI follow up. Furthermore, the incidences of stroke, myocardial infarction, acute kidney injury, endocarditis, and pacemaker placement at one and two years after TAVI and SAVR are identical (8).

It was concluded that TAVI is not inferior to SAVR as a treatment of AS in patients with high surgical risk factors. It has been proposed that TAVI should be considered in patients who may be candidates for surgery, but where less invasive approach is favourable based on individual risk profile. TAVI is now considered a well-established procedure for AS in high surgical risk factors, as well as it is considered effective and safe for intermediate surgical risk patients (8).

1.3 TAVI endocarditis.

Prosthetic valves are a known risk factor to develop IE. As the TAVI technique has expanded the treatment options to otherwise inoperable patients and become as prevalent as SAVR, TAVI IE has become a feared complication (1).

While a rare complication, TAVI IE has a high mortality rate and successful treatment depends on a multidisciplinary approach, long antibiotic (AB) cures and possibly surgery. Despite advances in diagnostics, the mortality rate seems to remain high. Due to its novelty, there are limited data and evidence on how to best diagnose and treat TAVI IE patients (9, 10).

IE has been observed with increasing incidence in high-income countries in elderly patients, (11). Even though IE is heterogenous in its presentation, identifying common characteristics among these patients might be beneficial in recognizing clinical manifestation of IE at an earlier stage.

1.3.1 Treatment of TAVI Endocarditis

Treatment of IE requires a multidisciplinary approach and entails infectious, cardiological and cardiothoracic surgical expertise as well as radiological and microbiological support. There are many factors that come into play in assessing how TAVI IE should be treated, such as infective agent, location, comorbidities, age, complications and hemodynamic stabilities to name a few.

Treatment can either entail conventional approach alone with AB or in combination with surgery. Surgical treatment has been recommended early in patients with congestive heart failure, perivalvular complications and high risk embolism (12). When following these

recommendations, a dilemma occurs: Should the patient who primarily received TAVI due to the high surgical risk be treated for TAVI IE with surgery.

The optimal course of action is highly debated in high-risk patients. However, the new generation of TAVI patients are younger, and represent an intermediate risk profile. Question arises, how best to treat this new generation of TAVI IE patients: surgical or conservative.

As mentioned earlier there is little data on treatment of TAVI IE, this leads to uncertainty. The aim of this systematic review is to find knowledge on how TAVI IE patients are diagnosed, and treatment as stated in the literature.

2.0 Methods and study design

A systematic database search based on the following questions where performed: How is TAVI IE diagnosed and their clinical presentation? How is TAVI IE treated, and with what outcome?

Identifying relevant studies was done with the help of a search specialist/librarian (Reierth), who worked with the other project members to design and execute the literature searches (Figure 1). Following databases were searched: MEDLINE, EMBACE. We also contacted experts and examined the reference lists of relevant review and included studies. The strategy would be finalized by the search specialist and built on the population (TAVI associated IE) and phenomenon of interest (diagnostic and treatment).

Following MeSH terms used to screen studies: “Transcatheter Aortic Valve Replacement (MeSH-term) OR Transcatheter ADJ3 Replacement.mp OR Transcatheter ADJ3 implantation.mp OR TAVR.mp OR TAVI.mp” AND “Endocarditis (MeSH-term) OR Endocarditis.mp”.

Next step in the process involved selecting studies and records management. All records from the search were imported into an EndNote database. There was a check to delete all duplicate. From EndNote we imported all identified reference into Rayyan (http://rayyan.ai), a web-base for managing the process of screening, selecting studies and used to examine all record for inclusion based on the inclusion and exclusion criteria specified below. After screening on

abstract and title, EPPI-REVIEWER (http://eppi.ioe.ac.uk) was applied to further keep record, distribute word and code papers.

The selection process involved three researchers (Martyn, Håheim, Skogen,), who independently assessed all study titles and abstracts from the search against the inclusion criteria. All disagreements between the three researchers were discussed until agreement.

Next, all three of the researchers independently assessed whole study texts in pair of two (full texts) against the same inclusion criteria. If the researchers cannot agree on inclusion, the same procedure was applied to determine inclusion as with study titles and abstracts.

2.1 Inclusion criteria

Study population included adult humans of either gender who underwent TAVI and later diagnosed with IE.

On the bases of phenomenon of interests, studies that included samples of patients with definite or possible endocarditis according to the European Cardiology Societies Modified Dukes Criteria in patients with TAVI/TAVR, were included. The studies must provide data on either clinical presentation, diagnostic procedures, treatment and or outcome of TAVI IE patients.

Study design was based on empirical retrospective, prospective and observational studies, including case reports and series. Examples of studies: 1: Studies following patients after TAVI with focus on IE as outcome (prospective studies). 2: Studies describing patents diagnosed with IE following TAVI (retrospective studies, case studies/series).

2.2 Exclusion criteria

Following studies were excluded: Existing review studies, follow-up studies on TAVI patients mentioning IE (but not with IE as primary outcome/phenomenon of interest), or with lack of clinical, diagnostic or treatment data, non-English papers, scientific conventions posters, abstracts or oral presentations.

2.3 Data summary

When reviewing the studies, we differentiated between *"Baseline data"* and "*IE data"*. Baseline data is based on the patients clinical condition when receiving TAVI, while IE data is focused on factors surrounding the diagnosis, treatment and complications of IE.

Data included in these studies varied in scope and level of detail. We encountered some missing data points, so not all TAVI IE patients had all the information we were looking for. This has led us to specify for each data point how many TAVI IE patients are included. For instance: even though there are 980 TAVI IE patients in retrospective/prospective studies, we only have available data on 370 TAVI IE patients regarding chronic renal failure, and of these 370 patients only 162 have confirmed chronic renal failure. This will be stated as 162/370 patients. For the remaining patients, we simply do not have data on the specific data point.

3.0 Results

Following the first screening, based on Mesh terms, we were left with 990 articles to consider (Figure 1).These articles were transferred to Rayyan where we selected studies based on title and abstract, at the end of this process we had 254 articles that were then transferred to EPPI-REVIEWER. These articles were read in full text and included/excluded based on the criteria's mentioned above.

The final selection process left us with 16 empirical retrospective/prospective studies and 51 case studies, between year 2005-2019. However, it was decided that 8 out of 16 retrospective/ prospective studies would be considered as case studies, since these had detailed patient data for the participants and not just cohort data (Figure 1) (13-20). Therefore, a total of 8 empirical retrospective/prospective studies and 59 case studies are included in the review.

3.1 Retrospective/prospective studies

Patient data in the 8 retrospective/prospective studies included here, are either collected from different databases or follow up data with additional data from registries.

The selected studies are as follows, with their patient population: Kolte et al. include 224 TAVI IE patients out of 86372 TAVI patients (21). Mangner et al. have included 64 TAVI patients where 20/64 have received surgical treatment for TAVI, and 44/64 have received AB

(21, 22). Tabata et al. have 17 TAVI IE patients out of 1448 TAVI patients (23). Bjursten et al. have 103 TAVI IE patients out of 4336 TAVI patients (24). Regueiro et al. have 250 TAVI IE patients out of 20006 TAVI patients (25). Yeo et al. have 120 TAVI IE patients out of 41025 TAVI patients (26). Stortecky et al. have 149 TAVI IE patients out of 7203 TAVI patients, and Amat-Santos et al have 53 TAVI IE patients out of 7944 TAVI patients (27, 28). These represent a total of 980 TAVI IE patients out of 168398 TAVI/TAVR patients.

3.2 Case studies

In total 59 case studies/series were included (13-20, 29-79). This included a total of 134 patients (Supplement data 3 and 4). Patient baseline data and IE clinical data was extracted for each patient and summarized. Median age and LogEuro score were calculated across all available patients while the rest of the data is summarized as fraction of available data, referring to the section 3.1.

3.3 Baseline data

3.3.1 Age and gender

TAVI IE patients in the retrospective studies had an average age spanning 62.1-85 years old, in the case studies the average age was 80 years old. According to retrospective/prospective studies, men represented 61.4 % (602/980) of patients. In the case studies men represent 55.5% (60/108).

3.3.2 Comorbidities

Baseline data from retrospective/prospective studies showed that 39.1% (65/166) of patients with available data had a NYHA class of I or II, while 65% (147/227) of patients had a NYHA class of III or IV. LogEuro score varied between 12.9 ± 8.0 and 24.85 ± 13.82 based on available data from 290 patients. While 30% (40/134) of patients with available data in case studies had a median of 23,5. Society of Thoracic Surgeons (STS) score has been between 4.6 ± 3.0 and 23.3 based on 230 patients.

Data from retrospective/prospective studies show 44.6% (156/350) have had coronary artery disease (CAD), 43.8% (162/370) had chronic renal failure, 42.5% (235/553) had atrial fibrillation, 33.3% (252/756) patients had underlying diabetes, 23.8% (180/756) had chronic obstructive pulmonary disease (COPD), 17.5% (18/103) had a history of cancer/malignancy.

The case studies showed chronic renal failure in 30.7% (20/65) of patients, 27.7% (18/65) with diabetes, 27.7 % (18/65) with COPD, 23.1% (15/65) with CAD, 23.1% (15/65) with heart failure, 20% (13/65) with atrial fibrillation and 6.1% (4/65) with a history of cancer.

Data from retrospective/prospective studies showed patients with previous cardiac surgery represented 20.4% (55/269), with stroke 12.3%, (72/583) and with prior PCI 12.5% (30/240). Our data also showed 23.5% of patients had prior carotid disease, but this represents only 4/17 available patient data. Prior myocardial infarction (MI), valve surgery and coronary artery bypass graft (CABG) represented between 8.3-10.4 % of available patient data.

3.3.3 Data on surgical procedure and complications

Data on valve implant location was available in our retrospective/prospective studies only. Catheterization lab represented 49.1% (222/452), while operating/hybrid rooms represented 51% (230/452).

The majority of the procedural access was transfemoral in more than 75.5% (>419/555) of patients while transapical was chosen in 18.2% (123/675) of patient. Our case studies show 81.2% (39/48) of patients receiving transfemoral access, and 12.5% (6/48) receiving transapical access.

Prosthetic valves used in TAVI procedures can broadly be classified into two types of devices: Self expandable valves (Core Valve and Evolut R) and balloon expandable valves (Sapiens). According to the available data in our retrospective/prospective studies, 46% (215/469) patients with TAVI IE received Self expandable valves, while 50.3% (236/469) patients received balloon expandable valves. Case studies show 44% (35/79) of patients received self-expandable valve, while 43% (34/79) of patients received balloon expandable valves.

The most common in-hospital complication during TAVR/TAVI procedure according to retrospective/prospective studies, seems to be either aortic regurgitation in 15.6% (39/250) patients, acute kidney injury 13.2% (33/250) and permanent pacemaker implant in 17% (63/370) of patients.

3.3.4 Antibiotic prophylaxis

Based on available data from the retrospective/prospective studies, 90% (516/572) of patients received prophylaxis (25-27). Stortecky et al. have a detailed overview over AB prophylaxis, 92.6% (138/149) of their patients received prophylaxis, it was effective in 60.1% (83/138) of patients. While Yeo et al. documents 92.5% (111/120) patients received prophylaxis and was effective in 48% (53/138) patients (26).

Furthermore, Stortecky et al. report 63% (84/138) of patients received AB 30-60 min pre TAVR intervention (27). Data from the review suggests when prophylaxis is used, Beta-lactam alone is the most prevalent choice, being used in over 80 % of available patient data, compared to vancomycin alone used in 6.4% of patients.

3.4 IE data

3.4.1 Symptoms and onset

Time between TAVI and IE in days are in average 147.46 days/4.7 months in the retrospective/prospective studies, while case studies indicate 5.2 months.

Most frequent symptoms based on retrospective/prospective studies are as follows: Fever in 78% (300/385), heart failure in 46.2% (177/383), neurological symptoms in 16% (51/320), systemic embolism in 13.5% (36/267), sepsis in 33.8% (27/80) and vascular phenomena in 13.2 % (22/167) of patients with available data.

Case studies showed, fever in 86% (68/79), heart failure in 12.6% (10/79), dyspnea in 18% (14/79), embolism in 5% (4/79) and lethargy/weakness in 16.5% (13/79) of patients.

3.4.2 Microbiology

According to the retrospective/prospective studies 58.1 % (273/470) of patients IE were exposed to sources associated with healthcare associated and nosocomial bacteria, while unknown sources represent 66.3% (201/303) of patient cases. It is not well documented what is considered as healthcare associated and nosocomial bacteria.

Review of the retrospective/prospective studies, show causative microorganism blood cultures with staphylococci in 34% (324/962) of patient. Most common amongst staphylococci is S.aureus (incl. MSSA, MRSA) and CoPS combined representing in 22.3%

(215/962) of staphylococci. While coagulase-negative staphylococcus (CoNS) was present in 15% (91/618) of available data.

Streptococci has been evident in 21% (198/962) of patients included in the retrospective/prospective studies. Viridans streptococci was present in 12% (54/451), while nonviridans streptococci was present in 6% (9/149) of cases. Other streptococci represented the majority of this group with 26% (135/528) of patients.

Enterococcus was present in 22% (212/962) of patients, fungi in 2.4 (4/169) of patients, gram negative bacteria in <5% (<18/373) of patients and other organisms in 9% (52/590) of patients. Polymicrobial patients have been evident in 5.6% (21/373) of patients, while no organisms were found in 5% (19/388) of patients.

In our case studies staphylococci represented 26.1% (35/134) of patients, with S.aureus being the most common among them with 51.4% (18/35) of patients. Enterococci was present in 27.6% (37/134), with E. faecalis being the most common with 76% (28/37) of patients being affected. Streptococci was present in 28.4% (38/134) of patients. Blood cultures were negative in 2.2% (3/134) of patient cases, while 4% (5/134) showed polymicrobial blood cultures.

3.4.3 Echocardiography

Transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE) are two of the most used modalities in diagnosing IE. Bjursten et al. and Stortecky et al both have specified that TEE was used in 80.1% (202/252) of patients. While Stortecky et al. additionally documents that 76.5% (114/149) of their patients were examined with TTE. A total of 5 studies have data on echocardiography, but not for all their patients (22, 24, 25, 27, 28).

In the retrospective/prospective studies, vegetation was found in 58.4% (358/613), fistula was found in 1.4% (3/202), abscess was found in 14.1% (52/369) and results were not conclusive in 40% (59/149) of patients. In our case studies, vegetation was found in 53.1% (17/32) and abscess was found in 6.3% (2/32) of patients.

Another complication of IE is aortic regurgitation confirmed through echocardiography, which was found in 25.5% (97/380) of patients in the retrospective/prospective studies, while 15.6 % (5/32) of patients were affected in our case studies.

3.4.4 Treatment and outcome

IE is treated either surgically or with AB. According to the retrospective/prospective studies, surgical procedures was as follows: valve explanation/replacement surgery was chosen in 19.1% (65/340) of patients and SAVR in 12.6%, redo TAVI in 2.1% (5/224), removal of pacemaker/ICD in <4.5% (4/224) and valve-in-valve procedure in 1.7% (5/303). The most common amongst the surgeries according to the data is valve explant/replacement done in 19.1% (65/340) of surgical treatment.

There are some missing patient data regarding the use of AB as treatment in the retrospective/prospective studies. Mangner et al., Reguerio et al, and Amat- Santos et al. have reported use of AB as treatment in TAVI IE patients. Based on these data, 86.1% (278/323) of their patients combined received AB. Beta-lactam in combination was used in 61.5% (126/205) of patient cases, while vancomycin alone or in combination was used in 27% (69/258).

In the case studies, surgical treatment was used in 21% (27/128) of patients, while 79% received AB treatment. Beta lactam in combination was used in 36% of the patients, while vancomycin in combination was used in 30% of the patients receiving antimicrobial treatment. It must be noted that there were no randomized control trials, regarding treatment option for TAVI IE patients

Several complications have been associated with treatment of TAVI IE. Among the retrospective/prospective studies, acute kidney injury was seen in 43% (221/515), acute heart failure in 32% (187/582), need for hemodialysis 30.2% (19/63), septic shock in 21% (132/635) and embolic event in 9.5% (55/577) of patients.

The case studies showed heart failure (21.6%) and renal failure (13.3%) are also among the common complications. Embolic event was found among 16.6 % (15/134) of case study patients.

Mortality rate is documented in various forms, either an overall in hospital death, 1 year mortality or death within 6 months of PVE was presented. In our retrospective/prospective studies overall in hospital death when patients were treated for TAVI IE was 28% (231/831), while 1 year mortality was 47% (99/212) and death within 6 months was 30% (31/103). Death within 6 months was presented only by Bjursten et al, based on a sample size of 103 patients. Data from case studies showed 32% (37/117) of patients died during treatment for TAVI IE.

4.0 Discussion

To give a short presentation of a TAVI IE patient based on our findings; TAVI IE patients are men, with high STS score and Euroscore between 12.9 ± 8.0 and 24.85 ± 13.82 based on available data from this review. They primarily present with fever and heart failure, within 6 months after TAVI procedure. These patients have often had stroke, and are affected by COPD, atrial fibrillation and chronic renal failure. When the procedure takes place, the most common access point for procedure is through the femoral artery, which can lead to either an infection caused by staphylococci, streptococci or enterococci. Treatment of IE can either be surgical or medical. While our case findings indicate that the common complication of this treatment is acute kidney failure or acute heart failure.

The presentation above gives us an idea of where TAVI IE patients are most medically vulnerable. The discussion further will be based on these vulnerabilities and highlight various aspects of literature to either confirm or deny the finding. In doing so hopefully we would be able to provide a complete picture of the diagnosis and treatment of TAVI IE patient.

4.1 The TAVI IE patient

The included studies provide a descriptive data on TAVI IE patients, however, is methodically limited to identify specific risk factors. This is dues to both the lack of a non-IE control group as well as a bias patient data collection. As this review primary aim is to investigate diagnostics and treatment of IE, baseline data is collected from only a small sample from the literature of only 8 studies. Multiple studies, beyond the reach of this review describe baseline data and risk factors to develop TAVI IE.

Identifying complications among patients could be a small part of diagnosing and treating TAVI IE, as it helps map out certain patient demographics post TAVI. Treatment

complications have been associated with baseline characteristics and risk factors (80, 81). Therefore, specific baseline data from the included studies will be discussed in the following section.

4.1.1 Age

TAVI IE patients in this review have been between 62.1-85 years old. On average TAVI IE patients are younger compared to those without TAVI IE, one study reports 79.4 ± 10.7 vs 81.3 ± 8.3 years (21).

This is in accordance with review studies by Tinica et al. and Harding et al who argued that a possible explanation for the age factor may be the selection criteria of patients for TAVI where these patients might be young but are chosen for TAVI based on severe comorbidities which in turn predisposes them to IE (5, 10).

It is estimated that IE occurs in 1-6% of patients who have had SAVR performed (25). This number includes both older and younger patients who have had valve replacement performed. Even though the patients receiving TAVI are older, patient characteristic which predispose recipients to TAVI IE is confirmed to be more related to comorbidities rather than advanced age (82).

The age profile for TAVI is expected to fall especially after the PARTNER trial (9). When age becomes less relevant compared to comorbidities, it could be argued that TAVI can be considered as alternative treatment to SAVR for AS in both high as well as intermediate risk patients (83).

