Surgical management of aortic prosthetic valve endocarditis

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Gothenburg, 2016

Cover: Leonardo Da Vinci: The aortic valve and the blood flowing through the aorta. (Pen and dark brown ink.) Drawings of eddies in blood passing through the aortic valve, closing the cusps from the inside. Leonardo only worked in detail on the heart during the last years of his life. The drawings of the heart are dated around January 1513. His research was mainly concentrated on the aortic valve, and he built a model of the aorta with its cusps to study the flow of water (and therefore of blood) through it. However, he did not discover blood circulation. The sketch is one of the Windsor Folios, part of the Royal Collection, held at Windsor.

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ISBN 978-91-628-9547-1 (Printed edition)
ISBN 978-91-628-9548-8 (Electronic edition)

To my beloved family

Abstract

Background: Infective endocarditis (IE) is still associated with high mortality and morbidity despite advances in diagnostic, medical and surgical management.

Aims: 1. To report short- and mid-term results after surgical treatment of IE in the current era and to compare the results between native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE). 2. To prospectively compare the ability of electrocardiogram (ECG)-gated computer tomography (CT) and transoesophageal echocardiography (TEE) to diagnose aortic PVE. 3. To report our experience with implantation of aortic homografts in patients with aortic PVE or NVE with abscess. 4. To report the outcome of all patients operated for aortic PVE at our institution over the past 20 years and to examine whether the results have improved over time.

Methods and methods: In Study I, outcome after all consecutive patients operated for IE from 2008 to 2015 (n=254) was analysed. In Study II, 27 consecutive patients with aortic PVE underwent 64-sliced ECG-gated CT and TEE, and the results were compared and related to surgical findings. In Study III, outcome and Quality of life (QoL) in patients (n=62) with aortic PVE or NVE with abscess operated with implantation of an aortic homograft were analysed. In Study IV, outcome after all consecutive patients operated (n=87) for aortic PVE from 1993 to 2013 was analysed.

Results: In Study I, overall 30-day mortality was 8.7% and there was no statistically significant difference in 30-day mortality between patients with NVE and PVE (7.7% vs 11.1%, p=0.31). Thirty-nine percent of the patients had severe perioperative complications. Overall survival at one and five years was 86% and 75%, respectively. In Study II, agreement was good between surgical findings and imaging with ECG-gated CT and TEE and very good for the combination of CT and TEE. ECG-gated CT identified more abscesses and thickened aortic root wall while TEE detected more valvular dehiscence and vegetations. In Study III, overall 30-day mortality was 15%. Thirty-five percent of the patients had severe perioperative complications. Cumulative survival was 82%, 78%, 75%, and 67% at one, three, five and ten years, respectively. QoL did not differ significantly between the homograft patients and an age- and gender-matched normal control group. In Study IV, overall 30-day mortality was 10%. Forty-one percent of the patients had severe perioperative complications. Cumulative survival was 81% at five years and 75% at ten years. Thirty-day mortality was higher (22% vs 3.6%, p=0.007) and five-year cumulative survival was lower (66% vs. 88% p=0.013) during the first decade.

Conclusions: Surgery for infective endocarditis was associated with high early mortality and a considerable complication rate. Long-term outcome was acceptable. Morbidity and mortality were comparable in NVE and PVE patients. ECG-gated CT had comparable diagnostic performance to TEE in patients with aortic PVE and may be a complement to TEE. Acute aortic PVE and NVE with abscess formation treated with aortic homograft had substantial early complication rate and mortality. Long-term survival and QoL were satisfactory in patients surviving the immediate postoperative period. Aortic PVE was associated with a high rate of early complications and substantial early mortality. Long-term survival was satisfactory. The results have improved markedly during the past decade.

Keywords: infective endocarditis, prosthetic valve endocarditis, surgery, aortic valve endocarditis.

ISBN 978-91-628-9547-1 (Printed edition)
ISBN 978-91-628-9548-8 (Electronic edition)

List of publications

This thesis is based on the following papers, referred to in the text by their Roman numerals:

I. Perrotta S, Jeppsson A, Fröjd V, Svensson G. Surgical treatment for infective endocarditis: A single center experience. Submitted

II. Fagman E, Perrotta S, Bech-Hanssen O, Flinck A, Lamm C, Olaison L, Svensson G. ECG-gated computed tomography: a new role for patients with suspected aortic prosthetic valve endocarditis. Eur Radiol. 2012 Nov;22(11):2407-14.

III. Perrotta S, Aljassim O, Jeppsson A, Bech-Hanssen O, Svensson G. Survival and quality of life after aortic root replacement with homografts in acute endocarditis. Ann Thorac Surg. 2010 Dec;90(6):1862-7.

IV. Perrotta S, Jeppsson A, Fröjd V, Svensson G. Surgical treatment of aortic prosthetic valve endocarditis: A twenty-year single-center experience. Ann Thorac Surg. 2015 Oct 7. pii: S0003-4975(15)01342-9. doi: 10.1016/j.athoracsur.2015.07.082.

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1. Introduction

Historical notes

In the mid-17th century, Lazare Rivière [1], physician to Louis XIII of France, first described the autopsy findings of infective endocarditis (IE). In the 18th century, Morgani, Lancisi, and Sandifort described hearts with probable endocardial vegetation at autopsy. In 1806, Corvisart [2] described mitral valve vegetations found at autopsy in a 39-year-old-man. In their book on heart disease, Bertin and Bouilland [3] discussed indurations and vegetations on valves of patients dying with endocarditis. It was a French author, Bouilland, who introduced the term endocarditis when he described clinical and pathologic features of the disease in 1841.

In 1885, Osler W [4] presented the first comprehensive description of the classic clinical features of the disease. Around the same time, 1886, Orth [5] and Wyssokowitch [6] designed an experimental model for endocarditis in which aortic valve leaflet of animals were traumatised and the animal subsequently injected with bacterial suspension taken from patients with IE. The animal was seen to have developed murmur, embolic complication and valve lesion at autopsy. In the 1910s, Sir William Osler expressed pessimism about ever finding a cure for IE.

In the 1940s, penicillin revived hope of a cure for IE, but morbidity and mortality were only partially altered [7]. In 1961, Kay reported the first surgical treatment of a patient with medically resistant IE [8]. In 1965, Wallace reported the first valve replacement in active IE [1]. Successes in many studies after surgical treatment of selected patients led to a paradigm shift in management of complicated IE. The role of surgery in active IE has expanded progressively since these early reports of successful outcome. Subsequent declines in mortality may be attributed to a variety of improvements in management, although surgery in carefully selected patients has played a major role [9].

The epidemiological profile of IE has changed considerably over the past few years, especially in industrialised nations. IE was originally seen to affect young adults with previous well defined (mostly rheumatic) valve disease, but now it is affecting older patients, who may develop IE as result of healthcare associated procedures, patients with no previously known valve disease or patients with prosthetic valves [10]. As a result, there is a general trend toward a more acute presentation, with more abrupt complications as opposed to a subacute presentation with extensive peripheral stigmata as described originally. The treatment of IE has continued to evolve but still represents a diagnostic and therapeutic challenge.

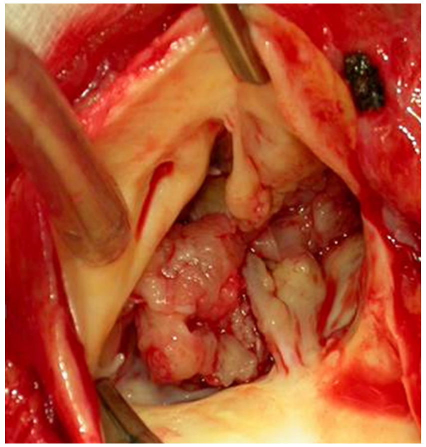


Figure 1. The aortic root during surgery for infective endocarditis. The outflow tract is obstructed by vegetations and the native cusps are barely visible.

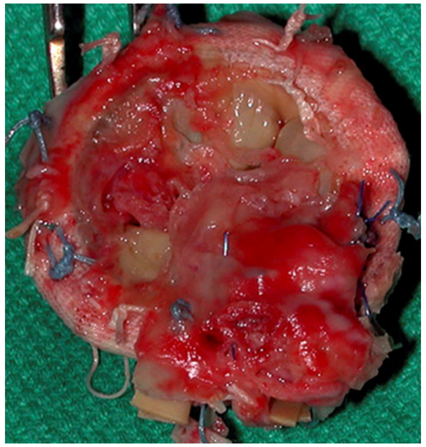


Figure 2. Biological valve prostheses observed from the ventricular outflow tract. The orifice is completely covered by vegetations.

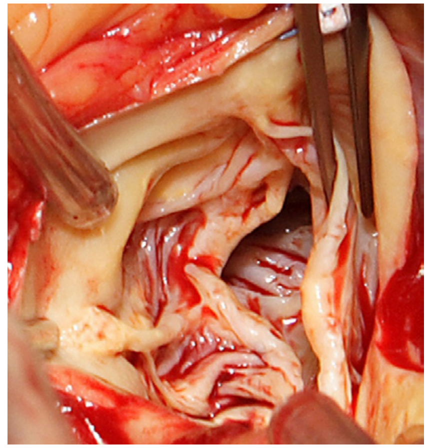
Types of infective endocarditis

Infective endocarditis is an infection of the endocardial surface of the heart, which may affect heart valves or the mural endocardium, or a septal defect. It may lead to severe valvular insufficiency, to heart failure, and to abscess formation.
IE can be classified in various ways. Depending on the localisation, it can be divided into left-sided (aortic or mitral valve), or right-sided (tricuspid or pulmonary valve). Depending on the presence or absence of intracardiac foreign material, it can be divided into native valve endocarditis (NVE) (Figure 1) or prosthetic valve endocarditis (PVE) (Figure 2), and device-related IE (IE developing on pacemaker or defibrillator wires with or without associated valve involvement). Prosthetic valve endocarditis is divided into early prosthetic valve endocarditis, when the infection occurs within one year after surgery, and late prosthetic valve endocarditis, when the infection occurs one year or later after surgery [10]. According to the mode of acquisition, IE is divided into healthcare-associated infection (subdivided into nosocomial and non-nosocomial endocarditis), community-acquired endocarditis, and intravenous drug abuse endocarditis [10].

Since the 1960s, the clinical characteristics of infective endocarditis have changed significantly. Some varieties of endocarditis uncommon in the early antibiotic era have become common, and PVE, drug user-related infective endocarditis, nosocomial and

infective endocarditis caused by intravascular devices or procedures have increased [10]. The underlying valvular pathology has also changed. Aortic stenosis is the underlying pathology in approximately 50% of elderly patients. Congenital heart disease accounts for 15% of the cases, with the bicuspid aortic valve being the most common etiologic factor [11] (Figure 3). Only few patients with rheumatic heart disease develop IE in developed countries [11], unlike developing countries where most cases of IE develop in patients with rheumatic valve disease [10]. The incidence of IE between countries ranges from 3 to 10 episodes/100,000 person-years [12]. The incidence of IE is low in young patients but increases dramatically with age, and the peak of incidence is 14.5 episodes/100,000 person-years in patients aged between 70 and 80. In all epidemiological studies of IE, the male-to-female ratio is approximately 2 to 1 [13].

Figure 3. Bicuspid aortic valve with fusion of the left and right coronary cusp.



Clinical course

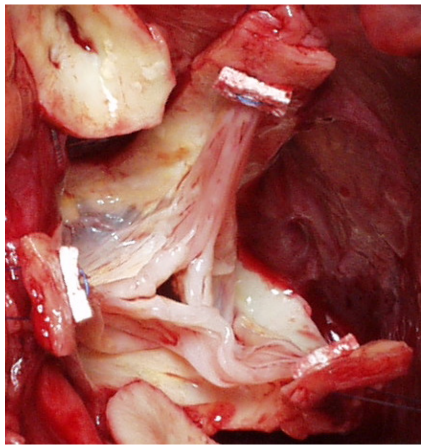
The clinical course of IE can be acute or subacute. Antibiotics have changed the natural clinical expression of the disease [11]. Acute endocarditis may involve a normal valve when the causative agent is a high virulent bacteria of the Staphylococcus or Streptococcus families. [14]. Subacute native valve endocarditis often affects abnormal valves. Its course is more indolent and causative agents are often streptococci or enterococci [14].