Valve IE is generally uncommon both in TAVI and SAVR patients, but when TAVI expands into low-risk patients with a larger target patient population, comes an increased risk of infection (84, 85). Especially when younger patients with longer life expectancies receive TAVI, attention should be paid to whether younger patients really are more prone to TAVI IE, as there is no clear explanation for the relationship between young patients and IE (23, 24).

In addition, this review indicates that earlier studies have a higher mean age on patients receiving TAVI, compared to the newer studies, where patients mean age are lower. As

studies show there is a quest to test the viability of TAVI in younger and lower surgical risk patients with AS, based on the fact that patients with TAVI have a favourable in-hospital outcome, compared to SAVR (86).

4.1.2 Gender

This review shows that mostly men contracted TAVI IE. According to a retrospective observational analysis done at the university of Zurich, men undergoing TAVI tend to be significantly younger than women and have outnumbered female in the following comorbidities: diabetes, cardiovascular disease, COPD, renal impairment and often are in need for regular dialysis (87).

Men are also less hypertensive and have lower left ventricular ejection fraction (LVEF) then woman. The study states that there is no obvious explanation for why women do better than men after TAVI. It is most likely a combination of risk factors, co-morbidities and gender-related cardiac pathology that determines this outcome (87). This is also reflected in the baseline data presented here where all studies show men to be the majority of TAVI IE patients.

4.1.3 Comorbidities

This review also indicates patients have NYHA class III/IV, log Euroscore between 4.3 ± 4.0 and 24.85 ± 13.82 and had STS score between 3.1 ± 2.3 and 17.6. TAVI IE patients suffer from several comorbidities such as hypertension, dyslipidaemia, hyperlipidaemia, immunosuppressive therapy, cancer, diabetes mellitus, chronic renal failure and chronic lung disease.

The most common being COPD (retrospective studies:17.5%, case studies: 6.1%), chronic renal failure (23.8%, 27.7%), atrial fibrillation (44.6%, 23.1%) and CAD (58.3%, 23.1%). Reguiero et al. and Harding et al. also found that moderate to severe paravalvular leakage and residual ≥moderate aortic regurgitation was significantly associated with TAVI IE (9, 25, 88). This is further discussed under section 6.3.

Baseline data in this review indicates that TAVI IE patients often had a previous history of stroke, previous cardiac surgery, surgery in general, MI and PCI. Cahill et al. state that TAVI IE patients are associated with more comorbidities and exposed to high invasive

procedures (9). These factors might make TAVI patients more susceptible to bacteraemia and subsequent IE.

4.2 Procedural technique

TAVI procedure requires an artificial flap of biological material to be compressed and inserted into the heart through a percutaneous entrance, the flap then expands, pushing the native flap aside. According to Overtchouk et al. TAVI can be performed either through transfemoral and transthoracic (transapical, transaortic, transcarotid, trans-subclavian and transcaval) approaches (89).

Transfemoral was the preferred option found in this review, being used in 75.5% and 81.2% patient's vs transapical used in 18.2% and 12.5% patients. Literature states that transfemoral is reported superiority to the transthoracic approach (89).

The treatment approach is based on the clinical evaluation of the patient. Conditions of the vascular access (presence/absence of peripheral arterial disease, calcifications, diameter of the arteries). The transapical approach is independent of the patient's peripheral arterial disease. If the status of iliac femoral arteries allows it, transfemoral implantation should be performed as the primary option. Transapical implantation is considered a more difficult technique and is being abandoned as a result of invasiveness and poor outcome (82, 89). According to a nationwide study using univariable and multivariable cox analysis, transapical access is considered a risk factor for developing late (>1 year) TAVI IE (24).

Literature also states depth placement of the valve can be seen as a procedural risk factor. Olsen et al reported that 61 % of valves were implanted at least 6 mm below the aortic annulus. It has been stated that a low-lying valve may affect the opening and closure of the leaflets and is associated with hemodynamic and by biomechanical measures associated with flap defect and thereby TAVI IE.

5.0 TAVI diagnostics

IE is a syndrome diagnosis that is based on multiple findings rather that a single test result (90). Current clinical guidelines for diagnosis and management of IE recommend the use of new modified Duke criteria (MDC) also in patients with TAVI IE. MDC consists of 2 major

diagnostic criteria (with 3 sub criteria's each) and 5 minor diagnostic criterions. IE is divided into "definite IE", "Possible IE" and "rejected IE", all three have different requirements (91).

To diagnose a patient with "rejected IE", there has to be a firm alternate diagnosis for IE, any infection resolved within 4 days of the start of AB therapy or no pathologic evidence of IE discovered at surgery/autopsy after start of AB (91-93).

To give a diagnosis of "definite IE", different combinations of the criteria can be met; 2 Major Criteria and 0 Minor Criteria, 1 Major Criteria and 3 Minor Criteria or 0 Major Criteria and 5 Minor Criteria (91, 93).

In the review of retrospective/prospective studies, 82% (507/619) of patients are diagnosed with definite IE, 28.2% (57/202) were diagnosed with possible IE. The case review states 82.8% (111/134) of patients with definitive IE diagnosis and 17.2% (23/134) of patients are diagnosed with possible IE.

Patients that are classified as having "possible IE", are harder to classify within the parameters of MDC. Li et al. indicates that the original duke criteria had a much to wider reach. Simply explained "possible IE" were patients that fell in between "definite IE" and "rejected IE". This meant that it was possible for patients with 1 minor criterion to be considered as having "possible IE"(90).

Li et al. proposed that "possible IE" have at least 3 minor or 1 major and 1 minor criterion. In raising the floor for what qualifies as "possible IE" means that the specificity of the criteria increases, but at the same time there will be a decrease in sensitivity. Again according to Li et al., the decrease is small compared to the large gain in specificity (90).

This trade-off in sensitivity to a higher specificity might not be all negative. The consequence of a high sensitivity with a lower specificity is a larger "false positive" population. With IE this entails as much as 6 weeks intravenous AB treatment and hospital admission, which then increases risk of in hospital complication. On the other hand, not treating these patients might not be the optimal course either, as we assume patients might actually have IE.

5.1 Modified duke criteria: Major

5.1.1 Major Diagnostic Criteria #1 (sub criteria a and b)

requires positive blood culture for typical IE organisms (S. viridans or S. bovis, HACEK organisms, S. aureus without other primary site, Enterococcus), "from 2 separate blood cultures or 2 positive cultures from samples drawn > 12 hours apart, or 3 or a majority of 4 separate cultures of blood (first and last sample drawn 1 hour apart)"(91).

The difficulty here is to retrieve blood without contamination, and with cultures drawn 1 or 12 hours apart. Cultures should be sent for both aerobic and anaerobic incubation, even though IE caused by anaerobic infection is uncommon. These cultures should be drawn before start of any AB therapy. Patients who have already started AB, can present a dilemma, according to Beynon et al. "the risks of stopping treatment to allow fresh culture specimens to be taken may be outweighed by the advantages of identifying the causative organism", this is to give the patient a targeted treatment (94).

In this review, blood cultures were negative in 5% of available patient data. This is higher than our case review where 2.2% where negative. A possible explanation for the difference might be that the retrospective/prospective studies had 11.1% more patients with a "possible IE" diagnosis.

Although according to Beynon et al. who did a review in 2006 on IE management, blood cultures were negative in 14 % of IE cases, most often are these associated with previous administration of AB. According to the same review negative blood cultures can also be caused by fastidious pathogens like L*egionella, Coxiella*, the HACEK group, and fungi (94).

When cultures are negative, serological or histological testing should be considered, molecular techniques are more likely to detect fastidious and non-culturable agents. Serological testing is useful for investigating Coxiella burnetti (Q fever) and Bartonella infection. Histological testing can be relevant for TAVI patient if the infected tissue is available from surgery/intervention. It can also be relevant when there is a retrieval of embolic material (94).

As mentioned earlier, this review of the retrospective/prospective studies show Staphylococcus was present in 34% (324/962), Streptococci in 21% (198/962) and enterococcus in 22% (212/962) of available patient data. Meanwhile, case studies show

staphylococci in 26.1%, streptococci were present in 28.4%, and enterococci in 27.6% of available patient data.

It has been stated that staphylococci are the most common microorganisms found in blood cultures related to IE (2). The retrospective/prospective cases also show the same, but not in our case studies. Interestingly our second most common organism is enterococci both in our retrospective/prospective and case studies.

Eisen et al also found enterococci (20%) to be the second most causative specie after CoNS (30%) (95). It must be pointed out that Eisen et al. is a review based on 10 cases between 2008-2012 on TAVI IE. We can assume that the amount of TAVI procedures have risen as well as transfemoral procedure since then, and thereby rise in enterococci IE (95).

Amat- Santos et al. reported 34.4% of organism causing TAVI IE to be enterococci, while the second most common is CoNS (18.7%) (96). Khan et al. a systematic review published year 2020, found enterococci (25.9%), to be the most common cause of TAVI IE, followed by s. aureus in 16.1 % and CoNS in 14.7% of cases (10).

Chourdakis et al. and Dahl et al., indicate that the increase in incidence of enterococci is a result of the number of patients who undergo transfemoral TAVI compared to surgical replacement. The proximity to genitourinary/intestinal system predisposes the isolation of enterococci in the blood culture and echocardiography findings (81, 97).

Literatures further states that urinary tract infections are the most common type of enterococcal infection. Lower urinary tract infections, such as cystitis, prostatitis and epididymitis are often seen in older men (98). Considering that TAVI IE effects mostly older men who have undergone transfemoral procedure, an association between these factors should be considered.

Dahl et al. who did a study in 2019 to estimate the prevalence of IE in patients with E. faecalis (not TAVI IE), questioned whether there is a low-rate use of echocardiography in medical practice. It is possible that more patients are in actuality subject to infection with enterococci, and this would be evident if we increased the systematic use of echocardiography in patients with IE bacteremia (97).

5.1.2 Major Diagnostic Criteria #1, (sub criteria c)

requires single positive blood culture for "Coxiella burnetii or anti-phase 1 IgG antibody titer> 1: 800." (91)

Coxielle burnnetii is uncommon and causes Query (Q) fever endocarditis. IE is severe and the most common presentation of Q fever, which explains why this is considered a major diagnostic criterion. The disease may be acquired through the respiratory/digestive route and effect exclusively patients with pre-existing valvular disease (99). It is required that patients that are suspected of this have antigen greater than 1: 800, since patients with acute Q fever may have antibodies to phase I antigen greater or equal to 1:800 and thereby give a false positive result (100). Based on our review there has been no Q fever related TAVI IE.

5.1.3 Major Diagnostic Criteria #2 (sub criteria a-c)

requires echocardiogram with "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 or new valvular regurgitation"(91).

This section will differentiate between Echocardiography (#2A) and other modalities (#2B).

5.1.3.1 Major Diagnostic Criteria #2A: Echocardiography

TTE is the gold standard for investigating IE. Greaves et al. did a study in 2003 on the use of TTE for exclusion of IE, they show that there are five collective criterions that would increase the probability of detecting IE with TTE; "vasculitis/embolic phenomena; the presence of central venous access; a recent history of injected drug use; presence of a prosthetic valve; and positive blood cultures"(101).

With TAVI patients these criterions will always be fulfilled, and performing a TTE is advised as the initial diagnostic test for TAVI IE (90). Still there are cases where TTE does not give conclusive results. Stortecky et al. report that 40% of patients had echocardiography that was not conclusive (not specified whether TTE or TEE was used) (27).

TEE has a closer proximity to the heart valves and is considered to have higher sensitivity and specificity than TTE. Study done by Shaprio et al in 1994, compared TTE with TEE on

patients with suspected IE (not TAVI IE). TEE had a sensitivity of 85%, while TTE had a sensitivity of 60% in comparison (102). TEE should therefore be considered in "not conclusive" cases.

With TAVI IE there is a higher risk of valvular regurgitation and perivalvular abscesses which are easier detected with TEE. Case studies included in this review show that TTE was performed in 20.1%, while TEE was performed in 68% cases. TTE showed vegetation in 18.51% of cases, while TEE showed vegetation in 73.6% of cases (Supplement data 3 and 4).

In the retrospective/prospective review, 2 studies specified type of echocardiography (24, 27). TEE was used in 80.6% (202/252), while 76.5% (114/149) were examined by TTE. Vegetation was found in 58.4% (358/613), not specifying type of echocardiography used, in available patient data.

Echocardiograms can show vegetation in different locations, including vegetation on tricuspid valve, PM/ICD lead, other lead, aortic leaflets and stents. Unfortunately, it is not possible to exclude the fact that patients may have had vegetation in several places and thus have been counted multiple times in the statistics included in this review. The case studies show that they were mostly affected in the prosthetic valve/stent, as well as with affected mitral valve.

Even though echocardiographic findings are the cornerstone in diagnosing IE, according to Cahill et al. up to 30% of patients with IE in general are only suspected of having the diagnosis without clear evidence, on the other hand, there are too many patients that are categorized within the term "possible IE" (2). In echocardiography any small vegetation in post TAVI IE is difficult to interpretate and diagnose as the prothesis contains large amounts of metal that creates a reflectance and shadow effect (10).

According to Østergaard et al. intracardiac echocardiography (ICE) could be considered as a diagnostic tool in diagnosing patients with prosthetic valve IE, when TTE and TEE give inconclusive findings. Østergaard et al. had 19/38 patients (incl. TAVI IE patients) reclassified to definite IE, and there was low frequency of relapse among patients where ICE could not confirm IE. Østergaard et al. point out that there is little data on this, but ICE could help in guiding treatment option (103).

5.1.3.2 Major Diagnostic Criteria #2B: Other radiological modality

^{18}F-FDG Positron emission tomography–computed tomography (PET/CT) has been used in some cases to diagnose IE, where primary investigation does not yield conclusive results. F-FDG actively «incorporates into activated leukocytes, macrophages, and CD4-positive T cells present at the sites of infection» to give more accurate identification (104). In other words, it can detect inflammatory cells early in the infection process, before any morphologic damage occurs (105).

Information obtained by PET/CT and its results in detecting IE and ICED infection, has made it possible to incorporate its findings in MDC major criterion for prosthetic endocarditis. In a cross-sectional study done by Granados, U. et al ^{18}F-FDG PET/CT was able to reclassify 90% of cases initially classified as possible IE, 26% of these cases went from being classified as possible to definite IE, and finally 64% of these cases changed from possible to rejected IE, additionally 8 cases of septic embolism was identified (104).

Still there are not many case studies that have used PET/CT in their diagnostics process. The diagnostic value of PET/CT is highly dependent on the method used and interpretation. It should be noted that it is difficult to distinguish a sterile, post- operative inflammatory response from infection, which means that PET data should be interpreted with caution. Especially in the early post-operative phase (106). However, Scholtens et al. show that delayed imaging was more prone to false positive PET results. According to the study, delayed imaging is 150 min post injection of radiotracer, as increased accumulation of radiopharmaceutical can cause false positives (107, 108).

To increase the use of PET/CT there might be a need to standardise various imaging, dietary preparation for the patients, timing of image acquisition/processing with/without CT correction, and develop image interpretation criteria. However, this has no value if the availability of the equipment is low, or the resolution compared to CT is lower. Nuvoli et al. suggest an interesting alternative to PET/CT: The use of the hybrid PET/MRI imaging camera, which has a lower radiation exposure than PET/CT, specific Magnetic resonance imaging (MRI) characteristics, and the possibility for repetitive scanning (105).

Septic embolism is a common and potentially severe complication of IE. While CT has been considered a feasible modality for detecting vegetation and perivalvular abscess to diagnose IE, MRI can be used in identifying valvular and perivalvular damage (109, 110). Studies have

shown MRI could detect subclinical cerebrovascular complications in about 50% of IE patients. Study done by Duval et al. suggest that cerebral MRI finding can affect the clinical management plans (111).

5.2 New duke criteria: Minor

5.2.1 Minor Diagnostic Criteria #1

"requires predisposing heart condition or intravenous drug use" (91).

This requirement will be met by all TAVI patients, as they all have predisposing heart condition with AS. According to the old, modified duke criteria's, 1 minor criterion was enough to be considered as having "possible IE". This questions whether having a "possible IE" diagnosis is as preventive and effective as we would hope for, especially considering the treatment strategy for IE.

5.2.2 Minor Diagnostic Criteria #2

"requires Temp> 38 degrees" (91).

Review of the retrospective/prospective studies state that 78% (300/385) of patients had fever > 38.0, while case studies state 86% (68/79) of patients had fever as a clinical presentation of TAVI IE. Fever post-TAVI could be a normal response to foreign body implantation, with no sign of infection (81).

On the other hand, it should not be underestimated as TAVI IE patients have presented with infection from an intravascular source in 10.4% (26/250) and 6.6% (20/303) urological sources in our retrospective/prospective cases. Unfortunately, most infections were from unknown sources representing 66.3% (201/303) of available patient data among our retrospective/prospective cases.

According to a study done by Hoen et al. in 1996 for evaluating the specificity of the original duke criteria, they analysed 100 patients with acute fever or fever of unknown origin. They concluded that high specificity of the original duke criteria's applies especially in *ruling out IE* in patients with acute fever or fever of unknown origin (112). Considering that the revised criteria's have increased specificity, this statement could still be appliable.

5.2.3 Minor Diagnostic Criteria #3, #4 and #5

#3 “requires Vascular phenomena: arterial emboli, pulmonary infarcts, mycotic aneurysms, intracranial bleed, conjunctival haemorrhages, Janeway lesions” (91).

#4 **“**requires Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor” (91).

#5 “requires Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with endocarditis (excluding coag neg staph, and other common contaminants)” (91).

Vascular phenomena were found in 13.2% (22/167) of patients in the retrospective/prospective studies, while only in 5% (4/79) of patients in the case studies. Vascular symptoms might be harder to clinically identify, as patients present this at an earlier stage, or these symptoms can be associated with the patient’s comorbidities. Peripheral stigmata of IE are often Osler’s node, Janeway lesions, splinter haemorrhages and Roth spots (94).

5.3 Summary of New Modified Duke Criteria

In these criteria the gold standard is pathological findings, whether it is evidence of microorganism and/or pathological lesions, in vegetation or intracardiac abscess. Once clinical manifestation is recognized, most TAVI IE patients fall into the category of definite IE. Clinical suspicion of IE is what triggers the diagnostic criteria that must be met in order to receive rapid/targeted treatment.

The most common first symptoms recognized in the case and retrospective studies included here are fever, heart failure, systolic murmur and vascular symptoms. It is unclear whether this is a newfound heart murmur or an increase in grade. Atypical presentation, where textbook symptoms are not present and symptoms are masked by coexisting diseases, can occur in elderly or immunocompromised patients which makes TAVI patient even more difficult to diagnose.

The Duke criteria was primarily developed to aid epidemiologic/clinical research, where the purpose was to compare and differentiate clinical features and outcome of various patient cases. A criteria scheme like this could not integrate the highly variable clinical presentations

that IE represents. Any change in specificity would alter the add sensitivity and vice versa. Clinical judgement is still the cornerstone of diagnosing TAVI IE (90).

6.0 Management and outcome of IE

Managing IE is based on a preventive treatment and/or active treatment of the infection.

AB prophylaxis represents the preventive measure of TAVI IE. Retrospective multicentre study done by Amat-Santos et al. included 21 centers in America and Europa, according to them the most commonly used prophylaxis is Cephalosporins (67%), vancomycin (28%) and piperacillin/tazobactam (5%) (28). Most centers only gave one dose before procedure, while 2 centers gave 2-3 doses after TAVI procedure as well (28).

According to Adnan Khan et al. prophylaxis should be directed against the 3 most common organisms (10). However, even though a broad prophylaxis is simple to administer, the problem of AB resistance should be considered (27). Further measures should be taken to prevent TAVI IE like minimizing unnecessary healthcare interventions (both during and after TAVI) and reducing residual paravalvular leaks through better procedural technique and device.

Active treatment consists of conventional treatment with AB or surgical treatment. Treatment strategy is based on disease characteristic where microbe, focus (right / left IE), native or prosthetic valve, other foreign bodies, comorbidity and the patient's clinical condition (22). In this review indication for cardiac surgery was present in 79.3% (50/63). Indication is based on heart failure, uncontrolled infection, preventive measures of septic embolism (91). Despite indication, surgery could be impossible to perform due to comorbidities and high risk. AB therapy is then considered (25).

6.1 Conventional treatment, Antibiotics

AB should be administrated based on microorganism and the estimated minimum inhibitory concentration (81, 95). Any biofilm formation reduces the effect of antimicrobials, this increases with valve prostheses such as with TAVI. The biofilm prevents both the patient's immune system and antimicrobial agents from reaching the infected valve or prosthesis. The plasma concentration must therefore be high to ensure diffusion into the areas that are already poorly vascularized.

The epidemiology of IE should be the primary guide for the diagnostic testing and management. As mentioned in section 5.1.1, early literature states staphylococci and streptococci combined cause about 80% of the cases, while enterococci accounts for 10% of cases. New data suggests that enterococci is on the rise. Gram negative bacilli (incl. HACEK, non-HACEK) accounts for 5% of cases and fungi can cause IE, and is rare (113). Microbe specific treatment are outlined in International consensus guidelines, and should be accordingly followed along with national guidelines.

Based on our retrospective/prospective studies and case studies, 86.1% and 79% received AB treatment. As mentioned above, the most common AB used is beta-lactam in combination (36%) or vancomycin in combination (30%).

6.1.1 Length of antibiotic treatment

When treatment is started with AB, treatment time must be considered. The guidelines for the treatment of IE in artificial heart valves require AB treatment at six weeks (91). Based on 58/138 case studies in this review, 6 weeks of treatment (median) was given. According to Wang et a. left sided vegetations are more likely to have a higher bacterial density which in term leads to an extended course of treatment (114).

6.2 Surgical intervention

Even after starting AB treatment, surgical intervention may be required for complicated prosthetic endocarditis. As mentioned in the introduction, early surgery is recommended and is considered to reduce the risk of in- hospital death and embolic event (12). Surgery consists of debridement and valve replacement for patients with heart failure, severe valve dysfunction, cardiac abscess, highly resistant organisms or persistent bacteriemia (12, 25).

Surgical treatment was used in a total of 6.6% in our retrospective/prospective and 21% (27/128) case studies. Reguiero et al. and Kolt et al. both had the largest TAVI IE patient population included in our review, representing 250 and 224 patients. In both studies only 14.8% and 4% of the patient population received surgical treatment, even though in Reguiero et al study 81.2% had at least 1 indication for surgical intervention. They compared their surgical rate to Lalani et al where the rate of surgical treatment was 50% (115). According to Reguiero et al, their low surgical rate might be because of “high or prohibitive surgical risk of

such patients, in addition to the potential technical difficulties", also they concluded that valve surgery was not associated with a mortality benefit according to their study (25).

Mangner et al. compared cardiac surgery with AB in patients developing TAVI IE. This retrospective study looked at 20 patients who underwent surgical treatment, and 44 patients who were treated with AB. Surgery was considered in selected patients with echocardiographic evidence of IE, this represented 1/3 of all cases. However, 72.1% of patients who received AB had at least 1 indication for surgery based on guidelines (22).

According to Mangner et al the discrepancy between the number of patients who had indication surgery and was treated with surgery, is caused by "high operative risk and age of the patients considered inoperable or at high surgical risk, even for the initial TAVR procedure" (22).

According to the same study, patients treated with AB had a higher STS score and often had severe chronic kidney disease. It was concluded that 1 year mortality rate between these groups were not different, but rate of complication during treatment was higher in patients who received surgical treatment. The complications might explain the severity of IE and thereby justify a surgical procedure to start with. The "higher complication rate may outweigh the potential benefit of cankerous tissue removal" (22).

Surgery could therefore be considered beneficial in patients with severe symptoms. This includes patients with "valve regurgitation, vegetation, and dehiscence or paravalvular abscess/fistula, reflecting the indications for cardiac surgery in current guidelines" (22).

What makes the assessment interesting is that the TAVI patients are a highly selected group of patients with old age and comorbidity, who are initially excluded from open heart surgery in the primary assessment of whether TAVI is relevant or not. The question then is in which cases can one justify treatment of prosthetic endocarditis with surgery for such patients and how long can one wait before surgical intervention?

According to the studies mentioned above, surgical treatment does not seem reduce risk of mortality compared to AB, but surgery seems to be preferred and justified in patients where

AB will not cure IE, risk of embolic event is high and in patients who do not have comorbidities that make improvement of the condition distant (22, 114, 116).

6.2.1 Time until surgical intervention

Time until surgery depends on several factors, among them possible complications. It is disputed how long one should wait with surgical intervention with regard to embolization of the vegetation. This is especially true for left-sided IE.

Mangner et al. report that patients with native valve IE showed early surgery (< 48 hours), could reduce the risk of embolic events and in-hospital mortality within 6 weeks, with no difference in all-cause mortality after 6 months, compared to conventional treatment. This means that prolonged time from diagnosis to surgery may diminish the positive effects of surgery (22). The study also had a median time of 17 days between diagnosis to surgery, they assume that the prolonged time could have diminished the positive effect of surgery in their study.

6.3 Surgery or Antibiotics

TAVI patients are already considered high risk patients for surgery, with high STS score, this becomes even more pronounced when developing IE (22). Eisen et al. state that treatment choice for TAVI IE should be a case-by-case decision based on clinical judgment and managed individually. Surgical option according to Eisen et al "should be reserved for complicated cases and life-threatening clinical scenarios" as it sometimes might be the only viable choice (95).

As mentioned above, AB seems to be as effective as surgery, considering 1 year mortality, without the complication that follows with surgical procedure. This should be considered with caution as studies themselves state that the sample size is small, and p-values may not tell the truth in a small cohort (22).

On the other side, when TAVI expands into low- and intermediate-risk patients, surgery could be an option. Hypothetically according to Mangner et al., the complication rate should be reduced in this patient population (22).

Based on the discussion in section 6, there is no clear choice between surgery and AB for TAVI IE. There are limited data with limited patient population especially including the younger TAVI patients, and further studies should address this issue.

7.0 In hospital complication during treatment

Several complications are related to treatment of TAVI IE. Based on the review of retrospective/prospective and case studies, acute kidney injury (43%, 13.3%), septic shock (21%, 10%), septic embolism/embolization (9.5%, 16.6%) and acute heart failure (32%, 21.6%) are among the most common.

Tokarski et al. have associated acute kidney injury during treatment with baseline background and the severity of the infection (80). Treatment with AB for approximately 6 weeks, should take into consideration; renal toxicity of the infection microorganism versus the adverse effects of AB, change of AB treatment and polymicrobial treatment.

Six weeks of recommended intravenous AB treatment requires patient being hospitalized (91). Complications such as, embolic events caused by hospitalization should also be a focus as hemodynamic repercussions caused by paravalvular leaks/regurgitation increases the likelihood of systemic embolism. This is in addition to post procedural aortic regurgitation that can be caused by TAVI (9).

The retrospective/prospective studies show that new aortic valve regurgitation was present in 25.5% (97/380), new mitral valve regurgitation present in 16.5% (44/267) and paravalvular leaks in 5% (5/103) of the patients (24). The case studies showed 11.1% (3/27) of patients had paravalvular leaks, while 7.4% (2/27) had aortic regurgitation.

Vilacosta et al. assessed the risk of systemic embolization in patient with left sided IE, where 72/217 episodes involved prosthetic valves. Meanwhile, 12.9% patients had embolic events after the initial AB therapy, 52% of events effected the CNS, and 65% of the events occurred during the first 2 weeks. They concluded that there was no significant difference in risk according to infection microorganism, but embolism before AB therapy is a risk factor for new emboli, where the risk increases with increasing vegetation size (117).

8.0 Outcome

Detailed results from mortality rate are presented under section 3.4.4. In this review overall in hospital death when patients were treated for TAVI IE was around 28% both in the larger studies and case studies. Previous studies show in hospital death rate of being up to 36%-63.6% (25, 28, 118). This is different from Kolte et al. who reported an in hospital mortality rate of 15.6% (21). According to them the reason for their low rate is because they included both patients with definite IE as well as possible IE, while the other studies only had patients with definite IE.

This review is based on available data from other studies, which means that data from both definite and possible IE are included. Taken this into account our mortality rate is higher than results from Kolte et al. A possible explanation for this is that we have included more patients with definite IE than Kolte et al.

9.0 Conclusion

Diagnosing TAVI IE is based on the new modified duke criteria. The gold standard is pathological findings (microorganism and/or pathological lesions, vegetation or intracardiac abscess). Both review of the larger studies as well as case studies indicate a rise of enterococci as the causative microorganism for TAVI IE, while the most common first symptoms recognized here are fever, heart failure, systolic murmur and vascular symptoms.

The Duke criteria was primarily developed to aid epidemiologic/clinical research. A criteria scheme like this could not integrate the highly variable clinical presentations that IE represents. Clinical judgement is still the cornerstone of diagnosing TAVI IE along with objective findings.

TAVI patients are considered high risk patients for surgery, with high STS score, this becomes more pronounced when developing IE. Treatment choice for TAVI IE should be a case-by-case decision based on clinical judgment and managed individually.

A common thread for the individual studies included in this review is that surgical option as a treatment to TAVI IE should be reserved for complicated and life-threatening cases. Still, when TAVI expands into low- and intermediate-risk patients, surgery could be an option in a larger patient population. Unfortunately, there are no RCT comparing surgical and AB

treatment, and there are not enough observational or cohort studies/data to determine whether surgery or AB is appropriate and when.

As mentioned above, AB seems to be as effective as surgery, considering 1 year mortality. Some studies that indicate this unfortunately have a small sample size. Statements about AB being as effective as surgery should therefore be considered with caution, as well as considering surgery when the case is not complicated or life-threatening. Based on this review overall in hospital death when patients were treated for TAVI IE was around 28% both in the larger studies and case studies.

10.0 Limitations of the study

This review is based on several cohort and case studies. Studies combined lack certain patient data whether it is loss of follow up in the prospective studies or lack documented data in the retrospective studies. Other studies have only a small patient population, making it difficult to make an assumption based on that particular study. This might show a skewed distribution of patient data, and thereby skewed distribution in the statistics. Throughout the review, larger studies have been compared with the case studies and other literature to either support or contradict the results.

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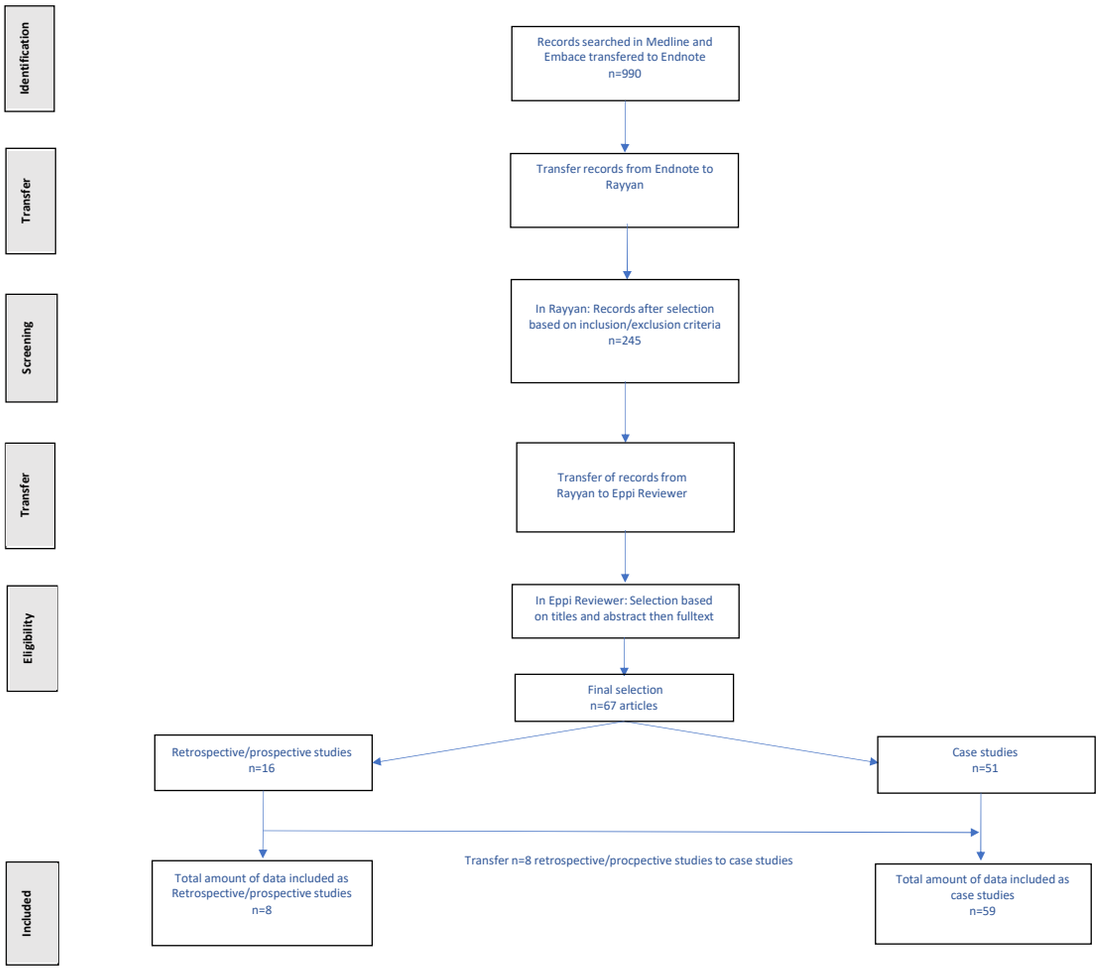
12.0 Figure 1


Identification
Transfer
Screening
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Eligibility
Included
Records searched in Medline and Embace transfered to Endnote n=990
Transfer records from Endnote to Rayyan
In Rayyan: Records after selection based on inclusion/exclusion criteria n=245
Transfer of records from Rayyan to Eppi Reviewer
In Eppi Reviewer: Selection based on titles and abstract then fulltext
Final selection n=67 articles
Retrospective/prospective studies n=16
Case studies n=51
Transfer n=8 retrospective/procpective studies to case studies
Total amount of data included as Retrospective/prospective studies n=8
Total amount of data included as case studies n=59

13.0 Supplement data 1
Baseline data

Author	Kolte et al.	Mangner et al.	Mangner et al.	Tabata et al.	Bjursten et al.	Regueiro et al.	Yeo et al.	Stortecky et al	Amat-Santos et al	Data summary
Study design		Retrospective	Retrospective	Prospective	Retrospective	Retrospective		cohort study	Prospective	
Time periode	2013-2014	2008-2017	2008-2017	2008-2018	2008-2018	2005-2015	2012-2014	2011-2018	2007 -2014	**2005-2018**
Treatment		surgical +AB	AB							**Surgery/AB**
Total IE	224/ 86372	20/64	44/64	17/1448	103/4336	250/20006	120/41025	149/7203	53/7944	**980/168398**
All patients or IE patients	IE patients	IE patients	IE patients	IE patients	IE patients	IE patints	IE patient	IE patients	IE patients	
Scores										
NYHA class:										
- I								60 (40.3) (I or II)		
- II				4/17 (23.5)				60 (40.3) (I or II)		**64/166 (38.5)**
- III		16/20 (80.0) (III/ IV)	30/41 (III/ IV)	12/17 (70.6)				89 (59.7) (III or IV)		**147/227 (65)**
- IV		16/20 (80.0) (III/ IV)	30/41 (III/ IV)	1/17 (5.9)				89 (59.7) (III or IV)		
Logistic EuroSCORE, median (IQR),				12.9 ± 8.0		17.9 (220 pas)			24.85±13.82	**/290**
STS score		17.2 (97- 21.6)	23.3 (13.7- 30.0)	4.6 ± 3.0				5.0 ± 3.9		**/230**
Left ventricular ejection fraction, mean		53 ± 13	54 ± 12 (51± 13)	56.7 ± 12.1		53 (13.9)		53.8 ± 15.5	56±12	
- Good (>55%)										
- Moderate (35–55%)					21/103 (20.4)					
- Poor (<35%)					6/103(5.8)					
Age, median or mean	83(76–87)	77.3 ± 5.1	81.5 ± 5.7	75.8 ± 7.2	82 (77–85)	80 (59-91)	62.1 (3.5)	80.1 ± 8.0	79±8	
Female	97/224(43.1)	7/20 (35.0)	19/44	9/17 (53)	40/103 (38.8)	91/250 (36.4)	45/120(37.5)	47/149 (31.5)	23/53 (43.4)	**378/980 (38.6)**
Men	127/224 (56.9)	13/20 (65.0)	25/44	8/17 (47.1)	63/103 (61.2)	159/250 (63.6)	75/120 (62.5)	102/149 (68.5)	30/53 (56.6)	**602/980 (61.4)**
Obesity							15/120 (12.5)			**15/120 (12.5)**
BMI		28.2(24.4 - 33.1)	28.2 (24.1-30.4)	30.3 ± 6.7	26.8 ± 3.1			27.5 ± 5.2		**/333**
Permanent pacemaker or ICD				1/17 (6.3)			15/120 (12.5)	15/149 (10.1)	6/53 (11.3)	**37/339 (10.9)**
Diabetes mellitus		9/20(45.0)	21/44 (47.7)	8/17 (47.1)	29/103 (28.2)	97/250 (38.8)	25/120 (20.8)	44/149 (29.5)	19/53 (35.8)	**252/756 (33.3)**
Hypertension					69/103 (67.0)		60/120 (50.0)	125/149 (83.9)		**254/372 (68.3)**
Dyslipidemia							20/120 (16.7)	81/149 (54.4)		**101/149 (67.8)**
Immunosuppressive										
Cancer/Malignancy					18/103 (17.5)					**18/103 (17.5)**
Human immunodeficiency virus							5/120 (4.2)			**5/120 (4.2)**
Immunosuppressive therapy		2/20 (10.0)	9/44 (20.5)							**11/64 (17.2)**
Previous										
Previous stroke		2/20 (20.0)	4/44 (9.1)	1/17 (5.9)	16/103 (15.5)	31/250 (12.4)		18/149 (12.1)		**72/583 (12.3)**
Previous IE						3/250 (1.2)				**3/250 (1.2)**
Previous cardiac surgery				5/17 (29.4)	28/103 (27.2)			22/149 (14.8)		**55/269 (20.4)**
Previous valve surgery/intervention				3 /17(17.6)		29/250 (11.7)	5/120(4.2)			**37/387 (9.6)**
Prior MI				2/17 (11.8)	8/103 (7.8)			18/149 (12.1)		**28/269 (10.4)**