Prosthetic valve endocarditis accounts for 7 to 25% of cases of IE in developed countries [15]. Early PVE is frequently hospital acquired and the main infectious agents are coagulase-negative staphylococci, gram-negative bacilli, and Candida species, especially within two months after surgery [15]. Late PVE are mainly caused by staphylococci, alpha-haemolytic streptococci, or enterococci, and are mostly community acquired [15].

The IE in intravenous drug-addicted patients may be localised on either side of the heart. In these patients, 25% have a valvular anomaly, the tricuspid valve is usually involved and Staphylococcus aureus is the most common causative organism [16]. Infection of pacemakers includes device pocket infections and infection of the leads in contact with the endocardium. This latter category represents true pacemaker IE; it is the least common infectious complication of pacemakers (0.5% of implanted pacemakers), and is challenging to treat. Coagulase negative and positive staphylococci are responsible for 75% of all pacemaker infections [17].

A nosocomial IE manifests 48 hours after the patient is hospitalised, or is related to a procedure performed within four weeks of clinical disease onset [10]. Two types of nosocomial infective endocarditis have been described. The right-sided variety affects a valve that has been injured by placement of an intravascular line and subsequently infected by a nosocomial bacteraemia. The second type develops in a damaged valve and occurs more often on the left side. Usually the nosocomial IE are caused by Staphylococcus aureus and Enterococcus [10].

Figure 4. Normal healthy cusps in an aortic root where the aortic wall was resected because of an aneurysm.



Pathophysiology

In most cases, a native valve (Figure 4) becomes infected if an underlying structural failure facilitates the adhesion of bacteria to its surface. In the case of Staphylococcus aureus infection, a normal valve can be affected [18]. In the presence of prosthetic material (Figure 5 and 6), pathogens have the ability to adhere to the surfaces of the foreign material and produce an antibiotic resistant biofilm that facilitates the infection [19].

The common denominator for adherence and invasion is the formation of a non-bacterial thrombotic formation, a sterile fibrin-platelet vegetation, and its development and location is influenced by the Venturi effect [20]. The Venturi effect is a phenomenon that occurs when a fluid flowing through a pipe is forced through a narrow section, resulting in a reduction in pressure and an increase in velocity. Perfusion is low immediately beyond the orifice, where the anomalous stream of blood produces a mechanical erosion and deposition of platelets and thrombin. This principle explains why fibrin-platelet thrombus and bacteria are deposited on the sides of the low-pressure sink that lies beyond a narrowing or a stenosis [20].

Bacteria adhere to the surface of the sterile fibrin-platelet and colonisation begins. When it is achieved, bacteria are immersed in a matrix. Here they multiply and are then covered by layers of thrombin and platelets, which protects them from host defences [21]. The development of an acute or subacute IE depends on a bacterial inoculum sufficient to allow invasion of the pre-existent thrombus [22]. Subacute infective endocarditis is characterised by vegetation in which bacteria and lymphocytes are present, and areas of healing are scattered among areas of destruction. Over time, the healing process falls behind, and valvular destruction and insufficiency develop.

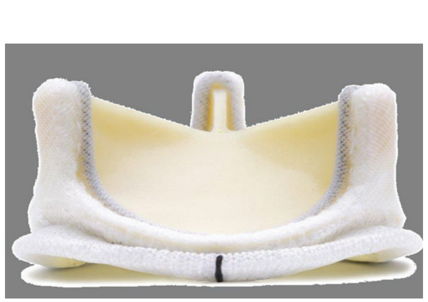


Figure 5. Biological prosthetic valve. Carpentier-Edwards Perimount Magna Ease (Courtesy of Edwards Lifesciences)

Figure 6. Mechanical prosthetic valve. St. Jude Medical Masters HP (Courtesy of St. Jude Medical)

Increasing levels of complement-fixing bactericidal antibodies and cryoglobulins are responsible for the formation of circulating immune complexes responsible for many extracardiac manifestations [23-25]. In acute endocarditis, vegetations and areas of necrosis develop rapidly, with no evidence of tissue repair [26]. This process rapidly destroys the heart tissue and can produce septic emboli.

Clinical features

The clinical features of patients with infective endocarditis are varied and diverse. In acute and destructive IE, symptoms may be dramatic; the infection is rapidly progressive and the patient needs emergency treatment. The clinical presentation varies according to the presence or absence of cardiac disease, the presence of comorbidity, the presence of complication of IE, the patient's characteristics, the presence or absence of a prosthetic valve, and the type of microorganism. In recent years, the distinction between acute and subacute endocarditis has become less clear, and the use of antibiotics can suppress bacterial growth within the valvular thrombus, giving rise to a muted IE [22].

Signs and symptoms of acute valve endocarditis

The patient usually presents with fever. The onset of illness is abrupt due to the rapid progressive destruction of the infected valve (or the paravalvular tissue in the case of PVE) and formation of friable vegetations. The infection may lead to valvular insufficiency, intraventricular abscesses, and presence of fistulas, sinus of Valsalva aneurisms, mycotic aneurysms, and septic embolism with a wide spectrum of peripheral

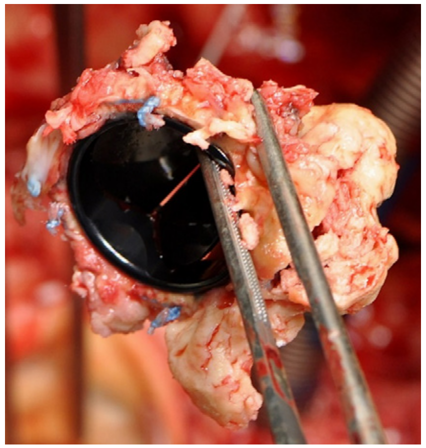


Figure 7. Prosthetic valve endocarditis with dehiscence. The mechanical prostheses was dehisced in 2/3 of the circumferences and only attached in the area seen to the right in the figure.

manifestation due to embolic events. At presentation, 30% of the patients have emboli to the brain, lung or spleen [27, 28]. The clinical symptoms develop rapidly. Heart failure in IE is the most frequent complication and can be caused by severe aortic or mitral insufficiency, dehiscence of a prosthetic valve (Figure 7), intracardiac fistulae or, more rarely, by valve obstruction, when a large vegetation partially obstructs the valve orifice [29, 30].

Signs and symptoms of subacute valve endocarditis

The symptoms of subacute endocarditis are nonspecific and may even present as a chronic disease. They include low-grade fever and influenza-like symptoms. Heart murmurs are found in most of the patients. Symptoms can be caused by the deposition of circulating immune complexes [31]. The deposition of immune complex in the kidney may produce interstitial nephritis or proliferative glomerulonephritis, leading to renal failure [31]. The peripheral lesions are observed in approximately 20% of patients, compared with 85% in the pre-antibiotic era, and the most common is petechiae [32]. These may occur on the palpebral conjunctivae, dorsa of the hands and feet, anterior chest and abdominal walls, oral mucosa, and soft palate. Subungual haemorrhages may be present. Roth spots are retinal haemorrhages with pale centres. Musculoskeletal symptoms arise from immunologically mediated synovitis. Patients may experience palpitations as symptoms of an immune-mediated myocarditis. Lumbosacral back pain in patients with subacute infective endocarditis results from the deposition of immune complexes in the disk space [32].

Duke criteria for diagnosis of infective endocarditis

The variability in clinical presentation of endocarditis requires a diagnostic strategy that is both sensitive for disease detection and specific for its exclusion across all forms of the disease.

In 1994, Durack [33], from Duke University, proposed a set of criteria called 'the Duke criteria' that combine the clinical, microbiological, pathological, and echocardiographic characteristics of a specific case with endocarditis.

The original Duke criteria stratified patients with suspected endocarditis into three categories: 'definite' cases (endocarditis proved at surgery or at autopsy), 'possible' cases (not meeting the criteria for definite IE), and 'rejected' cases (no evidence of IE at autopsy or surgery, rapid resolution of the symptoms, or a firm alternative diagnosis). Several refinements have been made recently to both the major and minor criteria, and the original version has been revised to form the modified Duke criteria that are now recommended for diagnostic classification [10].

Definition of infective endocarditis according to the modified Duke criteria [34].

Major echocardiographic criteria include the following:

a) Development of partial dehiscence of a prosthetic valve
b) Echocardiogram positive for endocarditis, documenting presence of vegetation
c) Myocardial abscess
d) New-onset valvular regurgitation

Major blood culture criteria include the following:

a) Three or more separate blood cultures drawn at least one hour apart
b) Two blood cultures positive for organisms typically found in patients with infective endocarditis (Staphylococcus viridans, Streptococcus bovis, a HACEK group organism, community-acquired Staphylococcus aureus, or enterococci in the absence of a primary focus)
c) Blood cultures persistently positive for one of the above organisms from cultures drawn more than 12 hours apart

Minor criteria include the following:

a) Echocardiogram results consistent with infective endocarditis but not meeting major echocardiographic criteria
b) Vascular phenomena, including septic pulmonary infarcts, major arterial emboli, intracranial haemorrhage, mycotic aneurysm, conjunctival haemorrhage
c) Predisposing heart condition or intravenous drug use
d) Fever of 38°C or higher
e) Immunological phenomenon such as glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
f) Positive blood culture results not meeting major criteria or serologic evidence of active infection with an organism consistent with infective endocarditis [e.g. Brucella, C Burnetii (i.e. Q fever), Legionella]

A definitive diagnosis of IE is established by demonstrating the presence of the microorganisms through culture or histology analysis, in vegetations, embolectomy, or drainage of an intracardiac abscess. Alternatively, a definitive clinical diagnosis is made based on the presence of two major criteria, one major criterion and three minor criteria, or by five minor criteria.

A diagnosis of possible endocarditis is made when the patient does not meet all the criteria for definite infective endocarditis but does not meet any of the criteria for rejection.

Rejection criteria for the diagnosis of infective endocarditis are as follows:

a) The presence of a firm alternative diagnosis of the manifestations of endocarditis
b) Resolution of manifestations of endocarditis after four or fewer days of antimicrobial therapy
c) No pathologic evidence of infective endocarditis at surgery or autopsy after four or fewer days of antimicrobial therapy

In our studies, we have used the modified Duke criteria to diagnose the presence of IE. Because IE is a heterogeneous disease with highly variable clinical presentations, the use of criteria alone will never be sufficient. The Duke criteria are meant to be a clinical guide for diagnosing IE and must not replace clinical judgment.

Overview of etiologic agents causing endocarditis

Causative microorganisms are most often staphylococci, streptococci, and enterococci [35]. Streptococci are the etiologic agents of community-acquired native valve endocarditis. The species that most commonly cause endocarditis are Streptococcus sanguis, Streptococcus mitis, Streptococcus salivarius, Streptococcus mutans, and Gemella morbillorum [36].

IE may be caused by staphylococci that are coagulase positive (Staphylococcus aureus) or coagulase negative (CNS) (Staphylococcus epidermidis and various other species). Staphylococcus aureus is the most common cause of IE in the developed world and is primarily a consequence of healthcare contact [10]. CNS is also a common cause of and is associated with a high mortality rate [37, 38].

There are more than 15 species within the Enterococcus genus. Few therapeutic options are available for antimicrobial therapy of enterococcal endocarditis caused by multiple resistant enterococci [36]. Endocarditis caused by Gram-negative bacilli of the HACEK group accounts for 5-10% of native valve community-acquired endocarditis [36].

Among Enterobacteriaceae, Salmonella species have an affinity for abnormal cardiac valves, usually on the left side of the heart [36]. Pseudomonas aeruginosa endocarditis has been reported, but is unusual [36]. Candida and Aspergillus species account for most fungal endocardial infections [36]. Patients who develop fungal endocarditis usually have multiple predisposing conditions, including the use of prosthetic cardiac valves and central venous catheters. Despite aggressive combined medical and surgical interventions, mortality rates for fungal endocarditis are high [36].

Blood culture endocarditis may remain negative for many days after antibiotic discontinuation [10]. Diagnosis in such cases relies on serological testing, cell culture or gene amplification [39].

Imaging techniques for diagnosing infective endocarditis

Echocardiography is the gold standard for diagnosing IE [10]. Echocardiographic diagnostic criteria for IE are evidence of vegetation (Figure 8), annular abscess, prosthetic valve dehiscence, and new valvular regurgitation (Figure 9) [33].

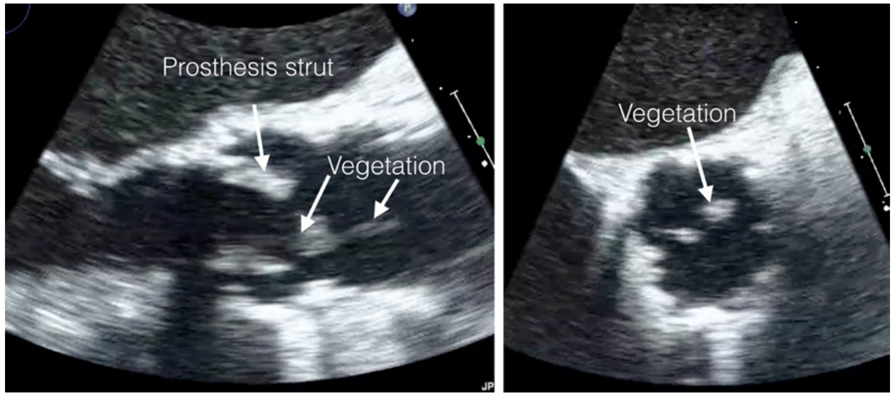


Figure 8. Echocardiographic image: Prosthetic valve affected by vegetations, long axis (to the left), and sagittal axis (to the right).

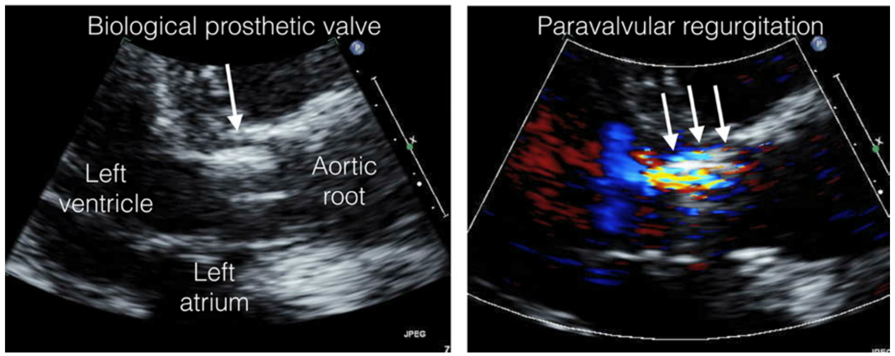


Figure 9. Echocardiographic image: Prosthetic aortic valve affected paravalvular regurgitation. To the right demonstrated with colour Doppler.

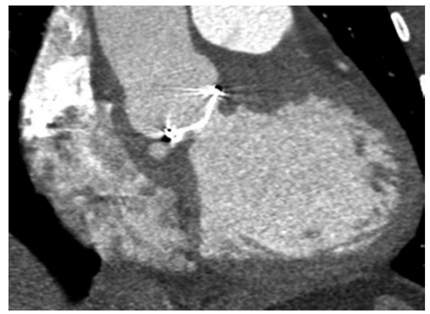
Echocardiography should be performed in all cases of suspected IE. It is reasonable to perform transthoracic echocardiography to rule out IE if the clinical suspicion is low and imaging is of good quality. If clinical suspicion of IE is high (prosthetic valve, staphylococcal bacteraemia, or new atrioventricular block), a negative transthoracic echocardiography will not rule out the presence of IE [10]. Transthoracic echocardiography images can serve as baseline for rapid and noninvasive comparison of vegetation size, valvular insufficiency, or change in abscess cavities during the course of the patient's treatment [40].

Transoesophageal echocardiography should be performed in patients with clear IE [41, 42]. It is more sensitive than transthoracic echocardiography in detecting vegetations and abscesses [43] and it makes easier to assess the perivalvular area in the setting of a prosthetic valve [44]. If vegetations are small, both transoesophageal echocardiography and transthoracic echocardiography may produce false-negative results [45].

In the early stage of the disease, transoesophageal echocardiography may not identify perivalvular abscesses, which may appear only as a nonspecific perivalvular thickening [46]. Similarly, perivalvular fistulae and pseudoaneurysms develop over time, and negative early transoesophageal echocardiography images do not exclude their potential development. Echocardiography cannot predict embolic events [47-49], and the greatest risk appears to occur when vegetation larger than 10 mm in diameter is present [50].

Echocardiography is essential in the diagnosis and management of IE [10]. However, other imaging techniques, including magnetic resonance imaging (MRI), multislice computed tomography (MSCT), and nuclear imaging, have also been shown to be useful for diagnosis, follow-up and decision-making in patients with IE [10, 51].

Figure 10. Aortic prosthetic valve endocarditis. A pseudoaneurysm cavity at annulus level.



Cardiac MSCT can be used to identify pseudoaneurysms/abscesses with a diagnostic accuracy similar to echocardiography, and it provides more information about the extension of any perivalvular infection, including the anatomy of pseudoaneurysms, abscesses and fistulae (Figure 10) [52]. In aortic valve endocarditis, cardiac CT is used to define the anatomy of the aortic root and ascending aorta, which is useful for surgical planning. CT angiography can be used in detecting cerebral lesion, because it allows complete visualisation of the intracranial vascular tree with a sensitivity of 90% and specificity of 86% [53].

MRI increases the likelihood of detecting cerebral consequences of IE. It has a higher sensitivity than CT in the diagnosis of the cerebral lesion, particularly with regards to stroke, transient ischemic attack and encephalopathy, and it can detect cerebral lesions that are not related to clinical symptoms [54]. Cerebral MRI has no impact on the diagnosis of IE in patients with neurological symptoms, but it may influence the therapeutic strategy, in particularly the timing of surgery [54].

18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a functional molecular imaging technique that depicts metabolic activity [55]. Cells involved in inflammation and infection have an increased FDG uptake due to high glycolytic activity [55]. 18F-FDG PET/CT may provide information about the presence and localisation of perivalvular extension of infection, and increased FDG-uptake in the perivalvular tissue may be the first sign of infection before abscess formation is detected with TEE (Figure 11) [56]. In the recently published Guidelines for the Management of Infective Endocarditis 2015 by the European Society of Cardiology (ESC), 18F-FDG PET/CT is described as a promising method in the diagnosis of infective endocarditis, and an alternative diagnostic algorithm for PVE is suggested, including cardiac CT and 18F-FDG PET/CT [10].

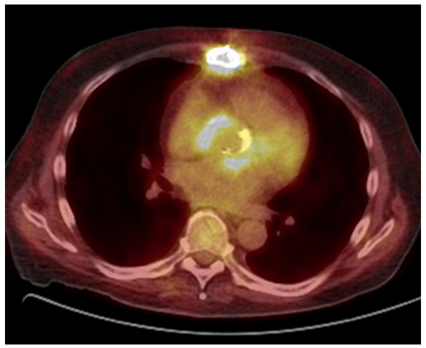


Figure 11. 18F-FDG PET/CT showed increased FDG uptake in the aortic wall.

Surgical therapy

Despite advances in medical therapy of IE, surgery is often required to eradicate the infection [15]. Surgery aims to eliminate the infection by removing all infected tissue, and to restore the valve function, and repair any cardiac defects caused by infection [57].

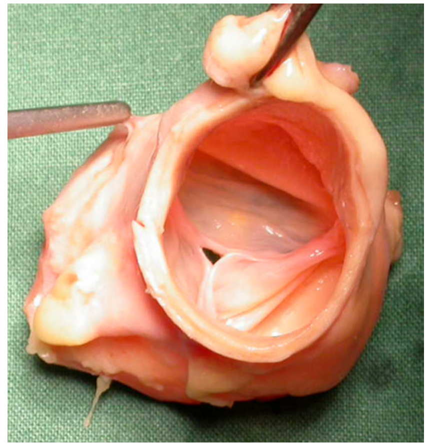


Figure 12. Aortic homograft. The homograft is used for aortic root and left ventricular outflow reconstruction when severe disruption of anatomical structures is present and after extensive debridement of infected tissue and removal of infected prosthesis.

Indication for surgery is based on development of heart failure (HF), abscess and signs of uncontrolled infection, and risk of embolization, despite aggressive medical therapy [10]. Heart failure is the most frequent complication of IE and represents the most frequent indication for surgery in IE [58]. It is also the most important predictor of in-hospital and six-month mortality [10]. Heart failure can be caused by severe valve insufficiency, intracardiac fistulae, or, more rarely, by valve obstruction, when a large vegetation partially obstructs the valve orifice. Uncontrolled infection is the second most frequent reason for surgery. Perivalvular extension of IE is the most frequent cause of uncontrolled infection and is associated with poor prognosis and high likelihood of need for surgery [14]. The exact role of early surgery in preventing embolic events remains controversial, and most of the embolic events are not treatable because the majority occur before admission [9, 27]. The risk of embolism is highest during the first two weeks of antibiotic therapy and is clearly related to the size and mobility of the vegetation, previous embolism, the type of microorganism, and duration of antibiotic therapy [10, 27].

Before surgery, it is important to be aware of the factors that may affect the outcome of the surgery, such as the phase of the infective process, the structural and functional status of affected valve, the presence of comorbidities and the need for concomitant cardiac procedures [14, 15, 26]. Surgery should be a part of the treatment strategy of endocarditis, and the surgical team should be included in the evaluation of the patient. This will enable the surgical team to work with the medical team to determine the timing of surgery [57].

Timing of surgery

Surgical treatment is used in approximately half of patients with endocarditis [10]. Correct timing of surgery is essential for a full recovery, but the optimal point in time remains controversial [9, 10]. Identification of patients requiring early surgery is often difficult [7]. Early surgery carries a higher risk of failure due to unstable patient condition; on the other hand, severely destroyed cardiac tissue may make reconstruction of anatomy difficult, with risk of peri-prosthetic leakage, and possible recurrence of endocarditis. Late surgery may also lead to a life-threatening systemic infection, or extensive structural destruction of the heart valves and surrounding tissues [57].

In some cases surgery has to be performed on an emergency or urgent basis irrespective of the duration of antibiotic treatment, and it is justified when the success of an antibiotic treatment is unlikely. When the patient is haemodynamically stable, surgery can be postponed to allow one or two weeks of antibiotic treatment under clinical and echocardiographic observation [57].

The management of patients with IE and cerebral complication is challenging, because these patients often present multiple neurological deficits and randomised controlled trials are not available [27, 35]. After a transient ischemic attack, when the risk of postoperative neurological deterioration is low, surgery is recommended without delay [59]. In the case of ischemic stroke, when the patient is not in coma and the presence of cerebral haemorrhage is excluded by cranial CT or MRI, surgery, indicated by heart failure, uncontrolled infection, abscess, or persistent high embolic risk, should be considered without delay [60]. The optimal time interval between stroke and cardiac surgery is conflicting, but recent data favours early surgery [61]. In cases with intracranial haemorrhage, neurological prognosis is worse, and surgery should generally be postponed for at least one month [62].

The optimal timing for cardiac surgery should be based on preoperative clinical condition of the patient and the type of neurological complication. When urgent cardiac surgery is needed, close cooperation with the endocarditis and neurosurgical team is mandatory [10].