Prior PCI				3/17 (17.6)	22/103 (21.4)		5/120 (4.2)			**30/240 (12.5)**
Prior CABG							10/120 (8.3)			**10/120 (8.3)**
Kidney										
Chronic renal failure/disease						117/250 (46.8)	45/120 (37.5)			**162/370 (43.8)**
CKD stage ≥3b		7/20 (35.0)	26/41 (63.4)							**33/61 (54.1)**
Acute kidney injury									11/53 (20.8)	**11/53 (21)**
Lung										
COPD		8/20 (40.0)	10/44 (22.7)	4/17 (23.5)	22/103 (21.4)	78/250 (31.2)	20/120 (16.7)	20/149 (13.4)	18/53 (34.0)	**180/756 (23.8)**
Pulmonary hypertension				36.3 ± 10.6			20/120 (16.7)			
Heart										
Heart failure							70/120 (58.3)			**70/120 (58.3)**
Atrial fibrillation		14/20 (70.0)	27/43 (62.8)	6/17 (35.3)	46/103 (44.7)	97/250 (38.8)	45/120(37.5)			**235/553 (42.5)**
Arteries/Hemoglobin										
CAD		8/ 20(40.0)	24/44 (54.5)	7/17 (41.2)			35/120 (29.2)	82/149 (55.0)		**156/350 (44.6)**
PAD		3/20 (15.0)	13/44 (29.5)	4/17 (36.4)						**20/81 (24.7)**
Coagulopathy							55/120 (45.8)			**55/120 (46)**
Peripheral vascular disease					14/103 (13.6)		15/120 (12.5)	23/149 (15.4)		**52/ 372 (14)**
Procedural characteristics										
Cardiopulmonary bypass							55/120 (45.8)			**55/120 (46)**
Orotracheal intubation						137/250 (54.8)			44/53 (83.0)	**181/303 (60)**
Antibiotic prophylaxis										
Antibiotic prophylaxis received						236/250 (94.4)	111/120 (92.5)	138/149 (92.6)	31/53 (58.5)	**516/572 (90)**
Antibiotic prophylaxis effective							53/120 (48)	83/149 (60.1)		**136/ 249 (55)**
Timing of prophylaxis:										
- After TAVR								1/149 (0.7)		**1/138 (0.7)**
- <30 min								44/149 (31.9)		**44/138 (32)**
- 30–60 min								84/149 (60.9)		**84/138 (61)**
- >60 min								9/149 (6.5)		**9/138 (6.5)**
β-Lactam alone						195/250 (78.0)				**195/236 (82.6)**
Vancomycin alone						15/250 (6.0)				**15/236 (6.4)**
Cefalosporin									14/21 centers	
Vancomycin									6 centers	
piperacilline/tazobactam									1 center	
Valve implant site										
Catheterization laboratory						107/250 (42.8)		83/149 (55.7)	32/53 (60.4)	**222/452 (49.1)**
Operating or hybrid operating room						143/250 (57.2)		66/149 (44.3)	21/53 (39.6)	**230/452 (51)**
Type of valve										
Self-expandable valve				16/17 (94.1)		119/250 (47.6)		61/149 (42.7)	19/53 (35.8)	**215/469 (46)**
Balloon-expandable valve				8/17 (47.1)		131/250 (52.4)		63/149 (44.1)	34/53 (64.2)	**236/ 469 (50.3)**

Lotus/mechanically expandable				2/17 (11.8)				19/149(13.3)		**21/166 (12.6)**
Mechanical ventilation							45/120 (37.5)			**45/120 (37.5)**
Intra aortic balloon pump							10/120 (8.3)			**10/120 (8.3)**
Approach										
Transfemoral					84/103 (81.6)	208/250 (83.2)		127/149 (85.2)	12±5	**>419/555 (75.5)**
Transapical					17/103 (16.5)	31/250 (12.4)	50/120 (41.7)	15/149 (10.1)	10/53 (18.9)	**123/675 (18.2)**
Transaortic					1/103 (1.0)	8/250 (3.2)			2/53 (3.8)	**11/406 (3)**
Other					1/103 (1.0)	3/250 (1.2)		7/149 (4.7)		**11/502 (2.2)**
Inhospital TAVI outcomes/complications										
Device success						204/250 (81.6)			50/53 (94.3)	**254/303 (83.8)**
Aortic regurgitation (≥moderate)						39/250 (15.2)				**39/250 (15.6)**
Stroke						12/250 (4.8)				**12/250 (4.8)**
Minor vascular				6/17 (37.5)						**6/17 (35.3)**
Major vascular complication						25/250 (10.0)				**25/250 (10)**
Acute kidney injury						33/250 (13.2)				**33/250 (13.2)**
Permanent pacemaker implant						53/250 (21.2)	10/120 (8.3)			**63/370 (17)**
Major or life-threatening bleeding						29/250 (11.6)				**29/ 250 (11.6)**
Length of hospital stay, median (IQR), days						9 (7-15)	22.9 ± 2.6 (19.0)	10.3 ± 6.8	10.3±7.6	

Supplement data 2
IE data

Author	Kolte, et al.	Mangner,et al.	Mangner,et al.	Tabata et al.	Bjursten et al.	Regueiro et al.	I. Yeo et al.	Stortecky et al.	Amat-Santos,	Data summary
Year	2013-2014	2008-2017	2008-2017	2008-2018	2008-2018	2005-2015	2012-2014	2011-2018	2007-2014	**2005-2018**
Treatment		Surgical+AB	AB							**Patients/Total available patient data**
Diagnositic criteria	Modified Duke criteria	Modified Duke criteria	Modified Duke criteria	modified Duke criteria	Modified Duke criteria	Modified Duke criteria	modified Duke criteria	modified Duke criteria	modified Duke criteria	**modified Duke criteria**
Total IE	224/ 86372	20/64	44/64	17/1448	103/4336	250/20006	120/41025	149/7203	53/7944	**980/168398**
Definite IE		20/20 (100)	38/44 (86.4)		54/103 (52.9)	250/250 (100)		94/149 (63.1)	51/53 (96.2)	**507/619 (82)**
Possible IE								55/149 (36.9)	2/53 (3.7)	**57/202 (28.2)**
Early IE		12/20 (60.0)	32/44 (72.7)		51/103 (49.5)	178/250 (71.2)		93/149 (62.4)		**366/576 (63.5)**
Late IE					52 /103 (50.5)			56/149 (37.6)		**108/252 (43)**
Time to IE,days										
Median (IQR)	66(34–124)	233 (60–578)	139 (23-412)	294 (133–608)		5.3 (1.5-13.4)				**147.46 days**
First symptoms/time of admission:										
Predisposition		20/20 (100)	44/44 (100)							**64/64 (100)**
Fever > 38.0		18/20 (90.0)	36/43 (83.7)	7/17 (41.2)		201/250 (80.4)			38/53 (71.7)	**300/385 (78)**
Sepsis		4/20 (20.0)	20/43 (46.5)	3/17 (17.6)						**27/80 (33.8)**
Heart Failure		13/20 (65.0)	25/43 (58.1)	8/17 (47.1)		100/250 (40.0)			31/53 (58.5)	**177/383 (46.2)**
Vasvular phenomena		5/20 (25.0)	7/44 (15.9)		10/103 (9.8)					**22/167 (13.2)**
At least 1 Indication for cardiac surgery		19/20 (95.0)	31/43 (72.1)			203/250 (81.2)				**253/313 (80.8)**
Neurological				5/17 (29.4)		42/250 (16.8)			4/53 (7.5)	**51/320 (16)**
Systemic embolism				4/17 (23.5)		32/250 (12.8)				**36/267 (13.5)**
Cutaneous						8/250 (3.2)			2/53 (3.8)	**10/303 (3.3)**
Exposure to sources of bacteremia before infective endocarditis										
Unknown						174/250 (69.6)			27/53 (50.9)	**201/303 (66.3)**

Skin infection									5/53 (9.4)	**5/53 (9.4)**
Presumed intravascular source/ Soft tissue infection						26/250 (10.4)				**26/250 (10.4)**
Gastrointestinal						17/250 (6.8)				**17/250 (6.8)**
Urologic						16/250 (6.4)			4/53 (7.5)	**20/303 (6.6)**
Odonatological						9/250 (3.6)			3/53 (5.7)	**12/303 (4)**
Pacemaker implant						8/250 (3.2)			1/53 (1.9)	**9/303 (3)**
Nosocomial/health care associated		8/20 (40.0)	18/44 (40.9)		94/103 (92)	132/250 (52.8)			21/53 (39.6)	**273/470 (58.1)**
Echocardiography										
TEE performed					83/103 (81.4)			119/149 (79.8)		**202/252 (80.1)**
TTE performed								114/149 (76.5)		**114/149 (76.5)**
Normal								12/149 (8.1)		**12/149 (8.1)**
Not conclusive								59/149 (39.6)		**59/149 (40)**
Fistula								1/149 (0.7)	2/53 (3.8)	**3/202 (1.4)**
Abscess		7/20 (35.0)	11/44 (25.0)		12/103 (11.9)			14/149 (9.4)	8/53 (15.1)	**52/369 (14.1)**
Aortic valve affected					54/103 (52.9)					**54/103 (52.4)**
Mitral valve affected					22/103 (21.8)	41/165 (24.8)				**63/268 (23.5)**
Tricuspid valve vegetation						7/165 (4.8)				**7/165 (4.2)**
Vegetation		19/20 (95)	34/44 (6.8)		45/103 (44.2)	165/244 (67.6)		54/149 (36.2)	41/53 (77.4)	**358/613 (58.4)**
No vegetation					32/103 (31.7)					**32/103 (31)**
Periannular complication						44/244 (18.0)				**44/244 (18)**
New aortic regurgitation					65/103 (63.1)	24/244 (9.8)			8/53 (15.1)	**97/380 (25.5)**
New mitral regurgitation						34/244 (13.9)			10/53 (18.9)	**44/267 (16.5)**
New valve regurgitation								13/149 (8.7)		**13/149 (8.7)**
New Paravalvular leaks					5/103 (5.0)					**5/103 (5)**

Causative organism(s)										
Staphylococcus										**324/962 (34)**
S aureus	50/224 (22.4)			2/17 (11.8)	23/103 (22.3)	54/232 (23.3)	20/120 (16.7)	32/149 (21.5)	**11/53 (20.8)**	**192/871 (22.1)**
Methicillin-sensitive S. aureus (MSSA)	25/224 (11.2)									**25/224 (11.1)**
Methicillin-resistant S. aureus (MRSA)	25/224 (11.2)								6/53 **(11.3)**	**31/277 (11.2)**
Coagulase-positive Staphylococcus (CoPS)		6/20 (30.0)	11/44 (25.0)							**17/64 (26.6)**
Coagulase-negativ Staphylococcus (CoNS)		2/20 (10.0)	4/44 (9.1)	5/17 (29.4)	7/103 (6.8)	41/232 (16.8)		19/149 (12.8)	13/53 (24.5)	**91/618 (15)**
Other/unspecified Staphylococcus	18/224 (8.0)									**18/224 (8)**
Streptococcus										**198/962 (21)**
Viridans streptococci				1/17 (5.9)		16/232 (6.9)		34/149 (22.8)	3/53 (5.7)	**54/451 (12)**
Nonviridans streptococci								9/149 (6.0)		**9/149 (6)**
Other streptococci	67/224 (29.9)	3/20 (15.0)	4/44 (9.1)	1/17 (5.9)	35/103 (34.0)		25/120 (20.8)			**135/528 (26)**
Enterococcus	46/224 (20.5)	8/20 (40.0)	16/44 (36.4)	4/17 (23.5)	21/103 (20.4)	57/232 (24.6)	10/120 (8.3)	39/149 (26.2)	**11/53 (20.8)**	**212/962 (22)**
Gram negative bacteria	<10/224 (3.1)							8/149 (5.4)		**<18/373 (<5)**
Fungal		1/20 (5.0)						3/149 (2.0)		**4/169 (2.4)**
Polymicrobial	18/224 (8.0)							3/149 (2.0)		**21/373 (5.6)**
Atypical non specified									13/53 (24.5%)	**13/53 (25)**
Other/unknown	18/224 (8.0)		3/44 (6.8)	4/17 (23.5)	12/103 (11.7)			2/149 (1.3)	13/53 (24.5)	**52/590 (9)**
No bacteria					5/103 (4.9)	12/232 (5.2)			2/53 **(3.8)**	**19/388 (5)**
In-hospital management										
Surgery /valveexplantation/replacement		20/20		4/17 (23.5)		37/250 (14.8)			4/53 **(7.5)**	**65/340 (19.1)**
Surgery during hospitalization					13/103 (12.7)					**13/103 (12.6)**
SAVR during hospitalization					2/103 (2.0)					**2/103 (2)**
Redo TAVI	5/224 (2.1)									**5/224 (2.1)**
Removal of PPM/ICD	4/224 (1.9)									**4/224 (<4.5)**

Transcatheter valve-in-valve procedure						3/250 (1.2)			**2/53 (3.8)**	**5/ 303 (1.7)**
Isolated pacemaker extraction					11/103 (10.8)	7/250 (2.8)	5/120 (4.2)			**23/473 (4.9)**
Antibiotics			20/20			205/250 (82)			53/53 (100)	**278/323 (86.1)**
Antibiotics used										
Beta lactam alone						38/205 (18.5)			21/53 (39.6)	**59/258 (22.8)**
Beta lactam combinations						126/205 (50.4)				**126/205 (61.5)**
Vancomycin alone/combinations						53/205 (21.2)			16/53 (30.2)	**69/258 (27)**
Gentamycin									20/53 (37.7)	**20/53 (38)**
Rifampicin									7/53 (13.2)	**7/53 (13.2)**
In-hospital complications										
Any complication	145/224 (64.7)	17/20 (85.0)	24/43 (55.8)			160/238 (67.2)			**36/53 (67.9)**	**380/578 (66)**
Heart										
Cardiac arrest	<10/224 (1.3)						10/120 (8.3)			**<20/344**
Complete heartblock	11/224 (4.9)									**11/224 (5)**
Acute myocardial infarction	16/224 (7.1)				1/103 (1.0)		15/120 (12.5)			**32/447 (7.2)**
Acute heart failure	60/224 (26.8)					87/238 (36.6)	40/120 (33.3)			**187/582 (32)**
Cardiogenic shock	<10/224 (0.9)						15/120 (12.5)			**<25/344 (7.3)**
Kidney										
Acute kidney injury	86/224 (38.4)					106/238 (44.5)			**29/53 (54.7)**	**221/515 (43)**
Need for hemodialysis		9/20 (45.0)	10/43 (7.1)							**19/63 (30.2)**
Infection										
eizures		4/20 (20.0)								**4/20 (20)**
Septic shock	35/224 (15.6)					66/238 (27.7)	20/120 (16.7)		11/53 (20.8)	**132/635 (21)**
Persistent bacteremia						51/238 (21.4)			**15/53 (28.3)**	**66/291 (23)**
Ischemia		3/20 (15.0)	1/42 (2.4)							**4/62 (6.5)**

Abscess formation	<10/224 (3.6)									**<10/224 (<4.5)**
Stroke										
Transient ischemicattack/stroke	14/224 (6.3)				8/103 (7.7)	25/238 (10.5)	5/120 (4.2)		4/53 (7.5)	**56/738 (7.6)**
Septic embolism/ embolization	11/224 (4.9)	7/20 (35.0)	10/42 (23.8)			22/238 (9.2)			5/53 (9.4)	**55/577 (9.5)**
Death	35/224 (15.6)	10/20 (50.0)	22/44 (50)	7/17 (41.2)	17/103 (16.8)	90/250 (36.0)	25/120 (20.8)		25/53 (47.2)	**231/831 (28)**
1 year mortality		13/20 (65.0)	30/44 (68.2)					56/148 (37.8)		**99/212 (47)**
Death within 6 months of PVE					31/103 (30.1)					**31/103 (30)**
LOS, days										
Mean ± SD	13.6 ± 17.4				38 (25–46)					
Median (IQR)	8(6-15)						22.9 ± 2.6 (19.0)			
*** Any complication: acute kidney injury,acute heart failure, septic shock, acute myocardial infarction, transient ischemic attack/stroke, complete heartblock, septic embolism, abscessformation, cardiac arrest or cardiogenic shock.**										

Supplement data 3
Case study, summary data

	Patens with data	Data
Age in years, median, (IQR)	134/134	80 (10)
Gender (female)	108/134	48/108
Level of diagnosis	134/134 (100)	
Definitive diagnosis		111/134
Possible diagnosis		23/134
Approach for TAVI	48/134	
Transfemoral		39/48
Transapical		6/48
Subclavian		2/48
Data on type of prostheses	79/134	
- CoreValve		35/79
- Edwards SAPIEN		34/79
Other		10/79
Logistic EuroSCORE, Median % (IQR)	40/134	23,5
Underlying diseases	65/134	
Diabetes mellitus		18/65
Chronic renal failure		20/65
History of cancer		4/65
Chronic lung disease		18/65
Immunosupressioon		7/65
Suspected infective focus		31/65
Heart failure		15/65
Atrial fibrilation		13/65
Valve-pathology		7/65
Pacemaker		11/65
ACB/CABG		6/65
CAD		15/65
Time between TAVI and IE in days, median (IQR)		5.2 (10,4)
Data on clinical presentation:	79/134	
Fever		68/79
Embolism		4/79
Vascular phenomena		4/79
Dyspnoe		14/79

Heart failure		10/79
Lethargy/weekness		13/79
Other		8/79
TTE preformed	27/134	
Presence of vegetations, n (%)		5/27
Perivalvular abscess		0/27
Paravalvular leak		3/27
Aortic regurgitation		2/27
TEE/ICE preformed	91/134	
>1 TEE before diagnosis		4/91
Vegetation		67/91
TAVI		50/67
Mitral		14/67
Tricuspid		1/67
PM/ICD		2/67
Abcess		14/91
Paravalvolar leak		16/91
Aortic reguritation		2/91
Echocardiography of unknown modality	32/134	
Vegetation		17/32
TAVI		5/17
Mitral		4/17
Tricuspid		0/17
PM/ICD		0/17
Unknown		8/17
Abcess		2/32
Paravalvolar leak		3/32
Aortic reguritation		5/32
Data on radiological prosedure	21/134	
CT		8/21
Results providing/strenghtening diagnosis		5/8
MRI		5/21
Results providing/strenghtening diagnosis		3/5
PET		6/21
Results providing/strenghtening diagnosis		4/6
Causative microorganism	134/134	
Enterococci	37/134	
E. faecalis		28/37