Types of surgical treatment

In the preoperative evaluation, the surgeon has access to a variety of information for use in planning the surgical intervention, but only the intraoperative findings will make clear what type of intervention is needed [9]. The surgical intervention is less complicated when only the leaflets or cusps are involved, but if the infection spreads beyond the annulus the surgery is more demanding. Surgery aims to eradicate the necrotic tissue and reconstruct the anatomy of the heart (Figure 13, 14 and 15) [63]. Aortic valve replacement is the most common surgery performed in the setting of aortic valve endocarditis [57]. In the mitral position, repair is the primary option but, if this is not possible, the valve is replaced [63]. Vegetectomy has also become common practice [64], and is considered in the presence of localized and limited vegetation, without destruction of the periannular tissue.

Several studies have evaluated the outcome after aortic valve replacement with a biological or mechanical valve in the setting of aortic valve endocarditis (Figure 5 and 6) [65]. No significant difference was found between mechanical and bioprosthetic valves in either short- or long-term survival [66]. The type of valve chosen depends on the surgeon's preference and according to the accepted indications for aortic valve replacement. In the case of perivalvular aortic root involvement with damage of aortic valve and root, aortic homograft is often recommended for its haemodynamic performance, and the ability to resist infection (Figure12) [67]. Aortic homograft is suited for reconstruction of the aortic root, because it is easier to handle than prosthetic materials and its anterior leaflet of the mitral valve can be used to patch defects caused by resection of the abscess [68].

In the mitral position, if the infection has extended to the surrounding tissue, the annulus has to be reconstructed with fresh autologous or glutaraldehyde-fixed bovine pericardium or Dacron fabric, and the valve replaced [69].

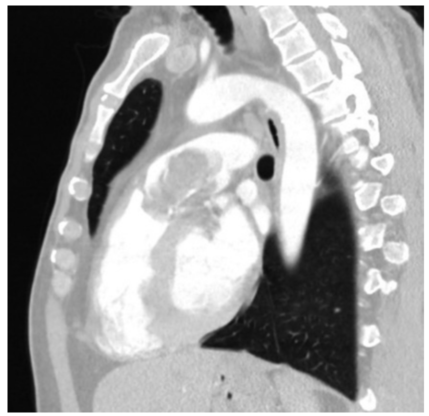


Figure 13. Preoperative computer tomography showing evidence of vegetation at the pulmonary valve and in the pulmonary trunk.

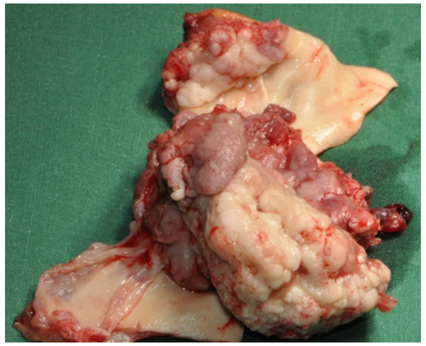


Figure 14. Excised pulmonary valve and pulmonary trunk affected by extensive vegetation.

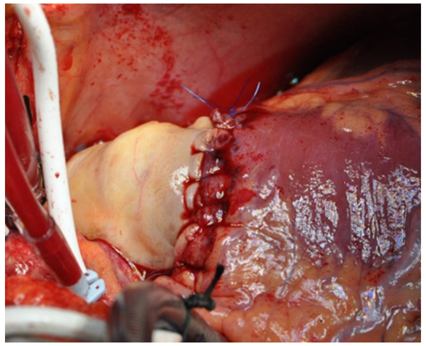


Figure 15. Replacement of excised pulmonary trunk with a pulmonary homograft.

There is no consensus on which prosthesis is optimal for implantation in patients with PVE [67]. The stentless prostheses have a reinfection rate and haemodynamic performance comparable to those of cryopreserved homografts [70], and are available at any time. A mechanical or biological composite graft is an option in patients with extensive root destruction [71-73]. Another surgical procedure that may be used in the setting of endocarditis is the Ross procedure [74, 75], but only a few studies reporting the use of the Ross procedure in aortic endocarditis have been published [76, 77].

Study objectives

Infection of the heart valves is a serious and potentially lethal disease that affects native valves or can complicate heart valve surgery. Mortality and morbidity remain high despite progresses in diagnostic, medical and surgical treatment [10]. Surgery is recommended in cases of advanced disease with heart failure or paravalvular damage or valvular dehiscence [78]. The overall early mortality after surgery ranges in contemporary series from 12 to 28% [79, 80], with large variations depending on

the severity and extension of the infection and the preoperative status of the patient [13]. In Study I, we analysed our experience with surgical treatment of infective endocarditis in the current era.

The first-line imaging method in patients with suspected PVE is TEE, but the initial TEE examination has been reported to be negative in 20% of cases [81]. This is a drawback, since it is important to detect perivalvular infection in the early phase. Examination of the perivalvular region with TEE can be difficult due to acoustic shadowing from the valve prosthesis [82]. Electrocardiogram-gated computed tomography (ECG-gated CT) has emerged as a new imaging modality for valve prostheses [83] and may be used in the diagnostic workup of PVE [44, 46, 84]. In Study II, we compared the agreement in findings between ECG-gated CT, TEE and surgical findings in patients with aortic PVE.

Perivalvular extension of IE with abscess formation is the most frequent cause of uncontrolled infection and is associated with a poor prognosis [10]. Surgical therapy involves radical excision of infected and necrotic tissue, complete removal of prosthetic material, replacement of the aortic valve, and reconstruction of the aortic root. We prefer to use a cryopreserved homograft in these cases for reconstructing the aortic root. In Study III, we analysed the outcome and quality of life in patients with aortic PVE or aortic NVE with periannular aortic root abscess formation treated with radical excision of all the infected and necrotic tissue and implantation of cryopreserved aortic homograft.

Aortic PVE is still a potentially fatal disease despite advances in medical and surgical treatment [85]. Neither the incidence nor the mortality of the disease has decreased in the past years [10]. The prevalence of PVE varies between 1% and 6% [86] and is increasing due to the increasing number of aortic valve prostheses implanted. Aortic PVE can be medically treated in patients without perivalvular extension of the infection and who respond to antibiotic treatment [87]. When antibiotic treatment alone is insufficient to eradicate the infection, surgical treatment is necessary [69]. Surgery can be demanding and is associated with high morbidity and mortality [88]. In Study IV, we describe our experience of surgical treatment of patients with aortic PVE over a 20-year period, and compare outcome of patients who underwent operation during the first decade with those who were operated on during the second decade.

2. Aims of the study

I. To describe our experience with surgical treatment of infective endocarditis in the current era, and to compare outcome in native and prosthetic endocarditis. (Paper I)

II. To prospectively investigate the agreement in findings between ECG-gated CT and TEE in patients with aortic PVE. (Paper II)

III. To analyse our single-centre experience with implantation of cryopreserved homografts in patients with aortic PVE or aortic NVE with periannular aortic root abscess formation. (Paper III).

IV. To describe our experience of surgical treatment of patients with aortic PVE over a twenty-year period, and to compare outcome between the first and the second decade. (Paper IV)

3. Material and methods

Study characteristics

The Human Ethics Committee at the Sahlgrenska Academy at University of Gothenburg approved and waived the need for informed consent for Studies I, III and IV, in Study II, patients were included after written informed consent. Study and patient characteristics are summarised in Table 1.

Table 1.
Study and patients characteristics in Studies I–IV. Mean and standard deviation or number (%).

	Study I	Study II	Study III	Study IV
Number of patients/operations	234/254	27/16	62/62	84/87
Age	56 ± 16	63 ± 15	57 ± 15	58 ± 14
Female gender	55 (22 %)	2 (7 %)	14 (22 %)	18 (21 %)
Study period	Jan 2008 – May 2015	Apr 2008 – Jul 2011	Jan 1997 – Jun 2008	Jan 1993 – Jun 2013
Study type	Retrospective	Prospective	Retrospective	Retrospective
Procedures studied	254 (100%)			
Aortic valve	146 (57%)	27 (100%)	62 (100%)	87 (100%)
Mitral valve	78 (31%)			
Double valve	23 (9%)			
Right-side valve	7 (3%)			
Prosthetic valve endocarditis	72 (28%)	27 (100%)	31 (50%)	87 (100%)
Native valve endocarditis	182 (72%)	0	31 (50%)	0
Total valve operated	277 (100%)	16 (59%)	62 (100%)	87 (100%)
Repair	66 (24%)			
Replacement	211 (76%)			
Aortic homograft	65 (31%)		62 (100%)	56 (64%)
Biological valve	112 (53%)			11 (13%)
Mechanical valve	34 (16%)			20 (23%)

Study design

Paper I

All patients operated for infective endocarditis at Sahlgrenska University Hospital from January 2008 to May 2015 were included in the study. The patients were identified in the SWEDEHEART registry, and additional data was collected from institutional databases and patient records. Preoperative patient characteristics, surgical details, and the outcome data after surgical interventions were registered, and the results compared between native and prosthetic valve endocarditis.

Paper II

All patients (n = 34) with suspected aortic PVE from April 2008 to July 2011 were considered for inclusion. Six of the patients were excluded for technical reasons. The remaining 27 consecutive patients with aortic PVE were included in the study, and were evaluated with TEE and ECG-gated CT. The results of these two diagnostic methods were compared. The images of both methods were compared with surgical findings of 16 patients who underwent surgery.

Paper III

All 62 patients operated with a cryopreserved homograft for active aortic PVE (n = 31) or aortic NVE (n = 31) with periannular aortic root abscess from January 1997 to June 2008 were included in the study. The preoperative patient characteristics, the perioperative variables, and the outcome data after surgery were collected from the patient´s medical records and from the institutional database. The following outcome variables were assessed: 30-day mortality, severe operative complications, mid-term survival and complications, reoperations, and quality of life.

Paper IV

All 84 consecutive patients operated on for isolated aortic PVE from January 1993 to June 2013 were included in the study. Three of these patients underwent a second operation, giving a total of 87 surgical procedures. Preoperative, perioperative, and postoperative variables were collected from an institutional database and from patients' clinical records. Early mortality, perioperative and early postoperative complications, long-term survival, reoperation and rate of recurrent endocarditis were assessed in all the study population, and the results between patients operated on during the first and the second decades were compared.

Surgical technique

All operations were performed with a cardiopulmonary bypass through a median sternotomy. When implantation of an aortic homograft was planned, prosthetic aortic valves or infected native valves were excised. All infected and necrotic tissue was radically and aggressively resected, and the right and left coronary ostia were excised from the aortic wall with a cuff. The outflow tract was reconstructed with a cryopreserved aortic homograft as full free-standing aortic root replacement.

The aortic valve replacement using biologic or mechanic prostheses was performed using standard techniques. The infected valve was resected and the patients received either a bileaflet mechanical valve or a stented porcine bioprosthesis according to local clinical practice. The prostheses were implanted in a supraannular position.

Surgery on the mitral and tricuspid valve was performed using bicaval cannulation, and the mitral valve was visualised through a paraseptal or transseptal incision. The valves were repaired or replaced using standard procedures.

Cardiac ECG-gated CT protocol

Electrocardiogram-gated CT examinations were either performed with a 64-slice spiral CT system or with a dual-source CT system. The images were post-processed and evaluated by two radiologists. The readers were blinded to the results of TEE but informed of the clinical history. Images of the aortic root and valve were reconstructed in short and long axis planes. Movement of the valve was studied with cine loops acquired by combining images from ten cardiac phases.

Echocardiography

All patients underwent preoperative echocardiography. Transoesophageal echocardiography was performed using a commercial ultrasound system equipped with a multiplane TEE transducer (Philips, Andover, MA, USA) Postoperative echocardiography was performed at discharge.

Quality of life

Quality of life was assessed using the 'short-form 36' questionnaire, a validated multipurpose, short-form health survey with 36 questions. It is a patient-reported survey of patient health and is a measure of health status. It yields an 8-scale profile of functional health and well-being scores, as well as psychometrically-based physical and mental health summary measures [67].

Briefly, the results of the survey are divided into the eight subsets believed to reflect the respondent's quality of life: ability to perform usual and vigorous activities (physical functioning, PF), ability to participate in social and occupational activities [social functioning (SF), physical role functioning (RP), and emotional role functioning (RE)], moods [mental health (MH)], amount of energy [vitality (VT)], amount of bodily pain (BP), and current health [general health perception (GH)]. The four scales (PF, RP, BP, GH) are then combined to a physical component scale and the other four (VT, SF, RE, MH) to a mental component scale [67].

These eight scaled scores are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score, the greater the disability and the higher the score, the higher the level of well-being. Patients' SF-36 scores were compared with a published age- and sex-matched Swedish reference population.

Statistical analysis

Categorical data is given as total number, and continuous variables are given as mean ± standard deviation. A p value less than 0.05 was considered statistically significant. Cumulative long-term survival was calculated according to the Kaplan-Meier method and group comparisons were performed with t-test or Mann-Whitney U test for continuous data and the $\chi 2$ test for categorical data (Studies I, III, IV). Normality was tested with Kolmogorov-Smirnov test (Studies I, IV). Cox regression was used to identify factors correlated to early (< 30 days) and overall mortality (Study IV). The strength of agreement between ECG-gated CT, TEE and surgical findings was assessed by kappa statistics. A kappa value 0.41-0.60 is considered moderate agreement, 0.61-0.80 good agreement and 0.81-1.0 very good agreement (Study II).

4. Results

Paper I

Procedures

There were 254 consecutive operations for infective endocarditis, performed in 234 patients. A total of 277 infected valves were replaced or repaired. There were 182 operations for NVE and 72 operations for PVE.

Microbiology

Blood culture results were available from 231 (91%) operations. Bacteria belonging to the Staphylococcus and Streptococcus families were the most common agents (42% and 34%). There was no significant difference in number of Staphylococcus infections between NVE and PVE, but there were more Streptococcus infections in the NVE group (40% vs 18%, $p = 0.002$).

Early mortality

Overall 30-day mortality was 22 patients (8.7%). Patients who died had significantly higher age, higher Euroscore and a higher incidence of hypertension and diabetes. Perioperative factors associated with 30-day mortality were postoperative dialysis, respiratory failure, myocardial infarction, postoperative heart failure and reoperation for bleeding.

Mid-term mortality

Overall survival at one and five years was 86% and 75%, respectively. There were no significant differences in cumulative survival between aortic, mitral and double valve endocarditis (Figure 16). Survival during follow-up did not differ significantly between native and prosthetic valve endocarditis ($p = 0.31$) (Figure 17). The cumulative survival at one and five years was 93% and 83% in patients with streptococcal infection, and 80% and 64% in patients with staphylococcal infection ($p = 0.021$).

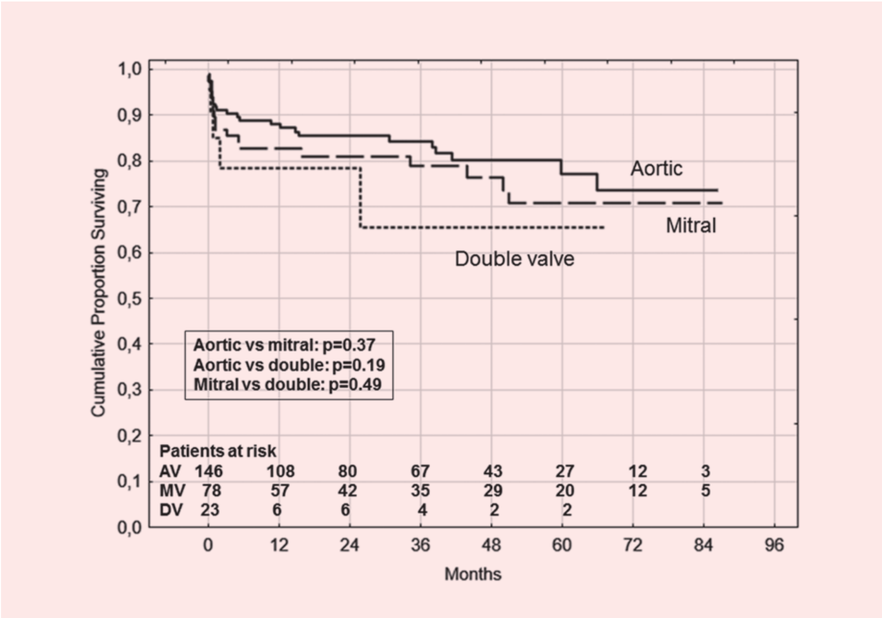


Figure 16. Cumulative survival in patients operated for aortic valve, mitral valve or double valve infective endocarditis.

Perioperative complications

Severe complications occurred in 99/254 operations (39% of the patients), and the incidence did not differ significantly between native and prosthetic valve endocarditis.

Recurrence of IE

There were 20 (8%) reoperations for recurrent endocarditis in 18 patients during the study period. Recurrence occurred within three months after the initial operation in 12 cases, from 3 to 12 months in 2 cases, and after 12 months in 6 cases.

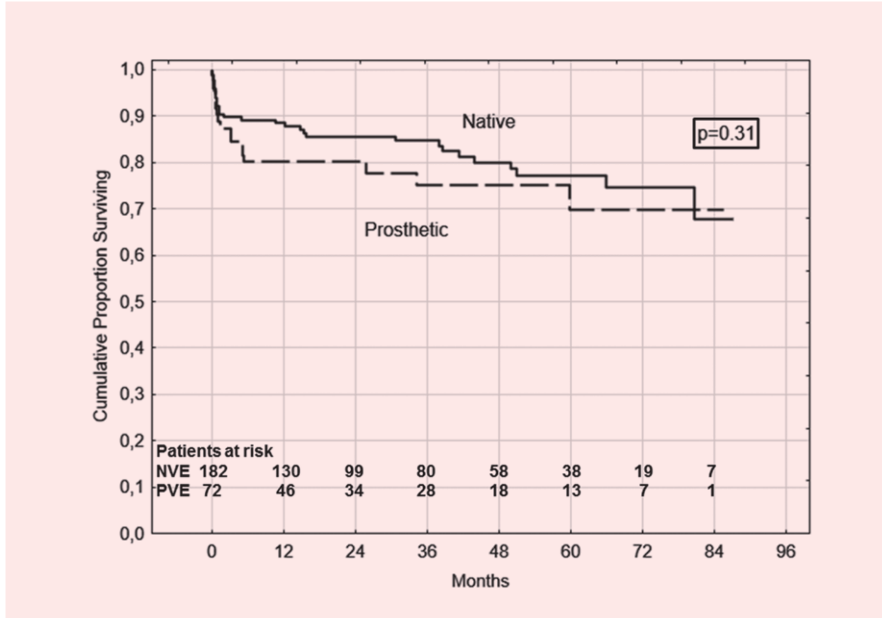


Figure 17. Cumulative survival in patients operated for native valve or prosthetic valve infective endocarditis.

Paper II

Procedures

Twenty-seven consecutive patients with aortic PVE were evaluated with TEE and ECG-gated CT. The results of these two diagnostic methods were compared. The surgical findings of sixteen patients were compared with the imaging of both diagnostic methods.

ECG-gated CT versus TEE

TEE suggested the presence of aortic PVE in all 27 patients and ECG-gated CT in 25. In the two cases that eluded detection with ECG-gated CT, vegetations were the only sign of endocarditis.

Thickened aortic wall

The strength of agreement between TEE and ECG-gated CT was very good (Figure 18). Nineteen out of 27 patients had a thickened aortic root wall on ECG-gated CT. TEE detected a thickened aortic root wall in 17 patients (Figure 19).

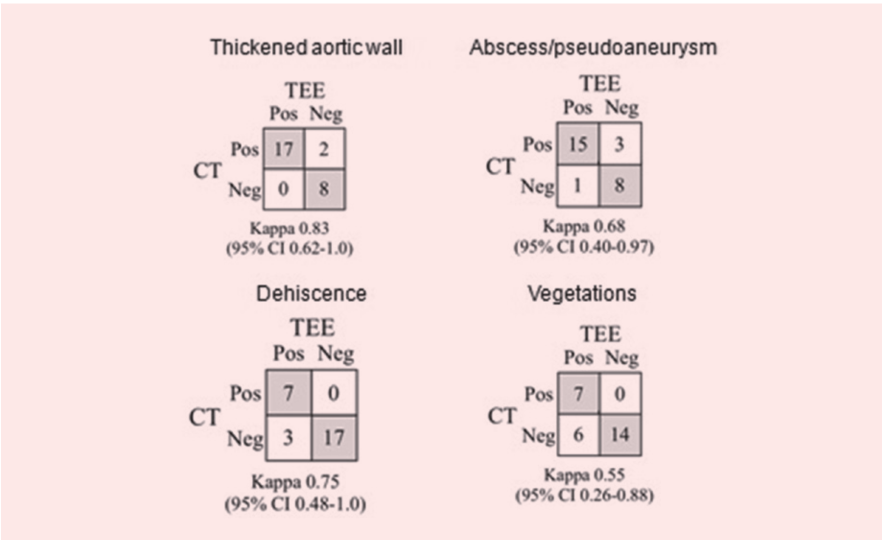


Figure 18. Crosstabs show the distribution of positive and negative findings for ECG-gated CT and TEE regarding thickened aortic wall (upper left), abscess/pseudoaneurysm (upper right), valvular dehiscence (lower left) and vegetation (lower right). Strength of agreement was calculated using kappa statistics.

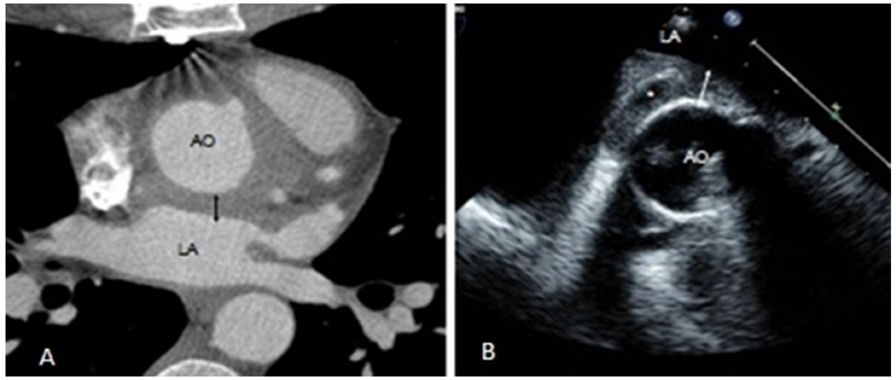


Figure 19. Panel A: Thickened aortic wall. The ECG-gated CT study shows increased aortic wall thickness (black arrow). Panel B: TEE, performed the same day, showed increased aortic wall thickness (white arrow) but also an abscess cavity (asterisk) that was not detected with ECG-gated CT (to the right).

Abscess/pseudoaneurysm

The strength of agreement between TEE and ECG-gated CT was good (Figure 18). ECG-gated CT detected abscess or/and pseudoaneurysm in 18 patients and TEE in 16 patients (Figure 20).

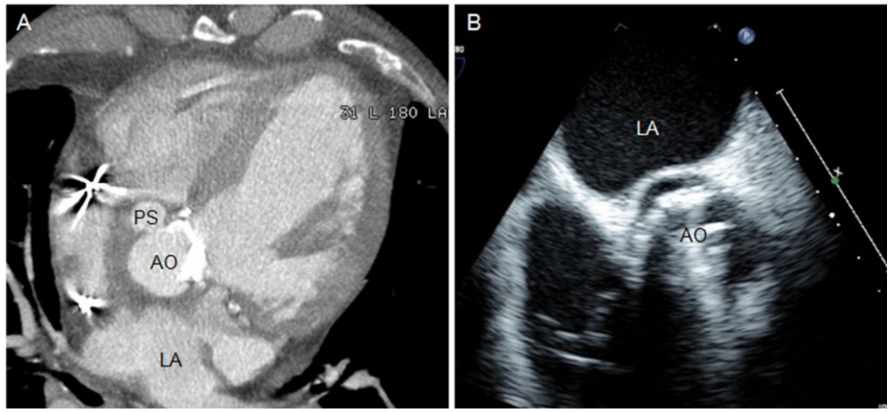


Figure 20. Pseudoaneurysm: detection of pseudoaneurysm with ECG-gated CT. Panel A: ECG-gated CT shows a pseudoaneurysm situated anteriorly. Panel B: With TEE, the mechanical prosthesis gives rise to acoustic shadowing (asterisks) and the pseudoaneurysm cannot be detected. AO = aorta, LA = left atrium, LV = left ventricle, PS = pseudoaneurysm, RA = right atrium, RV = right ventricle.