E. faecium		6/37
E. galloliticus		3/37
Staphylococci	35/134	
S. epidermidis		12/35
MRSE		1/35
S. aureus		18/35
MRSA		3/35
S. lugdunensis		2/35
Streptococci	38/134	
S. mitis		3/38
S viridans		7/38
S.anginosus		3/38
S.sanguinis		2/38
S.sanguis		3/38
S . Durans		1/38
S. salvarius		1/38
S. oralis		3/38
Nonhemolytic streptococcus		3/38
Hemolytic streptococcus		1/38
Coagulase negative streptococcus		1/38
S.salivarius		1/38
S. hemolyticus		1/38
S . Gordonii		3/38
S. capitis		2/38
S. acidominimus		1/38
S. enteritidis		1/38
Group B-streptococcus		1/38
Other	9/134	
E.coli		1/9
Klebsiellapneumonale		1/9
P. aeruginosa		3/9
Moraxella nonliqufacien		1/9
Cardiobacterium hominis		1/9
G. Adiacens		1/9
Acinetobacter species		1/9
Fungi	6/134	

Histoplasma capsulatum (pathology)		1/6
Aspergillus (histology)		1/6
C. albicans		1/6
C parapsilosis		3/6
Polymicrobial		5/134
Negative		3/134
Data on surgical vs medical treatment, n (%)	128/134	
Non-surgical		101/128
Surgical		27/128
Data on antimicrobial treatment, n (%)	128/134	
Not treated with antimicrobial		1/128
Unknown type		22/128
Antifungal alone		4/128
Beta-lactam alone		16/128
Beta-lactam in combination		46/128
Vancomycin alone		1/128
Vancomycin in combination		38/128
Rifampicine		23/128
>2 antibiotics during treatment		33/128
Weeks of treatment, median (IQR)	58/134	6 (0,10)
Any complications		48/134
Heart failure		17/134 (21.6)
Renal failure		12/134 (13.3)
Sepsis shock		14/134 (10,0)
Embolic event		15/134 (16,6)
Death during treatment	117/134	
		37/117

Supplement data 4
Case study, detailed data

Author	Sex and age	Euro SCORE	Type of prothesis	Approach	Time between TAVI and Hosp. for PVE	Level of diagnosis	Predisposing conditons	Clinical presentation	ECCO findings	Radio- logy	Pathogen	Antibiotic treatment, length	Surgery and indication	Comp- lication	Out-come
AUNG et. Al	Male, 72 y	28,14	Edwards SAPIEN 23 mm (B-E)	TA	107 days	Definitive (1b, 2a, 1, 2)	DM, frailty; CKD	Fever and chills	Native MV vegetation echolucent space anterior to the TAVR annulus, associated with mild paravalvular regurgitation	ND	*E. faecalis*	Benzyl-penicillin and gentamicin, 6 weeks	No	None	Alive after 1 year
AUNG et. Al	Female, 91 y	15,21	Edwards SAPIEN 29 mm (B-E)	TF	18 days	Definitive (2a, 1, 2, 5)	DM; cellulitis; CA, breast; CKD stage 3	High fever	Native MV vegetations, trivial intravalvular regurgitation with no obvious vegetations	ND	*S. mitis*	Benzyl-penicillin and gentamici, 6 weeks	No	None	Alive after 1 year
AUNG et. Al	Female, 88 y	55,28	Edwards SAPIEN 29 mm (B-E)	TF	36 days	Definitive (1b, 2a, 1, 2)	MV replacement, interstitial pulmonary fibrosis requiring high-dose steroid therapy	Fever and chills	Obvious vegetation and abscess on TEE, a large cavity with thickened tissue was identified just anterior to the CoreValve prosthesis	ND	*E. faecium*	Vancomycin, 6 weeks	No	None	Alive after 1 year
AUNG et. Al	Male, 90 y	26,5	Edwards SAPIEN 29 mm (B-E)	TF	90 days	Possible (1, 2, 5)	V-I-V, cellulitis, stage IV CKD, and DM	Celluliitis	TEE demonstrated well-seated CoreValve with mild paravalvular regurgitation	ND	*E. faecalis*	Benzyl-penicillin and gentamicin, 6 weeks	No	None	Alive after 1 year
Mangieri et. al	Male, 72 y	ND	Edwards Sapien 3 23 mm (B-E)	TF	1 year	Definitive (2a, 2b, 1, 2, 5)	Antiphospholipid syndrome, temporal arteritis, and Sjogren's syndrome, removed multiple rectal polyps	ND	TEE: diffuse thickening of the aortic cusps + increased gradients across prosthesis. No regurgitation TEE: revealed mass and new perivalvular leak	PET : intense meta-bolic activity on the pros-thesis	E. galloliticus	Ampicillin	Yes, perivalvular leak and clinical worsening	None	Alive
Carrel et al	Male, 76y	ND	ND	ND	9 mnd	Definitive (1b, 2a, 1, 2)	ND	Fever and new sys. murmur grade V	TEE: large vegetation causing substantial obstruction of the prosthetic valve	Chest X-ray: pul-monary edema	*C. Parap-silosis*	Antifungal	Yes, not spesified	Post-opeartive wound infection	Died from an aspiration event after 3 months
Santos et al	Female, 91 y	Not	Edwards Sapien 23 mm (B-E)	TA	1 day	Definitive (pathological criteria)	CKD and pulmonary hypertension.	Fever	TEE transvalvular aortic gradient of 20/10 mmHg with early mild paravalvular leak that disappeared thereafter	ND	C. albicans	Antifungal	No	Require intub-ation	Died during treatment
Averya et al	Male, 78 y		Edwards Sapien (B-E)	ND	2 years	Definitive (2a, 1, 2, 5)	Congestive HF, HT, hyperlipidemia, and prostate cancer status post radiation treatments.	Low feber, Anemia, sys. murmur, no peripher-signs of IE	TEE: small vegetation/ mass on the aortic valve with a mild to moderate perivalvular leak and no abscess	ND	*C. hominis*	Ciprofloxacin, 6,5 weeks	Yes, possible myocardial embolization. Valve replacement and bypass-surgery.	MI, mediastinal hematoma and cardiogenic shock	Alive after 14 months
Citro et al.	Female, 72 y	39,7	Sapien-Edwards 23 mm (B-E)	TF	5 months	Definitive (2a, 1, 2, 5)	HT, AF, Valve-in-valve	Fever	TEE paraprosthetic reguritation, echodense abscess, mitro-aortic intervalvular fibrosa fistula into the LV, elevated pulmonary presure, relapse of severe LV dynamic obstruction arising from septal contact of systolic anteri- or motion of the MV, with related regurgitation	ND	S. epider-midis	Vancomycin and gentamicin, and oral rifampicin	No	Multi organ failure	Died after 2 weeks of treatment

Amat-Santos et al	Male, 75 y	48	26-mm Sapien XT (B-E)	ND	4 mounths	Definitive (2a, 1, 2, 5)	ND	Heart failure, fever	Perforation affecting the base of the anterior mitral leaflet, The depth of the prostheses within the left ventricular outflow tract was adequate but presence of a pseudo-aneurysm from the stent frame of the valve extending to the anterior mitral leaflet	ND	S. epider-midis	Yes, ND	No, due to high risk patients medical tractment was chosen	Renaly failure, transetory cerebrovascular event	Died after 18 months
Spartera et al	Female, 83	ND	Edward Sapien 23 mm (B-E)	ND	1 year	Definitive (2a, 1, 2, 5)	Autoimmune disease, immunosupressive drugs	Heart failure, fever	TEE: high transprosthesis gradients and fluctuating vegetation on prosthetic leaflets. Leaflets were thickened and restricted in motion. TTE: persistent large vegetation with prosthesis dysfunction	ND	S. gallolyticus	Ampicillin and sulbactam	Yes, large vegetation and valve dysfunction	None	Alive
Ibrahim et al	Female, 87	ND	Portico Valve 25 mm (S-E)	TF	3 months	Definitive (2a, 1, 2, 5)	ND	Fever, shortness of breath, caugh, lethargy, myalgia, no stigmata of IE	TTE: normal left ventricular sys. function +mild dia. dysfunction. Prosthetic aortic valve was noted to be well seated with peak gradient of 27mm Hg and mean gradient of 13mm Hg, no obvious vegetation. TEE: confirmed vegetation attached to the stent frame at the level of the left ventricular outflow tract	Chest X-ray showed no evidence of acute infection	*S. aureus*	1. Rifampicin, vancomycin and gentamycin 2. Meropenem and daptomycin, 9 weeks	No	Drug induced acute renal injury	Alive
Chourdakis et al	Female, 77	18,79	Edward-Sapien-XT S3 26 mm (B-E)	TF	26 days	Definitive (2a, 1, 2, 5)	CAD, PAD	Fever, septic artheritis	Mobile mass, on aortic bioprothesis, satelite IE of the MV and aortomitral. Initial, no evidence for mycotic aneurysm, fistula or abscess formation. TEE: extension of IE lesions with MV involvement, formation of new abscess cavity and rupture with fistula between aortic annulus and left atrium. Mitral regurgitation increased without any difference on aortic regurgitation.	ND	S. aureus	Flucloxacillin and gentamycin	No, due to high risk patients medical tractment was chosen	ND	Unknown
Chrissoheris et al	Male, 84 y	23,5	*CoreValve 29 mm (S-E)*	*TF*	80 days	Possible (2a, 1, 2)	*cerebro-vascular disease, AF, chronic lung disease, chronic pancreatitis, and prior pacemaker im-plantation*	Sepsis	TEE: no clear evidence of vegetation on the Prosthesis.	ND	*S. epider-midis*	Empirically antibiotics, 4 weeks	No	None	Alive after 1 year
Lee et al	Female, 67 y	ND	CoreValve 26 mm (S-E)	ND	17 months	Definitive (2a, 2c, 1, 5)	Previosly pyleonephrittis with s. epidermidis and septic artherittis	Dyspnea	TEE: severe transvalvular regurgitation without any vegetation. TEE revealed trans-valvular regurgitation without abnormal leaflet thickening	CT: Defect, in the region of regurgitation flow	*S. epider-midis*	ND	Yes, valve failure	ND	Alive
Olsthoorn et al	Male, 62 y	15,5	CoreValve Evolut 34 mm (S-E)	ND	1 year	Definitive (2a,2b, 1, 5)	COPD, pulmonary embolism	ND	TTE: aortic wall thickening with an increased gradient and extensive pericardial effusion	PET: ab-normal uptake at the aortic valve pros-thesis	E. faecalis	ND, 6 weeks	Yes, despite AB treat-ment patient developed conduction disorders and therefore urgent surgery was needed	Complete heart block. Permanent PM	Alive

Castiglioni et al.	Male, 72 y	6,58	Edwards-Sapien XT 26 mm (B-E)	TF	1 year	Definitive (2a, 2c, 1)	Osler-Weber-Rendu, chronic anemia and regullary blood transfusion, erraticated for Hep C, complete atrioventricular block, requiring permanent implantation of a pacemaker, the patient had reported an odontoiatric treatment two months before, without antibiotic prophylaxis	*None*	TTE: severe aortic regurgitation, left ventricular remodelling + EF reduced to 30%. TEE: dehiscence of the aortic device and severe paravalvular leakage; non-active vegetations were discovered.	concomitant drained abscess present between the right coronary and the posterior non-coronary cusps, confirmed by chest CT.	Negative	Broad-spctrum	Yes, aortic abcess and reguritation	None	Alive
Gotzmann et al	Male, 81 y	39,7	CoreValve 29 mm (S-E)	TF	19 months	Definitive (2a, 1, 2, 5)	DM, CAD, mitral valve reguritation, PM, stroke	Fever and dyspnea	Paravalvular leaks with fistula between left ventricular outflow tract and left atrium,. found large mobile vegetation at the prosthetic stent with connection to the right atrium	ND	S. lugdunensis	Vancomycin, gentamicin, and rifampicin	No, due to high risk patients medical tractment was chosen	Heart failure	Dead during treatment
Morioka et al	Male, 80 y	ND	SAPIEN 23 mm (B-E)	TF	3 mnd	Definitive (2a, 1, 2, 5)	DM, CKD, chronic HF, surgically treated for ileus 5 days after TAVI	Fever and chills	Echo showed mobile vegetations attached to the SAPIEN3 valves without apparent destruction	ND	C. parapsilosis	1. Liposomal amphotericin 2. Micafungin/fluconazole, 8 months	Yes, possitive blood cultures with pathogendespite treatment	None	Alive
Head et al	Male, 78 y	ND	ND	ND	1 year	Definitive (histologically)	ND	Fever	TEE: demonstrated no vegetations on the prosthetic aortic valve, but evident worsening hemodynamics. TEE :showing extensive large vegetations on the percutaneous aortic valve	Chest radio-graph+ CT of ab-domen /pelvis: no inflammatory focus/ further abnormalities. MRI/ CAT scan no evidence of a cause of the fever.	Histo-plasma capsul-atum (pathology)	Braod spectrum antibiotics and antifungals	Yes, paravalvular leak and vegetations	None	Alive
Nelson	ND	ND	Edwards valve 23 mm B-E	ND	2 months	Definitive	ND	Lethargy	TEE: mass at the leaflet level confirmed imaging to be a large, oval-shaped echogenic mass	ND	Aspergillus (histology)	No, treated as trombus	No, treated as trombus	Valve obstuction	Dead before diagnosis
Merdler et al.	Male, 86 y	ND	ND	ND	2 years	Definitive (2a, 2c, 1, 5)	Previosly IE with e. faecalis 2 months prior to admittion. Treated with daptomycin	third-degree atrio-ventri-cular block	Echo showed high pressure gradients on the AV, and suspected thrombus or vegetation on the AV	CT scan : large filling defect on the pros-thetic aortic valve	*E. faecalis*	Yes, ND	Yes, AV-block and residual endocarditis	AV-block	Alive
Campana et al	Female, 76 y	ND	Medtronic Evolut R 26	ND	5 mnd	Definitive (2a, 1, 2, 5)	Rheumatoid arthritis, immunosupressive medication, AF on oral therapy with DOAK, HT cardiomyopathy with moderate mitral regurgitation, GERD with hiatal hernia, COPD, osteoporosis, dyslipidaemia and PAD	Fever, dyspnoe, weakness, weightloss, atrial fibrilation, bilateral pulmonary crackelings	TTE: thickening aortic pros-thetic cusps, IE. TEE: Same as TTE + residual moderate aortic regurgitation+ mild para-valvular leakage, already evident after TAVI. presence of mobile vegeta-tion of 7 mm attached to prosthetic valve extending to left ventricular outflow tract. severe left atrial dilation, a left ventricular concentric hypertrophy + moderate mitral regurgitation, a reduced left ventricular ejection fraction	CT thorax: bi-lateral pleural effusion with evidence of a compressive atelectasis of both the lungs	E. faecalis	Ceftriaxone and ampicillin	No, patient died before surgical evaluation	Bilateral pleural effucin and atelektasis, cardiac arrest	Dead during treatment
Kuwata et al	Male, 84 y	ND	25 mm LOTUS valve	ND	1 year	Definitive (1b, 2a, 1, 2)	AF, atrial pacemaker, Asthma, lung sarcoidosis	Fever	TEE revealed a large structure (10*9mm) on the TAVI valve	ND	S. gordonii.	Gentamycin, vancomycin, and rifampicin.	Yes, large vegetation and arterial emboliz-ation	None	Alive

Sulzenko, et al	Male, 84 y	30	Corevalve 29 mm (S-E)	Left sub-clavian	6 months	Definitive (1b, 2a, 1, 2)	Aorto-coronary bypass 7 years before TAVI	lack of appetite, dyspepsia, fever, weight loss	TTE unclear finding on the aortic root, suspected vegetation on leaflets of the prosthesis. TEE: demonstrated mobile vegetations on the leaflets of the aortic prosthesis. TEE performed 3 weeks after admission showed significantly regressed residual veg- etation. Aortic prosthesis function not impaired, but two mild paravalvular leak jets were found.	ND	S. viridans	1. Ampicillin and gentamicin, 2. Vancomycin, gentamicin and penicillin	Medical treatment oly	Renal failure	Alive
Lee et al	Male, 76, y	9,92	Corevalve 29 mm (S-E)	ND	2 months	Definitive (1b, 2a, 1, 2)	HT, AF, PM for SSS, ischemic heart disease, periodontitis with inciison for drainange of abcess 1 month before admition	Fever, dyspnoe, mild confusion	TTE: normal sized LV with normal sys. function. Severe mitral regurgitation noted just beneath the strut of the prosthesis. TTE: large mobile vegetation attached to anteri- or mitral leaflet + severe mitral regurgitation due to multi- ple perforations of the mitral valve leaflet. Abscess was also noted at the aortomitral continuity	Pleural effusion on chest X-ray	*S. anginosus*	Vancomycin, gentamicin and rifampin	No, family did not want sugical treatment due to high risk	Intracereberal and subarachnoid hemorhage	Alive
Rafiqa et al	Female 64 y	ND	Corevalve (S-E)	ND	2 months	Possible (1b, 1, 2)	Ischemic heart disease, myostenia gravis, thyoma,	Fever, malaise, no IE stigmata,	Neither TTE nor TEE showed evidence of vegetations, although there was echo-free space within the wall of the ascending aorta where the stents of the core valve were seen. The aortic valve functioning well	ND	M. nonliquefaciens	Amoxcillin and ceftriaxone, 6 weeks	Medical treatment only	None	Alive
	Male, 81 y	ND	ND	ND	3 weeks	Definitive (1b, 2a, 1, 2)	DM, HT, dyslipidemia, CAD, BPH	Fever	TEE: small mobile vegetation attached to the anterior mitral valve leaflet along with mild mitral regurgitation, no vegetation or regurgitation seen.	Chest x-ray was normal	S. acidominimus	1. Vancomycin and imipenem–cilastatin, 2. Vancomycin, 6 weeks	Medical treatment only	None	Alive
P Loh et al	Male, 85 y	52	Corevalve 29 mm (S-E)	ND	4 months	Definitive (2a, 1, 2, 5)	Dual chamber PM, complicated triple vessel coronary bypass graft surgery including, LV systolic dysfunction, DM, and HT. BPH	Fever, poor appetite, weight loss, soft systolic murmur	TTE:normal, TEE:confirmed prosthetic aortic valve vegetation without transvalvular regurgitation	ND	E. faecium	Vancomycin and linezolid, 6 weeks	No, medical treatment was chosen due to high risk	Accute coronary syndrome, heart failure, bone marrow supression	Alive
R. Junco et al	Male, 71 y	20,5	LOTUS Boston Scientific	TF	2 months	Definitive (1a, 2a, 1)	PM, HT	acute pulmonary edema, grade 5 systolic murmur	TTE: thickened/ perforated anterior mitral leaflet, causing severe mitral regurgitation, TEE: anterior mitral leaflet had hetero-geneous echogenicity and irregular margins, suggestive of an abscess. Pros-thetic aortic ring and leaflets thickened and had a mobile and filiform structure compatible with vegetation	ND	S. gallolyticus	Yes, ND	No, medical treatment was chosen due to high risk	Sepsis, heart failure	Dead during treatment
Y Koh et al	Male, 85 y	25	SAPIEN 26 mm (B-E)	TF	12 mounts	Definitive (2a, 1, 2, 5)	ND	Stroke and fever	TEE : multiple vegetations attached to the prosthetic valve + free-floating linear material	ND	S. anginosus	Empirical	Yes, due to cerebrovascular episode during antibiotic treatment.	Neurological sequele	Alive

T Nguyen et al	Male, 81 y		Edwards S3 29 mm (B-E)	ND	2 years	Definitive (1b, 2a, 1)	CAD, congestive HF, DM, PM, DVTwith inferior vena cava filter placement, and prostate cancer		TEE showed a 2.4-cm mobile mass attached to the previously placed valve	ND	E. faecalis	Yes, ND	Yes, long term bacteremia despite antibiotics	None	Alive
A Lane et al	Female, 86 y		ND	TF	3 months	Definitive (2a, 2c, 1,2,3, 5)	ND	fever and fatigue for three months, splinter hemorrhage	TTE: large vegetations as demonscribed on CT	CT : veg. TAVR leaflets+ anterior native mitral valve with ad-jacent thickening of the inter-valvular fibrosa.	S. lugdunensis	Yes, ND	No, high risk and diffcult		Dead during treatment
M Gedela et al	Male, 87 y	ND	Edwards S3 29 mm (B-E)	ND	11 months	Definitive (1a, 2a, 1)	CAD, HF, and polymyalgia rheumatica on chronic steroid therapy	Altered mental status and presumed pneumonia	TEE: vegetation on the prosthetic aortic valve	ND	S. sanguinis	Ceftriaxone, 6 weeks	No	None	Alive
M Gedela et al	Male, 76 y	ND	Edwards S3 29 mm (B-E)	ND	17 months	Definitive (2a, 1, 2, 5)	CAD, HF, ischemic cardiomyopathy status post-ICD, stage 3 CKD	Dizziness, Atrial fibrilation, fever	TTE: poorly defined mobile echo density on the prosthetic aortic valve for probable vegetation versus thrombus, TEE: valve vegetation	ND	*S. aureus*	Ceftriaxone, rifampin, and gentamicin, 6 weeks	No	Disseminated intravascular coagulation, renal failure	Alive
C Sarra et al.	Female, 75 y	ND	Edwards Saphien XT 26 mm (B-E)	ND	7 months	Definitive (histology criteria, 2a, 1)	RCA stenosis, AF, HT, pulmonary HT and CAD	Heart failure, palpitations, no fever, no endocarditis stigmata	TTE :aortic valve gradient + mild aortic regurgitation. TEE: large, accessory, oscillating structure on the right coronary cusp of the aortic valve that was suggestive of vegetation	ND	E. faecium	Gentamycin, ampicillin/sulbactam and rifampicin	Yes, no effect of antibiotics	Post-operative hemodynamic instability and arrythmias	Dead during treatment
Ruchonnet et al	Female, 75 y	23,6	ACURATE *neo TM* 25 mm	ND	7 days	Definitive (1a, 2a, 1)	HT, and dyslipidemia	dyspnea and intermittent profuse sudation, normotensive, apyretic, and otherwise healthy	TTE:no signs of IE. Normal left ventricular ejection fraction, and minor aortic paravalvular leak. TEE: paravalvular leak and thickening of the mitro-aortic junction, suggestive of paravalvular abscess or of a post-procedural hematoma.	ND	*S. aureus*	Trimethoprim sulfamethoxazole, ceftriaxone, acyclovir, and dexamethasone. Flucloxacillin, gentamicin, rifampicin, 43 days	Yes, abcess, first-degree atrioventricular block and a right bundle branch block,	Complete heart block. Permanent PM	Alive
Puls et al	Male, 80 y	30	Corevalve 29 mm (S-E)	TF	7 months	Definitive (1a, 2a, 1, 2, 3)	CABG, prosthetic mitral valve, moderately reduced LV function, PAD, CKD and DM	acute congestive heart failure and fever	*Prosthetic shadowing complicating detection of intracardiac masses. Valve prosthesis did not to fit into the aortic annulus.Para-valvular leak enlarging in diastole causing deformation of prosthesis. Thickening of aortic root, echolucent space between prosthesis and aortic root, and discontinuity in the native aortic annulus. made the Diagnosis of an aortic root abscess with mycotic aneurysm*	ND	MRSA	1. Rifampin, gentamicin and vancomycin	No	Refractory sepsis and cardiac decompensation	Dead during treatment
Puls et al	Female, 81 y	48	Edwards SAPIEN 23 mm (B-E)	TA	ND	Definitive (1a, 2a, 1,2)	End-stage pulmonary disease after lung tuberculosis, pulmonary HT, severely reduced LV function, DM	Fever	TEE: moderate paravalvular AR due to para-valvular leak and a new mobile vegetation attached to the prosthetic stent	ND	E. faecalis	Vancomycin and rifampin, 6 weeks	No	None	Alive

Puls et al	Female, 80 y	41	Edwards 23 mm (B-E)	TA	10 months	Definitive (criteria 1a, 2a, 1, 2, 3)	CABG, PAD, and chronic lung disease	Fever and chills	TEE: mild to moderate AR, no vegetation or abscess could be detected. Since mild AR was seen since the TAVI procedure. TEE: large oscillating vegetation attached to the prosthetic cusps and a moderate central AR . No paravalvular leak present	Cerebral MRI: sevrel lacunar strokes cardiac embolisation?	E. faecalis	1. Ampicillin 2. Ciprofloxacine 3. Ampicillin and gentamicin, 13 weeks	No	Stroke	Alive
Puls et al	Male, 85 y	23	Edwards 23 mm (B-E)	TF	5 months	Definitive (1b, 1, 2, 3)	Chronic pulmonary disease and pulmonary HT	Fever and urinary tract infection,acute cardiac failure with pleural effusions, Osler's nodes	TTE: moderate paravalvular AR without valvular vegetation		E. faecalis, E. coli, and C. albicans	Different antibiotic regimens, 7 weeks	No	Pleural effusion	Died during treatment
Puls et al	Female, 91 y	25	Edwards 23 mm (B-E)	ND	23 months	Possible (criteria 1a, 1, 2)	pulmonary HT	fever	TEE: mild paravalvular aortic regurgitation due to a small paravalvular leak (present directly after TAVI). No vegetation, pseudo-aneurysm or abscess.		S. gordonii	Ceftriaxone, 4 weeks	No	None	Alive
Ahmad et al	Female, 80 y	ND	Edwards-Sapien XT 23 mm (B-E)	TF	4 months	Definitive (2a, 1, 2, 3, 5)	DM, COPD, steroid treated gout arthritis,	fever, abdominal pain, nausea, diarrhoea, and vaginal bleeding	TEE: no signs of mal-functioning of the THV or signs of PVE. TEE:repeated revealed a 6 mm large vegetation on the TAVI prosthesis	Abdominal CT normal. CT: large spleen infarction and multiple small cerebral emboli	E. faecalis	Cancomycin and ampicillin, 6 weeks	Yes, no effect of antibiotics	None	Alive, 3 months
Zbroński et al	Male, 79 y	ND	Medtronic Evolut R 29 mm	ND	7 months	Definitive (1b, 2a, 1, 2)	COPD	Fever, redued excercise tolerance, At admission, physical examination was remarkable for systolic murmur over the mitral valve. No fever, chest pain, cough, or meningeal signs	TEE:mild mitral regurgitation and 15 mm hypere-chogenic structures on the MV described as possible vegetations	ND	*S. capitis*	Vancomycin, gentamicin and rifampin, 6 weeks	No	Renal failure	Alive
Skowerski et al	Male, 88 y	ND	LOTUS 27 mm	TF	2 months	Definitive (2a, 1, 2, 5)	AF, anticoagulation treatment, profuse atherosclerosis of the ascending aorta	fever and fatigue	TTE: slightly reduced left ventricular ejection fraction, no malfunction of the aortic prosthesis, no signs of PVE. TEE: vegetations on the prosthetic leaflets and large abscess in perivalvular tissues infiltrating native aortic root, aortic-mitral curtain, +The tricuspid annulus+mobile vegetation on the tricuspid valve was present, but there were no vegetations on the pacemaker leads.	ND	MRSE	1. Vancomycin, 2. Rifampicin, 15 weeks	No, medical treatment was chosen due to high risk	None	Alive
Gürtler et al	Male, 66 y	ND	ND	ND	1 year	Definitive (1b, 2a, 1, 2)	One week previously, after an incisional hernia repair, he had required a urinary catheter due to urinary retention, psoriasis vulgaris	Fever, abdominal pain	TEE:no sign of PVE. TEE: free-floating mass was identified on the aortic valve	CT scans of the thorax+ abdomen were unremarkable, 8FDG-PET/CT was not able to iden- tify any focus of infection.	P. aeruginosa	Ceftriaxone, Amoxicillin-Clavulanate, Piperacillin-tazobactam + ceftazidime. Meropenem + gentamicin, cefepime and gentamicin. Cefepime, tobramycin + ciprofloxacin, 11 weeks	Yes, no effect of antibiotics	None	Alive

Neragi-Miandoab et al	Female, 65 y	ND	ND	ND	4 months	Definitive (pathological criteria)	ND	ND	TEE: vegetations on the prosthetic valve causing a significant gradient	ND	E. faecalis	Yes, ND	Yes, large regurgitation	Post-operative respiratory failure, sepsis+ multi-organ failure	Died during treatment
Pabilona et al	Male, 77 y	ND	Edwards Sapiens 23 mm (B-E)	ND	17 months	Definitive (1a, 2a, 1, 2)	PCI, obstructive sleep apnea and severe emphysema	Intermittent fever with night sweats, loss of appetite, and progressive shortness of breath.	TTE: normal LV wall motion with normal systolic function. In comparison with the findings 7 months earlier, the patient's transvalvular peak gradient had now increased. TEE: vegetation obstructing the bioprosthetic aortic valve	ND	*S. viridans*	Vancomyocin, Ciprofloxacin, Penicillin, 6, 5 months	No	Transient ischemic attack, re-endocarditis	Alive
Dapás et al	Female, 62 y	20,5	ND	TA	9 weeks	Definitive (2a, 1, 2, 5)	arterial hypertension, atrial fibrillation, smoking, chronic obstructive pulmonary disease, obesity and bipolar affective disorder. Pseudomonas aerginosa empyema after TAVI - treated with cefepime for 6 weeks. Negative TEE for PVE	fever	TEE periannular abscess	ND	*P. aeruginosa*	Vancomycin +Cefepime, piperacillin-tazobactam +amikacin, Ciprofloxacin and cefepim, 4 weeks	Yes, due to abcess	Post-opeartive wound infection, peripheral embolism	Alive
Ochiai et al	Male, 79 y	ND	CoreValve 29 mm	TF	20 months	Definitive (1a, 2a, 1, 2, 5)	CAD, bypass surgery, Chronic lung disease	Fever, generally ill, GCS 13, Janeway lesions	TTE/TEE no obvious vegetation, only trivial paravalvular aortic regurgitation, no significant changes compared with the original post-TAVI. TEE: mobile vegetation on the leaflets of the aortic prosthesis but indicated a functioning prosthetic valve with trivial paravalvular aortic regurgitation	MR showed high signal intensity in the bilateral frontal lobe and cerebellar hemisphere, which suggested multiple acute cerebral infarcts caused by embolisms	S. aureus	Vancomycin and gentamicin, cefazolin, 6 weeks	No	Cerebral emboli	Alive after 1 year
Tosatto et al	Male, 86 y	ND	ND	ND	2 weeks	Definitive (1, 2, 5)	Diabetes, Klebisella bacteremia 5 times over the last 6 months after TAVI implantation	Fever, malaise, uspesifikk symptoms	TTE/TEE mild posterior valvular leak and an echolucent periprosthetic zone. Possible abcess	(PET) and 111In-leucocyte scintigraphy showed no sign of active infection.	K. pneumoniae	Cefuroxime, lifelong	No	None	Alive after 2 years
Zhigalov et al	Male, 75 y	ND	Edwards Sapien 29 mm (B-E)	TF	2 months	Definitive (2a, 1, 2, 5)	Concomitant diseases included CAD with implanted stents, myocardial infarction 4 years ago, permanent AF, DM, and PAD	fever, dyspnea, and signs of heart failure	TEE:large vegetation on the TAVR prosthesis, with severe aortic valve insufficiency and a moderately reduced LV function	ND	S. sanguis	bacteria sensitive antibiotic unknown length	Yes, no effect of antibiotics	Sepsis, heart and respiratory failure	Alive
Loverix et al	Male, 79 y	58	CoreValve 26 mm (S-E)	ND	7 months	Definitive (1a, 2a, 1)	MI, CABG, PM, Carotic artery stenosis, increased anorexia in months following TAVI, investigated with gastroscopy/colonoscopy	strongly increased complaints of dyspnea and fatigue	TTE: concentric thickening of the left ventricular muscle and nodular thickening at the level of one aortic valve cusp. TEE: large vegetation on the ventricular side of the aortic valve prosthesis, with a slight stenosing effect on the prosthetic aortic valve	ND	S. haemolyticus	Vancomycin+ rifampicin, Clindamycnin + rifampicin, months	No, due to high risk patients medical traetment was chosen	None	Alive

Takimoto et al	Male, 80 y	ND	ND	TF	2 weeks	Definitive (2a, 1,2,3,5)	cerebral infarction, bronchial asthma, HT, and prostatic cancer.	high fever, loss off appetite	TTE: large-sized mass on a native MV leaflet in addition to those on the aortic prosthetic valve, TEE: thickening of all three leaflets of the aortic prosthesis and medium-sized mobile mass on the aortic side of two of the three leaflets. The degree of paravalvular leakage remained the same, defined as only trivial. There were no findings of aortic root abscess.	MRI demonstrated new acute cerebral infarction in the bilateral frontal lobes and lateral lobes, although the patient was totally neurologically intact.	S. sanguis	Vancomycin and ampicillin. 2: penicillin/gentamicin 3: Ceftriaxon, 4 weeks	Yes, continued vegetation and cerebral infarction despite antibiotics	Kidney injury, cerebral infarction	Alive
Bozdağ-Turan et al	Male, 80 y	10	CoreValve (S-E)	TF	4 months	Definitive (2a, 1, 2, 5)	Transurethral prostatectomy and cystotomy 2 months prior to addmition	fever, dyspnea, disorientation	TEE showed a mobile 18x7mm mass on the CoreValve	ND	E. faecalis	Yes, ND, 6 weeks	No, medical treatment was chosen due to high risk	None	Alive
Gonzalez et al	Female, 97 y		SAPIEN 25 mm (B-E)	ND	3 years	Definitive (1a, 2a, 2)	HT, AF, PAD, and diastolic HF. Two weeks before admition treated with antibiotics for streptococcus mitis bacteremia with out focus	Alert and oriented, with mild receptive aphasia and generalized weakness	TTE: normal left ventricular function, mild-moderate mitral regurgitation, trivial aortic regurgitation, and normal aorticprosthesis function with mean gradient of 12 mm Hg. TEE 2D: No mobile vegetations, but 3D TEE: abnormal thickening and mobile vegetation on one of the leaflets of the TAVR valve	MRI were negative for an acute cerebral ischemic event.	S. mitis	Ceftriaxone, 8 weeks	No	None	Alive
Carnero-Alcazar et al	Female, 83 y	ND	Edwards Sapiens 23 mm (B-E)	TA	5 months	Definitive (pathological criteria)	CKD, and had a severe LV dysfunction with pulmonary HT and a porcelain aorta	Congestive heart failure, fever	TTE: large vegetation on the aortic side of the prosthetic valve	ND	E. faecalis	Yes, ND	No, due to high risk patients medical traetment was chosen	Multiple emboli and refractory heart failure	Died after two weeks
Orban et al	Male, 70 y	33,11	CoreValve (S-E)	ND	12 months	Definitive (2a, 1, 2, 3)	CAD with reduced left ventricular function, AF, DM and hemodialysis resulting from diabetic nephropathy, as well as kidney transplantation and subsequent kidney transplant failure in 2000	critical right forearm ischemia caused by acute thromboembolic occlusion and underwent operative embolectomy.	TEE: elongated mass in length around a longitudinal axis within the stent lumen of the prosthetic valve. Signs of paravalvular abscess at the noncoronary sinus. Minor paravalvular regurgitation at the left coronary sinus. Native valves no signs of IE lesions	ND	*S. epidermidis*	Vancomycin, gentamicin, and rifampicin	Yes, large vegetation and valve dysfunction	None	Alive

Naganuma et al	Male, 89 y	32,5	Sapien XT 26 mm (B-E)	TF	5 weeks	Definitive (2a, 1, 2, 5)	AF, COPD and left internal carotid artery stenosis was diagnosed with symptomatic severe AS	hypoxia, fever	TTE: no obvi- ous vegetation on the THV and native valves.Slightly increased paravalvular leak remaining mild. TEE: Valsalva sinus perforation at the non-coronary cusp level into the RA in the presence of an annular abscess	ND	*S. aureus*	Meropenem, vancomycin, gentamycin + rifampicin, 9 months	Yes, large paravalvular abscess, at non-coronary cusp and left coronary cusp, extending towards the mitral valve. Vegetation seen on all 3 THV leaflets	None	Alive
Nguyen et al	Male, 72 y	20	Corevalve 31 mm (S-E)	ND	13 months	Possible (2a, 1, 3)	V-I-V, poor general condition and severe COPD	ND	TEE: severe intraprosthetic aortic regurgitation with cusp prolapse. No definite vegetation	ND	S. sanguis	Amoxicillin, 5 weeks	Yes, treated with valve-in-valve-in-valve due to hemodynamic instability	Cerebral hematoma, cerebral mycotic aneurism.	Alive after 1 year
Rodriguez-Vidigala et al	Female, 85	5/10.5	ND	ND	13 days	Possible	Unknown	Pyrexia, CHF	TOE: VSD	ND	BC negative	Daptomycin	No	Cardiogenic shock	Died after 5 days
Rodriguez-Vidigala et al	Female, 80	2/3.1	ND	ND	27 days	Definitive (2a, 1, 2, 5)	TAVI procedure	Pyrexia, CHF	TOE: peri-annular fistula to RA	ND	S. epidermidis	Vancomycin and daptomycin	No	Cardiogenic shock	Died after 6 days
Rodriguez-Vidigala et al	Female, 79	5/4.6	ND	ND	36 days	Definitive (2a, 1, 2, 5)	Spontaneous bacterial peritonitis	Pyrexia	TOE: vegetation (13 mm) pseudoaneurysm	ND	E. faecalis	Vancomycin, ampicillin and gentamicin	No	AKI, splenic embolism, CHF, cardiogenic shock	Died after 42 days
Rodriguez-Vidigala et al	Male, 60	5/4.5	ND	ND	100 days	Possible (1, 2, 5)	Urinary catheter trauma	Pyrexia	TOE: leaflet thickening	ND	E. faecalis	Ampicillin and ceftriaxone	No	AF, CHF, AKI	Died after 385 days cancer
Rodriguez-Vidigala et al	Male, 71	5 / 3	ND	ND	102 days	Possible (1, 2, 5)	Peripheral venous catheters in previous admission	Pyrexia	TTE/TOE: leaflet thickening	ND	MRSA	Daptomycin and cloxacillin	No	Septic shock	Died after 12 days
Rodriguez-Vidigala et al	Female, 79	5/5.5	ND	ND	112 days	Definitive (2a, 1, 2, 5)	Unknown	Pyrexia, CHF	TTE/TOE: mitral vegetation	ND	S. epidermidis	Daptomycin	No	No	Died after 244 days
Rodriguez-Vidigala et al	Male, 76	4/7.7	ND	ND	246 days	Definitive (2a, 1, 2, 3, 5)	Unknown	Pyrexia, splenic embolism	TOE: vegetation (18 mm)	PET	S. epidermidis	Daptomycin and rifampicin	Yes	ND	Survivor
Rodriguez-Vidigala et al	Female, 73	5 / 3	ND	ND	492 days	Definitive (2a, 1, 2, 3)	Unknown	Pyrexia, vasculitis	TOE: Mitral IE, suspected Ao	ND	BC negative	Daptomycin and ceftriaxone	No	AKI	Survivor
Rodriguez-Vidigala et al	Male, 76	8/3.5	ND	ND	578 days	Definitive (2a, 1, 2, 5)	Excision basal cell carcinoma	Pyrexia	TTE/TOE: vegetation (7 mm)	ND	S. durans	Daptomycin, Ceftriaxone, Rifampicin	No	CNS embolism	Survivor
Rodriguez-Vidigala et al	Male, 78	5/7.2	ND	ND	595 days	Definitive (2a, 1, 2, 3, 5)	Bladder tumour	Embolism, CNS	TEE: vegetation	ND	E. faecalis	Vancomycin and ceftriaxone	No	CNS embolism	Survivor
Rodriguez-Vidigala et al	Male, 81	5/3.7	ND	ND	668 days	Definitive (2a, 1, 2, 5)	Repeated urinary catheters	Pyrexia	TEE: leaflet thickening, pseudoaneurysm, abscess	PET	E.faecalis	Ampicillin and ceftriaxone	No	AKI, persistent bacteraemia, spleen embolism	Survivor
Skaar et al	Female, 86	ND	Lotus 27 mm	ND	49 days	Definitive (1M, 3m)	ND	ND	No vegetation or PVL	ND	S. aureus	ND	ND	ND	Dead
Skaar et al	Male, 77	ND	Corevalve 31 mm (S-E)	ND	190 days	Definitive (2M,2m)	ND	ND	Aortic valve vegetation	ND	S.salvarius	ND	ND	ND	Alive
Skaar et al	Male, 80	ND	Core valve 31 mm (S-E)	ND	380 days	Definitive (1M, 3m)	ND	ND	New aortic PVL	ND	E. faecalis	ND	ND	ND	Alive
Skaar et al	Male, 79	ND	Corevalve 31 mm (S-E)	ND	407 days	Definitive (1M, 3m)	ND	ND	New aortic PVL	ND	S.sanguinis	ND	ND	ND	Alive
Skaar et al	Male, 77	ND	Corevalve 31 mm (S-E)	ND	448 days	Definitive (2M, 4m)	ND	ND	Aortic valve vegetation	ND	S. aureus	ND	ND	ND	Dead
Skaar et al	Male, 80	ND	Corevalve 31 mm (S-E)	ND	528 days	Possible (1M, 1m)	ND	ND	No vegetation or PVL	ND	S. oralis	ND	ND	ND	Alive