Valvular dehiscence

The strength of agreement between TEE and ECG-gated CT was good (Figure 18). Seven cases of valvular dehiscence were detected by both ECG-gated CT and TEE. TEE found signs of valvular dehiscence in a further three patients.

Vegetations

The strength of agreement between TEE and ECG-gated CT was moderate (Figure 18). In seven patients, vegetations were detected with both ECG-gated CT and TEE. TEE found vegetations in a further six patients (Figure 21).

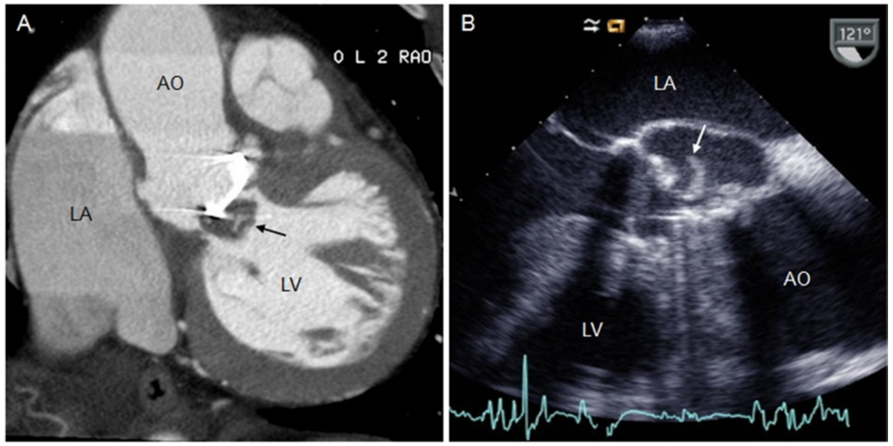


Figure 21. Vegetations on a mechanical prosthetic aortic valve. Panel A: ECG-gated CT sagittal oblique view shows large vegetations on the prosthetic aortic valve (black arrow). Panel B: TEE confirmed the findings of vegetations on the valve (white arrow) and valvular dehiscence. AO = aorta, LA = left atrium, LV = left ventricle.

ECG-gated CT and TEE versus intraoperative findings

A total of 16 patients underwent surgery. Eleven patients with abscess/pseudoaneurysm on ECG-gated CT and/or TEE underwent surgery, and the findings were confirmed during surgery in all cases. Six patients with valvular dehiscence detected with ECG-gated CT and/or TEE underwent surgery, and the finding was confirmed during surgery in all six. In six patients with vegetations detected with ECG-gated CT and/or TEE, surgery was performed and the findings were confirmed intraoperatively in four cases. In two cases where vegetations had been detected with ECG-gated CT and TEE, the vegetations were not found during surgery. The strength of agreement was good between surgical findings and ECG-gated CT and TEE. Combining the findings from ECG-gated CT and TEE improved the strength of agreement, which became very good (Figure 22).

CT	Surgery Pos	Surgery Neg
Pos	16	2
Neg	6	24

Kappa 0.66 (95% CI 0.49-0.87)

TEE	Surgery Pos	Surgery Neg
Pos	19	2
Neg	3	24

Kappa 0.79 (95% CI 0.62-0.96)

TEE/CT	Surgery Pos	Surgery Neg
Pos	21	2
Neg	1	24

Kappa 0.88 (95% CI 0.74-1.0)

Figure 22. Crosstabs show the distribution of positive and negative findings for ECG-gated CT (left), TEE (middle) and the combination of TEE and ECG-gated CT (right) versus surgery. Positive findings are vegetation, abscess/pseudoaneurysm and dehiscence. Strength of agreement was calculated using kappa statistics.

Paper III

Procedures

Sixty-two patients with native or prosthetic valve endocarditis underwent surgery with implantation of cryopreserved aortic homograft.

Early mortality

Nine patients (15%) died during the first 30 postoperative days; six in the prosthetic endocarditis group and three in the native endocarditis group (p = 0.28).
Preoperative and perioperative variables significantly associated with early mortality in univariate testing were Cleveland Clinic risk score (p = 0.014), extracorporeal circulation (ECC) time (p = 0.006), prolonged inotropic support (p = 0.03), reoperation for bleeding (p = 0.01), perioperative myocardial infarction (p<0.001), and postoperative serum creatinine (p = 0.04).

Mid-term mortality

Cumulative survival in the entire patient population was 82% at one year, 78% at three years, 75% at five years, and 67% at ten years (Figure 23). In the patients with prosthesis endocarditis, the corresponding figures were 78% at one year, 70% at three years, 70% at five years, and 51% at ten years, and in the native valve endocarditis group 88% at one year, 84% at three years, 79% at five years, and 79 % at ten years (p = 0.12) (Figure 24).

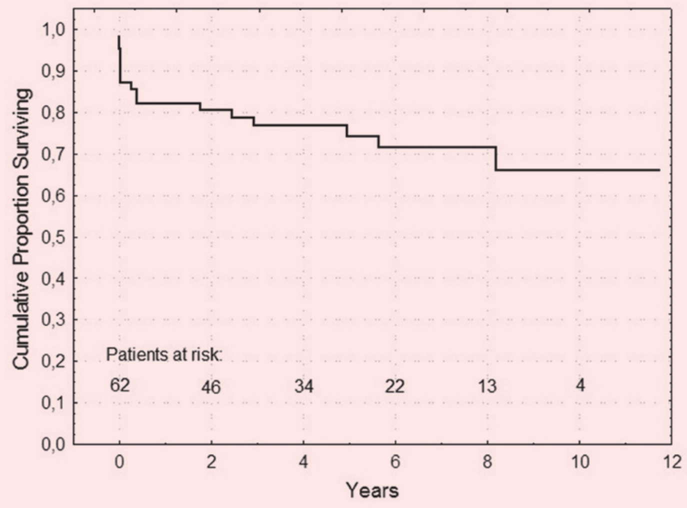


Figure 23. Cumulative survival in 62 patients operated with homograft due to infective endocarditis.

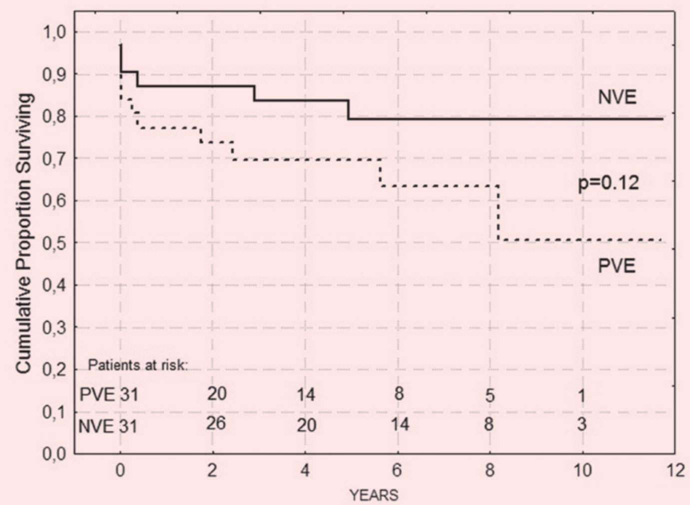


Figure 24. Cumulative survival in patients with prosthetic valve endocarditis (PVE; dotted line) and native valve endocarditis (NVE; continuous line).

Perioperative complications

Twenty-two patients (35%) had one or more severe perioperative complications. Six patients (10%) required dialysis, seven patients (11%) developed perioperative stroke, seven patients (11%) underwent pacemaker implantation for permanent atrioventricular block, while seven patients (11%) had a perioperative myocardial infarction, six patients (10%) required tracheotomy, and thirty-five patients (56%) required inotropic support. Fourteen patients (23%) underwent early reoperation for bleeding.

Recurrent IE and late reoperation

One patient (1.6%) was reoperated for an episode of recurrent endocarditis after nine months. A second patient was reoperated for homograft degeneration after 5.5 years. A third developed mitral valve regurgitation and underwent mitral valve repair three months after homograft implantation.

Quality of life

There was no statistically significant difference between patients operated with homograft and an age- and gender-matched general population in the combined physical component scale or in the combined mental component scale. In contrast, homograft patients had statistically significant inferior results in four of the eight subscales (Figure 25).

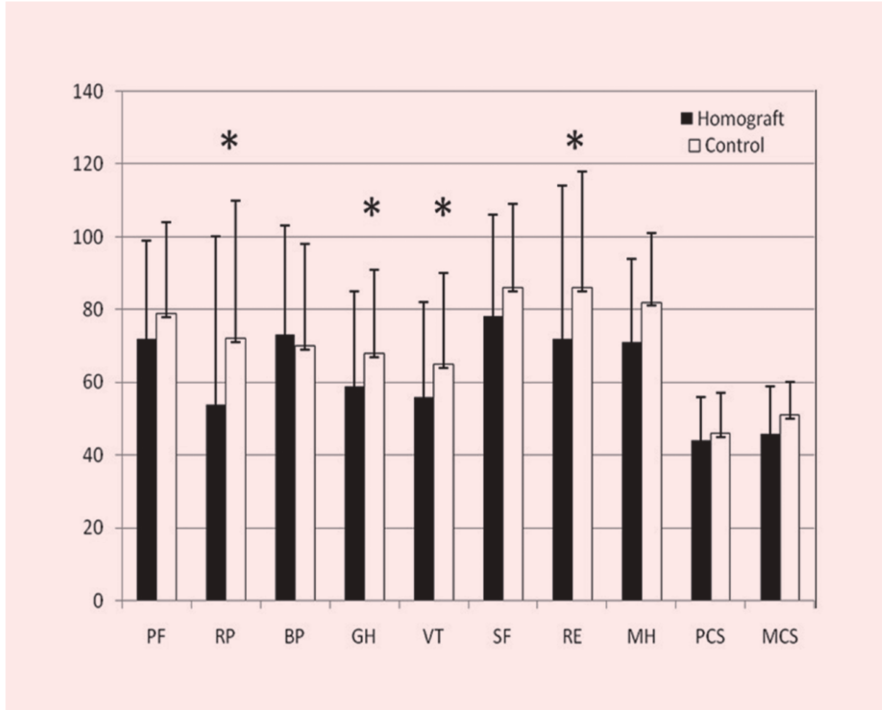


Figure 25. Quality of life as assessed by short-form 36 in homograft patients (n = 40) compared with an age-matched and gender-matched general Swedish population (n =160) (mean and standard deviation). (■ = homograft; □ = control; BP = bodily pain; GH = general health; MCS = mental component scale; MH = mental health; PCS = physical component scale; PF = physical functioning; RE = role-emotional; RP = role-physical; SF = social functioning; VT = vitality.)

Paper IV

Procedures

Twenty-eight (32%) of the operations were isolated valve replacements with either a mechanical prosthesis (n = 17) or a stented biological prosthesis (n = 11). Fifty-nine (68%) of the operations were root replacements with a homograft (n = 56) or a mechanical composite graft (n = 3). Patch repair of the aortic root was performed in five of the 31 patients who received prostheses.

Microbiology

The infective aetiology was diagnosed preoperatively by blood cultures in 67/87 patients (77%). Bacteria belonging to the Streptococcus and Staphylococcus families were the most common agents (32% and 27%, respectively). Thirty-day mortality was 10.7% in patients with streptococci infection and 8.7% in patients with staphylococci ($p = 0.81$). The cumulative survival at five years was 80% and at ten years 80% in patients with streptococci infection, and 81 and 65% respectively in patients with staphylococci infection ($p = 0.45$).

Early mortality

Nine patients (10%) died during the first 30 postoperative days, three in the isolated valve replacement group and six in the root replacement group ($p = 0.94$).

Long-term survival

Cumulative survival in the entire patient population was 80% at five years and 65% at ten years (Figure 26).

Reoperation and recurrent endocarditis

Three patients were reoperated for recurrent PVE, and one patient with recurrence was treated with antibiotics. The prevalence of recurrent PVE was significantly higher in patients treated with mechanical or biological valve prostheses (4/31, 12.9%) compared to patients treated with a homograft (0/56, 0%), $p = 0.006$.

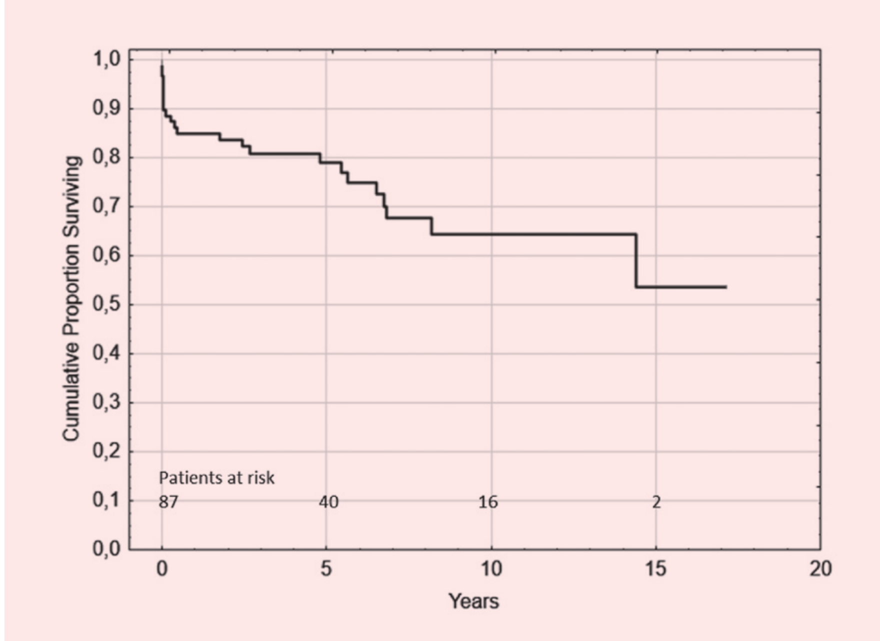


Figure 26. Cumulative survival after 87 operations for aortic prosthetic valve endocarditis performed 1993 – 2013.

Comparison between first and second decade

Fewer patients were operated in the first decade (32 vs. 55). Thirty-day mortality was higher during the first decade (22% vs. 3.6%, $p = 0.007$). The cumulative five-year survival was 66% and ten-year survival 53% during the first decade. Five-year survival was 88% in the second decade ($p = 0.027$ relative to the first decade) (Figure 27).

Homograft vs. prosthetic valve implantation.

An aortic homograft was implanted in 56 patients (64%). The 30-day mortality in homograft patients and prosthesis patients was not significantly different (10.7% vs. 9.7%, $p = 0.88$). There were no statistically significant differences in five- and ten-year survival in patients who received an aortic homograft (74% and 58%, respectively), and in patients who received a prosthesis (87% and 75%) ($p = 0.17$).

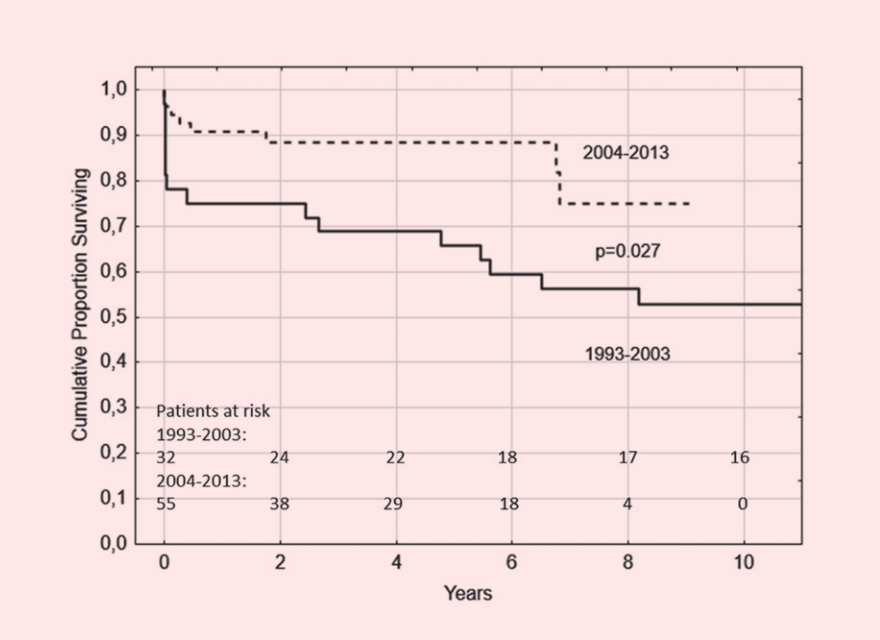


Figure 27. Comparison of cumulative survival after operations performed for aortic prosthetic valve endocarditis in the years 1993-2003 (n = 32) and in the years 2004-2013 (n = 55). There was a significant difference in survival (p = 0.027).

5. Discussion

Infective endocarditis remains a potentially life-threatening disease. Surgical treatment is considered in patients with progressive heart failure and irreversible structural damage and to prevent systemic embolism. The strategy for surgical treatment of endocarditis at our institution is a collaborative approach in the preoperative evaluation, involving infectious disease specialists, diagnostic radiology specialists, echocardiography specialists, cardiologists, and surgeons.

Selection of valve substitutes

Different valve substitutes are used to replace the infected valve in aortic IE, but the optimal choice remains controversial. The general opinion tends toward biological material rather than mechanical devices [89-92]. The aortic homograft is often recommended for its hemodynamic performance, and the ability to resist infection [68], and is widely used in surgery for IE. In our opinion, homograft is an attractive option for easier reconstruction; the pliable nature of the homograft makes it easier to handle than synthetic materials. Data comparing aortic homograft with prosthetic valves in patients with aortic PVE is limited [67, 73]. Comparisons are difficult because the degree of perivalvular infection and annular destruction may vary considerably between individual patients and study cohorts. Aortic root abscess seems be present more often in homograft series, and to a lesser degree present in the series with prosthetic valves [73, 93], suggesting that the disease is more advanced in homograft series.

This thesis does not give any clear indication on the potential advantage of any of the valve substitutes. In Study I, 63 homografts and six prosthetic composite grafts were used for aortic root replacements. In two cases of isolated pulmonary valve endocarditis, pulmonary homografts were used for replacement. The 30-day mortality was 4.6% for patients treated with a homograft. In Study III, an aortic homograft was used in all patients, and the overall mortality was 14.5% in this cohort of patients with complicated PVE and NVE. In Study IV, mortality was 10.7% for patients treated with homograft for aortic PVE. The mortality after homograft implantation in patients with infective endocarditis reported in literature ranges between 3.9% [68] and 40% [81]. This high variability after surgery probably depends on several factors, including patient selection, status of the patient, severity of the disease, and surgical experience.

A mechanical or biological composite graft is also an option, and has been used in patients with extensive root destruction [71-73]. This technique was only used in six patients in Study I and three patients in Study IV, so no conclusion can be drawn from our data. In literature, there are few articles that report the use of composite graft in aortic PVE [71-73]. These authors reported on a limited number of patients (n = 28, n = 31, and n = 13) with complex aortic PVE who had undergone Bentall surgery or Cabrol procedure. They reported a 30-day mortality between 11% and 15%, a recurrence of IE between 0 and 4%, and five-year survival between 75% and 85%.

Standard biological or mechanical valve prostheses are also often implanted in patients with endocarditis [65, 80]. In Study I, 277 infected valves were replaced or repaired, in patients with NVE and PVE, and biological or mechanical prostheses were implanted in 140 (51%) of these operations. In Study IV, 28 biological or mechanical prostheses were implanted in 87 aortic PVE operations (32%). This is in contrast to the study by Moon et al., where 92% biological or mechanical prostheses were implanted for aortic NVE and 88% for aortic PVE [65]. Musci et al. reported 81% homografts when aortic root replacement was performed in acute aortic endocarditis and 88% prostheses when only aortic valve replacement was performed [80].

Another alternative is the use of stentless prostheses which have a reinfection rate and haemodynamic performance comparable to those of cryopreserved aortic homografts [70], and are available at any time. Standard or biological or mechanical valve prostheses have been implanted in patients with PVE [65, 80]. None of the patients in the present studies were treated with a stentless valve. The Ross procedure has been described for endocarditis and may be useful in young patients, where the degeneration of the aortic homograft will expose the patients to a reoperative aortic root procedure [74-77]. In extreme cases where patients suffer from aggressive endocarditis with extensive involvement of the heart and when valve replacement is not considered a suitable treatment, heart transplantation has been suggested [94].

In Study IV, we compared short-term and long-term mortality in patients treated with homografts, or mechanical/biological prostheses. No statistically significant differences were found between homograft and prosthesis patients in 30-day mortality, in five-year or ten-year survival. However, it should be pointed out that our study populations are limited.

Reconstruction of the native valve

When the infection was limited to the cusps or leaflets of a native valve, surgical repair of the valve was preferred, especially in mitral or tricuspid valve infection. In Study I, surgical repair was performed in 54% of the patients with isolated mitral valve endocarditis. Valve repair for active infective endocarditis is widely performed and the surgical procedure can be performed not only with low operative mortality and satisfactory early and long-term survival, but also with excellent freedom from recurrent infection [95-99]. El Khoury et al. showed that 80% of patients with active mitral endocarditis underwent mitral valve repair [96]. In contrast, in a study from 661 centres in North America, mitral valve repair was used for patients with active IE in only 15.9% [97]. If the infection had extended to the surrounding tissue, the annulus may be reconstructed with fresh autologous pericardium or Dacron fabric and the valve replaced as described by David et al. [100].

Reinfection

The reinfection incidence in aortic homograft replacement in our studies was low; we had one patient out of 65 (1.5%) in Study I, in contrast to 9/66 (14%) after valve reconstructions, 12/112 (11%) after biological prostheses, and 1/34 (3%) after mechanical prostheses ($p = 0.024$ for homograft versus other techniques). In Study IV, the incidence of recurrent PVE was significantly higher in patients treated with mechanical or biological valve prostheses (4/31, 12.9%) than in patients treated with a homograft (0/56, 0%) ($p = 0.006$). Reports from other centres also show low incidence of reinfection after homograft implantation. Sabik et al. reported a reinfection rate of 3.8% [68] and Musci et al. 5.4% [101], while Glazier et al. reported a higher incidence 9.5% [102].

Several authors report no difference in rate of recurrent infection between patients who received a homograft and those who received a conventional prosthesis [65, 103, 104]. In our opinion, the low incidence of early and late recurrent IE reported in our studies and others is mainly the result of early diagnosis, aggressive surgical management, including complete resection of all infected tissue, adequate antibiotic treatment, and liberal use of aortic homografts.

Structural valve deterioration

All biological alternatives, including the homografts, deteriorate progressively, which may necessitate reoperation [101]. It has been demonstrated, mainly in patients without endocarditis, that the risk of dysfunction is substantial and higher for homografts than for unstented biological valves [105]. One patient (1.6%) in Study III and three (5.3%) in Study IV underwent reoperation for homograft dysfunction. This incidence is comparable to that reported by O'Brien et al. (2%) and Musci et al. (8.6%) in patients treated with homograft replacement for endocarditis [101, 106]. However, it should be pointed out that the number of patients who underwent reoperation only reflects the most severe forms of deterioration. Some patients may have severe deterioration of the homograft but are not reoperated due to their general condition, co-morbidity, or age.