Martínez-Sellés et al	Female, 79	ND	Corevalve (S-E)	TF	315 days	Definitive (2a, 1, 2, 3, 5)	AF, HF	Fever	AV Vegetation	ND	E. faecalis	Ampicillin and gentamicin, 4 weeks	No	Splenic abscess	Dead
Martínez-Sellés et al	Female, 79	ND	Corevalve (S-E)	TF	117 days	Definitive	Dementia, AD, HF, CKD, COPD, MI, PM	Fever	AV Vegetation and aortic root aneurysm	ND	S. epidermidis	Daptomycin, 7 weeks removal	Yes, PM removal	HF, heart block	Dead 184 days after TAVI, refractory HF
Martínez-Sellés et al	Male, 86	ND	Corevalve (S-E)	TF	330 days	Definitive (2a, 1, 2, 3, 5)	AF, CKD, COPD, MI, DM, permanent ICD,	Fever	AV Vegetation	ND	G. Adiacens	Daptomycin, Cefotaxim, Levofloxacin, 13 weeks	No	Petechiae, embolisms, glomerulonephritis, renal insufficiency	Yes, died after 490 days of respiratory failure
Martínez-Sellés et al	Male, 84	ND	Corevalve (S-E)	TF	25 days	Possilbe (1, 2, 5)	Rheumatoid arthritis, ischaemic HF, kidney disease, PM/	Fever	AV Valve rupture	ND	S. enteritidis	Cefotaxim and ciprofloxacin, 12 weeks	No	HF, renal insufficiency	Dead
Martínez-Sellés et al	Male 81	ND	Edwards SAPIEN (B-E)	TF	84 days	Definitive (2a, 1, 2, 5)	HF, COPD, MI, prostate cancer	Fever	AV Pseudoaneurysm and aortic root abscess	ND	E. Faecalis	Ampicillin + cefotaxin, 5,5 weeks	No	Heart block	Yes, died after 126 of respiratory failure
Martínez-Sellés et al	Female, 69	ND	Corevalve (S-E)	TF	161 days	Possilbe (1, 2, 5)	Haemolytic anaemia, corticosteroids, PM	Fever	AV thickening and MV ruptur	ND	E. Faecalis	Ampicillin + cefotaxim, imepenem, ampicillin/clavulanic acid and rifampicin, 6 weeks	No	Vascular embolism	No
Martínez-Sellés et al	Female, 79	ND	Corevalve (S-E)	TF	27 days	Definitive (2a, 1, 2, 5)	HF, CKD, MV Surgery, PM	Fever	MV prothesis vegetation	ND	Acinetobacter species	1. Ciprofloxacin, 2. Imipenem, 3 weeks	No	Septic shock, HF	Yes died after 40 days of HF
Martínez-Sellés et al	Female, 86	ND	Corevalve (S-E)	TF	423 days	Definitive (2a, 1, 2, 5)	AF, HF, CKD, PM	Fever	MV Vegetation	ND	S. viridans	Ceftriaxone, 6 weeks	No	Renal insufficiency	No
Martínez-Sellés et al	Male, 87	ND	Corevalve (S-E)	v	321 days	Definitive (2a, 1, 2, 5)	COPD, PM	Fever	MV Vegetation	ND	S. oralis	Ceftriaxone and gentamicin, 4 weeks	No	Splenic and renal emboli	Yes, 447, gastric adenocarcinoma
Martínez-Sellés et al	Male. 73	ND	Corevalve (S-E)	TF	20 days	Definitive (2a, 1, 2, 5)	Haemodialysis, AD, MI, MV surgery	Fever	MV prothesis Vegetation, valve dehiscence, and regurgitation	ND	C. Parapsilosis	Fluconazole and caspofungin, 6 weeks	No	Splenic emboli, renal insufficiency	No
Gallouchea et al	Female, 92	ND	Corevalve (S-E)	ND	ND	Possible (positive blood culture, fever, predisposition)	PM	Fever	ND	ND	S.epidermidis	Antibiotic treatment	Yes, PM removal		Recovery
Gallouchea et al	Female, 82	ND	Edwards SAPIEN (B-E)	ND	ND	Definite (positive echocardiography, fever, microbiological evidence, predisposition)	Urinary infection	Fever	ND	ND	E. coli	Antibiotic treatment	No		Recovery
Gallouchea et al	Female, 88	ND	Corevalve (S-E)	ND	ND	Possible (positive blood culture, fever, predisposition)	Skin infection	Fever	ND	ND	E.faecalis	Antibiotic treatment	No		Recovery
Gallouchea et al	Female, 85	ND	Edwards SAPIEN (B-E)	ND	ND	Possible (positive blood culture, fever, predisposition)	Gastrointestinal infection	Fever	ND	ND	S. gordonii	Antibiotic treatment	No		Death 17 days after IE diagnosis
Gallouchea et al	Female, 57	ND	Edwards SAPIEN (B-E)	ND	ND	Definite (positive echocardiography and blood culture, fever, predisposition)	Unknown	Fever	ND	ND	S.aureus	Antibiotic treatment	No		Recovery
Gallouchea et al	Female, 75	ND	Corevalve (S-E)	ND	ND	Possible (positive echocardiography, fever, predisposition)	Skin infection	ND	ND	ND	Unknown	Antibiotic treatment	No		Death 40 days after IE diagnosis
Olsen et al	79	ND	ND	ND	3 days	Definite	ND	ND	TEE: MV ulcerations and vegetation	ND	S.aureus	Cefuroxime and fusidic acid, dicloxacillin+fusidic acid (long-term)	No	Liver failure	Dead 5 months after diagnosis
Olsen et al	75	ND	ND	ND	8 days	Definite	ND	ND	TEE negative, AV vegetation on ICE	ND	E. faecium	Vancomycin and linezolid	No	No	Alive
Olsen et al	62	ND	ND	ND	11 days	Definite	ND	ND	TEE: AV vegetations	ND	S. aureus	Cefuroxime and fusidic acid, 6 weeks	No	No	Alive
Olsen et al	84	ND	ND	ND	14 days	Possible	ND	ND	TEE negative	ND	S.mitis	Ceftriaxone and rifampicin, 6 weeks	No	No	Alive

Olsen et al	83	ND	ND	ND	17 days	Definite	ND	ND	TEE: AV vegetation	ND	Nonhemolytic streptococcus	Penicillin and gentamicin, 6 weeks	No	No	Alive
Olsen et al	86	ND	ND	ND	41 days	Definite	ND	ND	TEE: PM lead vegetations	ND	Nonhemolytic streptococcus	Penicillin, 13 weeks	No	Yes, new PM implantation	Alive
Olsen et al	85	ND	ND	ND	162 days	Definite	ND	ND	TEE: aortic root abscess+atrial vegetations	ND	Hemolytic streptococcus	Penicillin and fusidic acid, 5 weeks	No	No	Dead during treatment
Olsen et al	75	ND	ND	ND	163 days	Possible	ND	ND	TEE negative	ND	Coagulase negative streptococcus	Vancomycin and rifampicin, 6 weeks	No	No	Alive
Olsen et al	81	ND	ND	ND	184 days	Possible	ND	ND	TEE negative	ND	Nonhemolytic streptococcus	Penicillin and linezolid, ampicillin and rifampicin, 6 weeks	No	No	Alive
Olsen et al	73	ND	ND	ND	223 days	Definite	ND	ND	TEE negative, AV vegetation on ICE	ND	E.faecalis	Penicillin and rifampicin, 6 weeks	No	No	Alive
Olsen et al	85	ND	ND	ND	257 days	Definite	ND	ND	TEE: AV vegetation	ND	E.faecium	Vancomycin and linezolid, 6 weeks	No	No	Alive
Olsen et al	67	ND	ND	ND	331 days	Definite	ND	ND	TEE: aortic root abscess+MV vegetations	ND	S.aureus	Dicloxacillin and rifampicin, 3 weeks	No	No	Dead during treatment
Olsen et al	76	ND	ND	ND	351 days	Possible	ND	ND	TEE negative, ICE negative	ND	E.faecalis	Ampicillin and gentamicin, 6 weeks	No	No	Alive
Olsen et al	88	ND	ND	ND	407 days	Definite	ND	ND	TEE negative, AV vegetation on ICE	ND	E.faecalis	Vancomycin and linezolid, 6 weeks	No	No	Alive
Olsen et al	85	ND	ND	ND	485 days	Definite	ND	ND	TTE: worsened aortic regurgitation	ND	S.aureus	Cefuroxime and fusidic acid, 6 weeks	No	No	Alive
Olsen et al	75	ND	ND	ND	611 days	Definite	ND	ND	TEE: AV vegetations	ND	S.epidermidis	Dicloxacillin and rifampicin, 6 weeks	No	No	Alive
Olsen et al	77	ND	ND	ND	653 days	Possible	ND	ND	TEE negative, CE negative	ND	E. faecium	Vancomycin and linezolid, 6 weeks	No	No	Dead after 8 weeks
Olsen et al	76	ND	ND	ND	888 days	Definite	ND	ND	TEE: thickened AV leaflets+MV vegetation and perforation	ND	S. salivarius	Cefuroxime and ciprofloxacin, 6 weeks	Yes	No	Alive
Scislo et al	79	17	CoreValve	TF	9 months	Definitive	HT, DM, CAD, COPD, CKD	Urosepsis	TEE: large vegetation involving leaflet and extending into the sub-leaflet/LVOT part of the frame, moderate paravalvular leak	ND	Klebsiella oxytoca, Streptococcus haemolyticus	Vancomycin, gentamicin, rifampicin	Yes	Multi organ failure	Died during treatment
Scislo et al	66	6,31	Edwards Sapien XT	TF	15 months	Definitive	DM, CAD, liver transplant	Sepsis	TEE vegetation attached to the temporal central line catheter, but THV was not involved.	ND	MRSA	Clarithromycin, metronidazole, anidulafungin	No	Multi organ failure	Died during treatment
Scislo et al	86	17,3	CoreValve	TF	3 days	Definitive	HT	Pneumonia	TEE vegetation found on the middle segment of anterior MV leaflet	ND	MRSA; MDR Enterococcus faecium	Gentamicin, vancomycin, rifampin, linezolid	No	No	Alive after 6 years
Scislo et al	80	14,3	CoreValve	SC	52 months	Definitive	CAD, AF, CKD	Pneumonia	TEE:vegetation was detected on the supra- leaflet/aortic part of the frame	ND	Pseudomonas aeruginosa	Piperacillin, tazobactam	No	Subarachnoid hemorrage, splenic infarction	Died during treatment
Scislo et al	79	8,67	Medtronic EvoluR	TF	7 months	Definitive	COPD	Pneumonia	TEE: vegetation was visible on the aortic surface leaflet	ND	Staphylococcus capitis	Vancomycin, gentamicin, rifampicin	No	No	Died after 3 years
Scislo et al	66	17,81	CoreValve	TF	9 months	Definitive	DM, CKD	Pneumonia	TEE: vegetation on the middle segment of posterior MV leaflet	ND	Staphylococcus aureus	Ceftriaxone, ciprofloxacin	No	No	Died after 3 years
Scislo et al	86	8,99	Boston-Scientific Lotus	TF	10 days	Definitive	HTA, DM	Pneumonia	TEE: Vegetation visible on the LVOT surface	ND	Staphylococcus aureus, Enterococcus faecium, Candida albicans	Gentamicin, vancomycin, rifampin, linezolid, fluconazole	No	Multi organ failure	Died during treatment
Moriyama et al.	86 / female	ND	SAPIEN XT	ND	128 days	Definite (M:1,2; m:1,2)	ND	ND	Vegetation, prosthetic valve regurgitation	ND	*Enterococcus faecalis*	Ampicillin, Vancomycin, Tobramycin	No	ND	Died after 102 days

Moriyama et al.	83 / male	ND	CoreValve	ND	372 days	Definite (M:1,2; m:1,2)	ND	ND	Prosthetic valve regurgitation	ND	*Staphylococcus aureus*	Cefuroxime, Piperacillin-tazobactam	No	ND	Died after 59 days
Moriyama et al.	76 / female	ND	PERIMOUNT Magna Ease	ND	336 days	Definite (M:1,2; m:1,2,3)	ND	ND	Vegetation, leaflet dehiscence, prosthetic valve regurgitation	ND	*Streptococcus pyogenes, streptococcus agalactiae*	Penicillin, Tobramycin	No	Spinal emboli	Dead during treatment
Moriyama et al.	87 / female	ND	SAPIEN 3	ND	285 days	Definite (M:1,2; m:1)	ND	ND	Vegetation	ND	*Streptococcus viridans*	Penicillin	No	ND	Died after 580 days
Moriyama et al.	91 / male	ND	TAVR / Lotus	ND	734 days	Possible (M:1; m:1,2)	ND	ND	Normal	ND	*Enterococcus faecalis*	Ampicillin	No	ND	Alive at follow up
Moriyama et al.	91 / female	ND	SAPIEN XT	ND	216 days	Definitive (M:1; m:1,2,5)	ND	ND	Normal	ND	*Group G ß-haemolytic streptococci*	Amoxicillin, Ceftriaxone, Vancomycin	No	ND	Died after 1263 days
Moriyama et al.	81 / male	ND	SAPIEN 3	ND	504 days	Definite (M:1,2; m:1,2)	ND	ND	Vegetation	ND	*Streptococcus viridans*	Penicillin, Tazobactam	No	ND	Alive at follow up
Moriyama et al.	90 / female	ND	SAPIEN 3	ND	103 days	Definite (M:1,2; m:1,2)	ND	ND	Vegetation	ND	*Streptococcus sanguinis*	Ceftriaxone and unknown	No	ND	Alive at follow up
Moriyama et al.	90 / female	ND	Lotus	ND	435 days	Definite (M:1,2; m:1,2)	ND	ND	Vegetation	ND	*Enterococcus faecalis*	Cefuroxime	No	ND	Alive at follow up
Moriyama et al.	68 / male	ND	Lotus	ND	110 days	Definite (M:1,2; m:1,2)	ND	ND	Normal	ND	*Enterococcus faecalis*	Cefuroxime	No	ND	Alive at follow up
Moriyama et al.	85 / female	ND	Evolut R	ND	212 sdays	Possible (m:1,2,5)	ND	ND	Normal	ND	*Streptococcus oralis*	Cefuroxime	No	ND	Alive at follow up
Moriyama et al.	91 / male	ND	Lotus	ND	26 days	Definite (M:1,2; m:1,2,4)	ND	ND	Vegetation	ND	*Staphylococcus aureus*	Ceftriaxone, Vancomycin	No	ND	Died during treatment
Moriyama et al.	91 / female	ND	SAPIEN XT	ND	544 days	Definite (M:1,2; m:1,2,3)	ND	ND	Vegetation	ND	*Streptococcus viridans*	Cephalosporin, Vancomycin	No	ND	Died after 88 days
Moriyama et al.	60 / male	ND	Evolut R	ND	380 days	Possible (M:1; m:1,2)	ND	ND	Normal	ND	*Streptococcus viridans*	Ampicillin, Vancomycin	Yes, ND	ND	Alive at follow up
Moriyama et al.	81 / female	ND	SAPIEN 3	ND	438 days	Definite (M:1,2; m:1,2)	ND	ND	New prosthetic valve regurgitation	ND	*Staphylococcus epidermidis*	Ceftriaxone, Vancomycin	No	ND	Died during treatment
Moriyama et al.	83 / female	ND	SAPIEN XT	ND	143 days	Definite (M:1; m) (Diagnosed by autopsy)	ND	ND	No (Vegetation found by autopsy)	ND	*Staphylococcus aureus*	Penicillin, Vancomycin	No	Cerebral emboli	Died during treatment

14.0 GRADES

Referanse:	**Studiedesign: Kohortestudie**
Bjursten H, Rasmussen M, Nozohoor S, Götberg M, Olaison L, Rück A, Ragnarsson S. Infective endocarditis after transcatheter aortic valve implantation: a nationwide study. Eur Heart J. 2019 Oct 14;40(39):3263-3269. doi: 10.1093/eurheartj/ehz588. PMID: 31433472; PMCID: PMC6911164.	Grade - kvalitet: ++

Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
The aim of the present investigation was to determine the "incidence, risk factors for, clinical presentation of, and outcome after prosthetic valve endocarditis (PVE) in patients treated with TAVI in a nationwide study" **Konklusjon** "The incidence of PVE was similar to that of surgical bioprostheses. Compromised renal function was a strong risk factor for developing PVE. In the context of PVE, TAVI seems to be a safe option for patients." **Land** Sweden **År data innsamling** 2008-2018	**Populasjon:** all patients who received a TAVI in Sweden from January 2008 to September 2018, a total of 4336 patients. **Kohorter**: TAVI IE patient and TAVI patients without IE. **Hoved utfall:** TAVI patient with a definite IE diagnose compared with TAVI patients with IE. Outcome of kidney funksjon associated with increased risk for IE. In addition outcome was also a comparisen of TAVI with SAVR in regards to IE. **Viktige konfunderende faktorer** Patient baseline is significant, amoung them Peripheral vascular disease is negatively associated with PVE according to the present study. **Statistiske metoder** - Kaplan-Meier-kurver illustrate accumulated PVE incidence and survival after PVE. - Cox modell used to find risk factors associated with PVE during the complete follow-up and the post 1-year analysis. - En binær logistisk regresjon used for determining risk factors for PVE during the first year. - Backwards Stepwise wald based exclusion was used with a P< 0.1 to stay in the model - Student t-test, v2-test, Mann – Whitney U-test was performed depending on the distribution of data.	**Hovedfunn** The risk for PVE after TAVI was 1.4% the first year and 0.8% per year thereafter. One-year survival after PVE diagnosis was 58%, and 5-year survival was 29%. "Body surface area, estimated glomerular filtration rate <30 mL/min/1.73 m2, critical pre-operative state, mean pre-procedural valve gradient, amount of contrast dye used, transapical access, and atrial fibrillation were identified as independent risk factors for PVE. Staphylococcus aureus was more common in early (<1 year) PVE. Infection with S. aureus, root abscess, late PVE, and non-community acquisition was associated with higher 6-month mortality." **Bifunn** Factors that were not associated with PVE. Other studies had identified orotracheal intubation as a risk factor, and this current study did not find such an association. Same regarding to diabetes , but reduced eGFR and sensitivity to contrast could be a better marker for severity of diabetes as compared to the limited information in the dichotomous variable diabetes.	**Sjekkliste:** • Formålet klart formulert? Yes • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias)Yes • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)* No • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?* Yes • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) **No • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?** No • Var studien prospektiv? Retrospectiv • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) Yes • Er det utført frafallsanalyser? (Eval. attrition bias) Yes • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall?Yes • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser?Yes • Tror du på resultatene?Yes • Kan resultatene overføres til den generelle befolkningen? For TAVI pas • Annen litteratur som styrker/svekker resultatene? Yes • Hva betyr resultatene for endring av praksis? Support overal practice **Hva diskuterer forfatterne som:** **Styrke** They encountered very few missing data points, eliminating the need for imputation and reducing the risk for attrition bias **Svakhet** Duke criteria of a positive echocardiogram finding is hard to meet in TAVI patients, as both the old valve and stent frame obscures the new valve. Therefor they included possible IE according to Duke criteria in this study. Larger cohort would have yielded more robust statistics, but as all patients who have ever received TAVI in Sweden were included it is impossible to increase the number. To avoid a Type II error in this cohort, they increased the P level to stay in the model to 0.1, which consequently increased the risk for a Type I error. Therefore, results should be interpreted with strength of the correlation in mind.

Referanse: Mangner N, Leontyev S, Woitek FJ, Kiefer P, Haussig S, Binner C, et al. Cardiac Surgery Compared With Antibiotics Only in Patients Developing Infective Endocarditis After Transcatheter Aortic Valve Replacement. J Am Heart Assoc. 2018;7(17):e010027.			**Studiedesign: Kohortestudie** Grade - kvalitet ++
Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
The objective is to "determine the impact of cardiac surgery (CS) and antibiotics (IE-CS) compared with medical treatment with antibiotics only (IE-ABx) on 1-year mortality in patients developing IE after transcatheter aortic valve replacement." **Konklusjon** In patients developing IE after transcatheter aortic valve replacement "CS provided no significant mortality benefit compared with medical therapy." **Land** Germany **År data innsamling** 2008-2017	**Populasjon:** Consecutive patients receiving TAVR between June 2008 and April 2017 and afterwards developing IE, which were treated in their center, were included this analysis **Kohorter**: 64 patients (58.2%) with echocardiographic evidence of IE were included. 20/64 patients (31.3%) received CS, while 44/64 patients (68.7%) received ABx only. **Utfall (outcome) validering** "All-cause 1-year mortality (after diagnosis of IE) was the primary end point of this analysis. In-hospital mortality was a secondary end point." **Viktige konfunderende faktorer** According to the P value, all baseline and IE-associated parameters were well balanced between theIE-CS and IE-ABx groups. But the authors point out that this was a small cohort group. P value thereby has its limitation. **Statistiske metoder** - Numbers (percentages) are given for categorical variables - meanSD and median (25th–75th percentile) are given for continuous variables. - The effect measures standardized mean difference and odds ratio, together with their 95% confidence interval (CI), were calculated before and after matching. - Frequencies were compared by v2 test or Fisher's exact test, as appropriate. - Groups were compared with respect to continuous variables by means of the Wilcoxon-Mann-Whitney U test. - In-hospital mortality and all-cause 1-year mortality were calculated by the Kaplan-Meier method, applying the log-rank test for group comparison. - Standard Cox regression was performed for the unmatched cohort, and conditional Cox regression was performed for the matched cohort	**Hovedfunn** "Neither an unadjusted nor an adjusted analysis revealed a statistically significant mortality benefit of CS compared with medical therapy in those highrisk patients developing IE after TAVR. Mortality was predicted by the severity of IE (eg, sepsis on admission or formal indication for CS) and concomitant mitral regurgitation (at the time of IE diagnosis) rather than by treatment choice." "However, because of the small sample size, adjustment was only possible for some parameters. Moreover, P values may not tell the whole truth in such a small cohort because there was a 10% absolute risk reduction by CS in the matched analysis and in the multivariable analysis." **Bifunn** In patients developing IE after TAVR, mortality was predicted by the severity of IE and concomitant mitral regurgitation.	**Sjekkliste:** • Formålet klart formulert? Yes • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? Yes • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? No, Severity of illness was different between the two groups. • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon? Yes • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) No • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?Nei • Var studien prospektiv? retrospective • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) everyone included in the study was followed up. • Er det utført frafallsanalyser? (Eval. attrition bias) No • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? Yes • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? Yes • Tror du på resultatene? Yes • Kan resultatene overføres til den generelle befolkningen? TAVI IE patients, with caution • Annen litteratur som styrker/svekker resultatene? Yes • Hva betyr resultatene for endring av praksis? Study supports earlier cohort in infectious Endocarditis After TAVR International Registry **Hva diskuterer forfatterne som:** **Styrke** - «decision to perform surgery or not was made by the same TAVR and endocarditis team during the whole study time, providing stability in personal judgement and readiness to assume risk" **Svakhet:** - The study was based on a small high risk population. Not randomized. Manual matching and multivariable testing were applied to adjust for relevant baseline and IE-associated factors. Because of the small sample size, adjustment was only possible for some parameters. - "the decision by the heart team conserning AB or CS might be an Important bias in this analysis" - Patients were selected according to the echocardiographic evidence of IE. Patients with negative imaging did not undergo 18F-fluorodeoxyglucose positron emission tomography/computed tomography and computed tomography angiography on a "regular basis, leading to a potential bias of missing definite IE in those patients."

Referanse: Regueiro A, Linke A, Latib A, Ihlemann N, Urena M, Walther T, Husser O, Herrmann HC, Nombela-Franco L, Cheema AN, Le Breton H, Stortecky S, Kapadia S, Bartorelli AL, Sinning JM, Amat-Santos I, Munoz-Garcia A, Lerakis S, Gutiérrez-Ibanes E, Abdel-Wahab M, Tchetche D, Testa L, Eltchaninoff H, Livi U, Castillo JC, Jilaihawi H, Webb JG, Barbanti M, Kodali S, de Brito FS Jr, Ribeiro HB, Miceli A, Fiorina C, Dato GM, Rosato F, Serra V, Masson JB, Wijeysundera HC, Mangione JA, Ferreira MC, Lima VC, Carvalho LA, Abizaid A, Marino MA, Esteves V, Andrea JC, Giannini F, Messika-Zeitoun D, Himbert D, Kim WK, Pellegrini C, Auffret V, Nietlispach F, Pilgrim T, Durand E, Lisko J, Makkar RR, Lemos PA, Leon MB, Puri R, San Roman A, Vahanian A, Søndergaard L, Mangner N, Rodés-Cabau J. Association Between Transcatheter Aortic Valve Replacement and Subsequent Infective Endocarditis and In-Hospital Death. JAMA. 2016 Sep 13;316(10):1083-92. doi: 10.1001/jama.2016.12347. PMID: 27623462.	**Studiedesign: Kohortestudie** Grade - kvalitet: +++

Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
To determine the "associated factors, clinical characteristics, and outcomes of patients who had infective endocarditis after TAVR." **Konklusjon** "Among patients undergoing TAVR, younger age, male sex, history of diabetes mellitus, and moderate to severe residual aortic regurgitation were significantly associated with an increased risk of infective endocarditis. Patients who developed endocarditis had high rates of in-hospital mortality and 2-year mortality." **Land** Data collected from 47sites in Europe, North America,and South America. Authors: Canada **År data innsamling** 2005-2015	**Populasjon:** 20 006 Patients who underwent TAVR between June 2005 and October 2015 from 47 centers **Kohorter**: 250 Patients with definite infective endocarditis after TAVR. 6290 Patients without infective endocarditis after TAVR **Hoved utfall:** Infective endocarditis and in-hospital mortality after infective endocarditis. **Viktige konfunderende faktorer** Adequacy of preventive measures is variable in patients. **Statistiske metoder** - Continuous variables are presented as mean (SD) or median (interquartile range [IQR]) and categorical variables as percentages. - Comparison between groups was performed using the t test or Wilcoxon rank-sum test for continuous variables and $\chi 2$ or Fisher exact test for categorical variables. - TheKaplan-Meier method was used to estimate the 2-year mortality rate. - A multivariable logistic regression model was constructed for factors associated with in hospital death in the global study cohort. - A multivariable Cox proportional hazard model was constructed for factors associated with infective endocarditis after TAVR were	**Hovedfunn** "Among patients undergoing TAVR, younger age, male sex, history of diabetes mellitus, and moderate to severe residual aortic regurgitation were significantly associated with an increased risk of infective endocarditis. Patients who developed endocarditis had a high rate of in-hospital mortality and 2 year mortality" **Bifunn** "Early surgery in patients with infective endocarditis and severe valve dysfunction or large vegetations reduces the risk of in-hospital death and embolic events.". This is not an exactly an additional finding in the study but is highlighted in comparison to other studies and current guidelines.	**Sjekkliste:** • Formålet klart formulert? Yes • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias) No • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)* No • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?* No • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) ** Yes • Er den som vurderte resultatene (endepunkt-ene) blindet for gruppetilhørighet?** No • Var studien prospektiv? Retrospective • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) Yes • Er det utført frafallsanalyser? (Eval. attrition bias) No • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? Yes • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? Yes • Tror du på resultatene?Yes • Kan resultatene overføres til den generelle befolkningen? Yes • Annen litteratur som styrker/svekker resultatene? Yes • Hva betyr resultatene for endring av praksis? Validates the change seen in other studies. **Hva diskuterer forfatterne som:** **Svakhet** - retrospective registry may be less relevant regarding the description of the "clinical characteristics and outcomes, it represents an important limitation when evaluating the incidence of infective endocarditis, their associated factors, source of entry, and adequacy of preventive measures." - there was no "external monitoring or event adjudication committee to verify the accuracy of the data reported by each center." - the influence of "confounding factors other than those included in the multivariable models cannot be completely excluded."

Referanse: Stortecky S, Heg D, Tueller D, Pilgrim T, Muller O, Noble S, Jeger R, Toggweiler S, Ferrari E, Taramasso M, Maisano F, Hoeller R, Wenaweser P, Nietlispach F, Widmer A, Huber C, Roffi M, Carrel T, Windecker S, Conen A. Infective Endocarditis After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2020 Jun 23;75(24):3020-3030. doi: 10.1016/j.jacc.2020.04.044. PMID: 32553254.			**Studiedesign: Kohortestudie** Grade - kvalitet ++
Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
The purpose of this study was to "provide detailed information on incidence rates, types of microorganisms, and outcomes of infective endocarditis after TAVR." **Konklusjon** "Infective endocarditis after TAVR most frequently occurs during the early period, is commonly caused by Enterococcus species, and results in considerable risks of mortality and stroke. " **Land** Switzerland **År data innsamling** 2011-2018	**Populasjon:** February 2011- July 2018, all patients undergoing TAVR using Conformité Européenne–approved devices were considered eligible for this study. **Kohorter**: Patients with and without TAVI IE. Patients with TAVI IE were then divided into early, peri-procedural, delayed and late patient population. **Hoved utfall:** "The primary outcome of the study was the incidence of infective endocarditis. Secondary endpoints included all-cause mortality and stroke (disabling and nondisabling stroke) after diagnosis of infective endocarditis. Detailed information on microorganisms and antibiotic prophylaxis were collected." **Viktige konfunderende faktorer** advanced age could be considered a "confounding factor and one of the reasons for the observed difference in microbiological spectrum of infective endocarditis" **Statistiske metoder** - Kaplan-Meier-kurver ble brukt for å illustrere akkumulert PVE-forekomst og overlevelse etter PVE - Cox modell ble brukt til finne risikofaktorer knyttet til PVE under oppfølging og etter 1 års analyse. - En binær logistisk regresjon ble brukt for å bestemme risikofaktorer for PVE i løpet av det første året. - Backwards Stepwise wald basert ekslusjon - Student t-test, v2-test eller Mann – Whitney U-test ble utført avhengig av om distribusjon av data.	**Hovedfunn** "The overall incidence rate of infective endocarditis during 5-year follow-up after TAVR was 1.0 events per 100 person-years. Patients in the early peri-procedural phase after TAVR were at highest risk of infective endocarditis. " Among patients with early peri-procedural infective endocarditis, Enterococcus spp. were the most frequently isolated microorganisms." "Patient developing peri-procedural endocarditis had a pathogen not susceptible to the peri-procedural antibiotic prophylaxis." " Independent predictors of infective endocarditis included younger age, male sex, lack of balloon aortic valvuloplasty before transcatheter valve implantation, and treatment in a catheterization laboratory as opposed to hybrid OR." "Patients with infective endocarditis were at almost 7-fold increased risk of mortality and 4-fold increased risk of stroke compared with a casematched control group." **Bifunn** Treatment in a hybrid OR was independently associated with a reduction in infective endocarditis.	**Sjekkliste:** • Formålet klart formulert? Yes • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias) Yes • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)* No • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?* Yes • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) ** No • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?** No • Var studien prospektiv? Retrospectiv • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) Yes • Er det utført frafallsanalyser? (Eval. attrition bias) No • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? Yes • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? Yes • Tror du på resultatene? Yes • Kan resultatene overføres til den generelle befolkningen? For TAVI pas. • Annen litteratur som styrker/svekker resultatene? Yes • Hva betyr resultatene for endring av praksis? Supports exisiting **Hva diskuterer forfatterne som:** **Styrke** - "source documents were critically revisited, and only if there was consensus on the type and the severity of the event, infective endocarditis was confirmed and considered for this analysis." - By including the Swiss infectious disease network, they were able to "provide effective rates of infective endocarditis at any time after TAVR by minimizing event-reporting bias." **Svakhet** - differences in "institutional practice and clinical decision algorithms might affect treatment and clinical outcomes of patients with infective endocarditis" - PET was not routinely performed. - the information on transcatheter heart valve expansion is "not collected in the registry, and potential effects of incomplete valve expansion or asymmetric valve deployment and the potential effect of pre- or post-dilation of the prosthesis on infective endocarditis cannot be investigated within this dataset" - incidence rates for late endocarditis (beyond 1 year after TAVR) might be underrepresented in this analysis due to the pre-specified follow-up modalities.

Referanse:	**Studiedesign: Kohortestudie**
Tabata N, Al-Kassou B, Sugiura A, Shamekhi J, Sedaghat A, Treede H, Tsujita K, Werner N, Grube E, Nickenig G, Sinning JM. Predictive factors and long-term prognosis of transcatheter aortic valve implantation-associated endocarditis. Clin Res Cardiol. 2020 Sep;109(9):1165-1176. doi: 10.1007/s00392-020-01609-w. Epub 2020 Feb 4. PMID: 32020270	Grade - kvalitet: +++

Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
The objective of the present study was to "investigate the predictor and long-term outcome of TAVI endocarditis." **Konklusjon** "identified lower age and residual PVL ≥ 2 as predictors for THV endocarditis, which itself may be considered as an independent predictor of long-term mortality after TAVI." **Land** Germany **År data innsamling** 2008-2018	**Populasjon:** Consecutive patients undergoing TAVI at their center between January 2008 November 2018 were included in this study **Kohorter**: TAVI IE patient and TAVI patients without IE. **Hoved utfall:** "The primary outcome was all-cause death within a 5-year follow-up." **Viktige konfunderende faktorer** Valve types and baseline **Statistiske metoder** - Statistical analyses were performed using SPSS version 25. - means standard deviations, median values with interquartile ranges. - Categorical data are presented as numbers and percentages. - Differences between two groups were tested using a Fisher's exact test or a Chi-square test for categorical variables. - logistic regression, and linear regression analyses. - The Kaplan–Meier method was used to estimate the probability of mortality at 5 years and a log-rank test was performed to compare the distributions of survival times among the groups. - Cox proportional hazard analyses - multivariable analyses	**Hovedfunn** A multivariable logistic regression analysis identified age and residual paravalvular leakage after TAVI as the main predictors for the occurrence of TAVI endocarditis. Additional analyses revealed that younger patients were significantly associated with higher rates of diabetes, hemodialysis, prior cardiac surgery, and chronic obstructive pulmonary disease (COPD). A Kaplan–Meier analysis showed a significantly worse prognosis in TAVI patients with endocarditis than in patients without during the 5-year follow-up. "A multivariable Cox proportional hazard analysis revealed that TAVI endocarditis is an independent predictor of long-term mortality"". **Bifunn** While data from TAVI endocarditis patients upon hospitalization owing to THV endocarditis showed low rates of surgical valve explantation, the rate of in-hospital death was remarkably high.	**Sjekkliste:** • Formålet klart formulert? Yes • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias)Yes • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)* No • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?* Yes • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) **Yes • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?** Yes • Var studien prospektiv? Yes • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) Small cohort with IE, but all followed up. • Er det utført frafallsanalyser? (Eval. attrition bias) no • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? Yes • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser?yes • Tror du på resultatene?Yes • Kan resultatene overføres til den generelle befolkningen? For TAVI pas • Annen litteratur som styrker/svekker resultatene? Yes • Hva betyr resultatene for endring av praksis? Supports other literature **Hva diskuterer forfatterne som:** **Styrke** Investigators blinded to the study performed the observations and the information regarding death was ascertained by reviewing the medical records and/or was confirmed by direct contact with the families or physicians **Svakhet** - single-center, retrospective study and includes a relatively small numbers of patients, especially for TAVI endocarditis cases. - study included various valve types and we cannot exclude that the differences in the valve structure was a factor.