Microbiology

Bacteria belonging to the Streptococcus and Staphylococcus families were the most common agents in our study cohorts. Streptococcus was primarily detected in native aortic valve endocarditis, whereas Staphylococcus was identified in patients with prosthetic valve endocarditis. These findings are in accordance with previously published reports [81, 107-110]. We found in Study I that patients with Staphylococcus infection have a poorer prognosis than patients infected with other bacteria. Similar data has been reported in the literature [10, 88, 111]. In the more homogeneous group of patients in Study III, no statistically significant difference was observed in mortality between Staphylococcus- and Streptococcus-infected patients. The lack of difference may be explained by insufficient statistical power (type II error).

Imaging in infective endocarditis

Several imaging techniques may be used in patients with infective endocarditis. Transoesophageal echocardiography is the recommended imaging technique in aortic PVE [10], but the diagnostic performance for the detection of endocarditis is limited and there may be a role for complementary imaging methods [44, 46, 83]. In the present series, imaging with transthoracic and transoesophageal echocardiography, ECG-gated CT and in some cases PET-scan were performed since 2008 in patients with aortic PVE. In cases with aortic NVE, mitral, tricuspid and pulmonary endocarditis, the diagnosis was mainly based on transthoracic and transoesophageal echocardiography. Negative ECG-gated CT was used to exclude significant coronary disease [112]. In a few cases, stenosis shown on CT was confirmed with invasive coronary angiogram.

The first study that tried to assess the value of ECG-gated CT for assessment of infective endocarditis, in comparison with transoesophageal echocardiography and intraoperative findings, was published by Feuchtner et al. in 2009 [112]. CT had a sensitivity of 97% in diagnosing pseudoaneurysms. The results are consistent with those reported by Gahide et al. [113], who found a sensitivity of 100% for depicting aortic perivalvular pseudoaneurysms. Most of the infected valves studied were native (89% in both studies). In Study II, the strength of agreement between TEE and ECG-gated CT was good when abscess/pseudoaneurysm was studied in patients with PVE (Kappa 0.68). We also showed that CT was able to detect more patients with thickened aortic wall and presence of abscess than echocardiography, while echocardiography detected more vegetations and valve dehiscence. Our findings are in accordance with those of Feuchtner et al., who showed that CT missed some small vegetation but provided better anatomic information than TEE in terms of the perivalvular extent, such as myocardial, pericardial, and coronary sinus involvement.

In Study II, cardiac CT detected more patients with abscesses than TEE, especially those localised anteriorly, close to the right coronary cusp. In this region the acoustic shadowing of the prosthesis makes TEE detection of an abscess difficult. CT seems to be less reliable than TEE in identifying vegetations, which could be related to an insufficient temporal resolution of the CT scanners. TEE seems to be superior to computed tomography in detecting valve leaflet perforations and paravalvular regurgitations [10]. TEE using the Doppler technique allows visualisation of blood flow in paravalvular regurgitation. When a larger dehiscence is present, CT can detect the rocking motion of the prosthesis during the cardiac cycle.

Quality of life

Quality of life (QoL) assessment has become an important instrument for validating the outcome of cardiac surgery [114]. Patients with pulmonary autografts have better QoL than patients with mechanical valves [115], and valve surgery patients have better postoperative QoL than patients undergoing coronary artery bypass surgery [116]. Patients treated with aortic valve replacement without endocarditis have comparable QoL with matched healthy population and with no difference between bioprostheses and mechanical valves [117, 118]. There is little information about the effect of endocarditis on QoL. Patients with endocarditis may be exposed to long hospitalisation, painful or uncomfortable diagnostic procedures, cardiac surgery, and hospitalisation in the intensive care unit, all of which may reduce QoL.

To the best of our knowledge, Study III is the first article in which the patient-perceived QoL after homograft implantation is reported. QoL was assessed with the SF-36 questionnaire. The combined SF-36 scale for physical health and mental health did not differ significantly between the surgery and non-surgery groups, but there were significant differences between the groups in four of the eight subscales: role physical (RP), general health (GH), vitality (VT), and mental health (MH). Consequently, it seems likely that patients operated with homograft for acute severe endocarditis have an inferior mid-term QoL compared with a healthy matched control group, but the reduction in QoL is small or moderate.

Study limitations

The most important limitations of our three clinical studies (I, III, IV) are the retrospective study design and the limited number of patients included. The retrospective design infers inevitable selection bias and the limited number of patients a pronounced risk for statistical type II errors. In Studies III and IV, patient data was collected over a long period. The diagnostic preoperative assessment of patients with IE differed during the study period and the patients were operated with different surgical techniques by different surgeons. One limitation of our QoL measurements is that they are not recorded at the same time after surgery. Another limitation is that comorbidities, such as stroke and heart failure, may influence the QoL results.

6. Key results and conclusions

I. Surgery for infective endocarditis is still associated with high early mortality and a considerable complication rate. Long-term outcome is acceptable. Our study showed that population, morbidity and mortality were comparable in native and prosthetic endocarditis.

II. ECG-gated CT has comparable diagnostic performance to TEE in patients with aortic PVE. ECG-gated CT may be a valuable complement to TEE.

III. Acute aortic native valve endocarditis with periannular aortic root abscess and aortic prosthetic valve endocarditis can effectively be treated with aortic root replacement with a cryopreserved aortic homograft. The procedure is still associated with a substantial early complication rate and mortality. Relapse and recurrence of endocarditis is rare. Long-term survival and QoL are satisfactory in patients surviving the immediate postoperative period.

IV. Surgically treated aortic PVE was associated with a high rate of early complications and substantial early mortality. Patients who survived the immediate postoperative period had satisfactory long-term survival and the risk of recurrent infection was low, especially in those treated with a homograft. The results have improved over the past decade.

7. Future perspectives

The sustained significant mortality and morbidity associated with infective endocarditis stimulate efforts to improve preventive, diagnostic, and therapeutic strategies.

Vaccine

Given the high morbidity and mortality rates associated with Staphylococcus aureus infections and the limited therapeutic options, the development of a safe and effective vaccine against Staphylococcus aureus represents a genuine need for the medical community [119]. Several proteins have been tested as vaccine candidates for Staphylococcus aureus infections [120-122]. However, despite promising results obtained in pre-clinical and initial clinical studies, no Staphylococcus aureus vaccines are so far available [123].

Imaging modalities in the diagnosis of IE

Real-time transthoracic three-dimensional (3D) echocardiography is now available thanks to advances in computer processing and transducer construction techniques. Software programs to analyse 3D echocardiography are also now readily available; this combination of new instrumentation and software has been shown to provide highly accurate assessment [124]. The use of 3D echocardiography may be a useful tool in diagnosing IE.

The spatial, contrast and temporal resolutions of CT images have improved, and CT now provides high-resolution 3-D images depicting accurate anatomical and functional information of the coronary arteries and the anatomical structures involved in endocarditis [125-127]. This technique will most probably develop further in the future, and its potential is not yet fully demonstrated.

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a functional molecular imaging technique that depicts metabolic activity. ^{18}F-FDG PET/CT is mainly used in oncology, but there is increasing interest in its ability to identify infectious processes [55]. The sensitivity is likely to be influenced by disease activity and extension of the infection. Four recent studies have shown promising results in the diagnosis of PVE [56, 128-130]. The prospectively designed and detailed study by Pizzi et al. examined 92 patients and found a sensitivity of 87% and a specificity of 92% in the diagnosis of PVE [56]. ^{18}F-FDG PET/CT has lower temporal and spatial resolution than TEE and CT and the fast movement of the valve leaflets might lead to blurring and inability to detect FDG-uptake in small vegetations.

ECG-gating of the PET/CT examination, where image acquisition is synchronised with the heart rhythm, may improve the resolution and increase the sensitivity of the method in detecting vegetations. Another limitation is that the studies in patients with suspected PVE were performed after a meal rich in fat and low in carbohydrates and an 18-hour fasting period as a standard procedure in cardiac PET/CT imaging, to reduce physiological FDG-uptake in the myocardium. Further evaluation of the accuracy of ^{18}F-FDG PET/CT in the diagnostic work-up for PVE is warranted.

Surgery

The timing of and the indications for surgery are essential in order to improve outcome in patients with IE. There is a trend towards earlier interventions and the indications for surgery are now more precisely defined than in the past [10]. However, the optimal timing and indications for surgery needs to be improved, especially in patients with vegetations and preoperative embolization. Refinement of the surgical technique, debridement and methods of reconstruction are also vital in order to further improve results.

The future will hopefully see more solid evidence to guide management strategy. However, decision-making in individual patients will remain challenging: expert input and multidisciplinary collaboration between cardiology, infectious disease specialists and cardiac surgery teams will be required to achieve optimum outcome.

8. Sammanfattning på svenska

Kirurgisk behandling av protesendokardit i aortaklaffen

Bakgrund

Infektiös endokardit är en infektion som är lokaliserad till hjärtklaffar eller i sällsynta fall enbart till hjärtats endokard (innerhinna). En infektion kan angripa en nativ (kroppsegen) klaff eller en tidigare inopererad klaffprotes (protesendokardit). Den vanligaste klaffen som drabbas av endokardit är aortaklaffen. De flesta studier visar att en infektion i anslutning till aortaprotes är förenad med högre risk än infektion i nativ klaff. Trots förbättrad diagnostik och förbättrad medicinsk och kirurgisk behandling är dödlighet och sjuklighet fortfarande hög i samband med endokardit. Rekommenderad undersökning vid utredning av endokardit är ultraljudsunderökning via matstrupen (TEE). Med TEE säkerställs i många fall (men inte i alla) diagnos och utbredning av infektionen. Antibiotikabehandling kan bota infektioner som är begränsade till själva klaffbladen och utan spridning i hjärtat utanför klaffen. Kirurgisk behandling rekommenderas när sjukdomen är mer avancerad och spridd. Avsikten med kirurgi är att avlägsna den infekterade vävnaden och att ersätta aortaklaffen och rekonstruera aortaroten (klaffen samt första delen av kroppspulsådern) när det behövs och ge förutsättning för läkning. Olika typer av klaffsubstitut används vid kirurgisk behandling. När infektionen är begränsad till klaffen (nativ eller protes), används ofta en mekanisk eller biologisk protes. I avancerade fall är det vanligaste alternativet ett homograft (donerad mänsklig klaff). Ökad kunskap om resultat i samband med och efter kirurgisk behandling av endokardit samt hur sjukdomen bäst diagnostiseras är önskvärd.

Syften

Att beskriva kirurgisk behandling av endokardit i hjärtats samtliga klaffar och att jämföra resultat efter operation av infekterade nativa klaffar och infekterade klaffproteser. Att fastställa värdet av en ny teknik, EKG-styrd skiktröntgen (CT) i förhållande till undersökning med ultraljud (TEE) hos patienter med protesendokardit i aortaklaffen. Att analysera vår erfarenhet av användandet av homograft vid kirurgisk behandling av svår infektion i nativ aortaklaff med abscess eller infektion i en aortaklaffprotes. Att beskriva vår erfarenhet av kirurgisk behandling av infektion på aortaklaffprotes under en 20-årsperiod och att jämföra resultatet av kirurgi under första decenniet med det andra.

Material och metoder

I delarbete I analyserades resultaten efter 254 operationer för infektiös endokardit hos 234 patienter. I delarbete II undersöktes prospektivt patienter med protesendokardit i aortaklaffen (n=27) med EKG-styrd CT och TEE (ultraljud via matstrupen) varefter resultaten jämfördes inbördes och gentemot kirurgiska fynd. I delarbete III studerades patienter opererade med insättnjing av homograft i aorta på grund av infekterad aortaklaffprotes (n = 31) eller endokardit i nativ aortaklaff med abscess (n = 31). I delarbete IV studerades alla patienter (n = 84) opererade (87 operationer) mellan 1993 och 2013 med protesendokardit i aortaklaffen. Resultaten från de första 10 åren jämfördes med den senaste 10-års perioden.

Resultat

I delarbete I var 30-dagarsdödlighet för samtliga patienter 8.7% och det var inte någon signifikant skillnad i 30-dagarsdödlighet mellan patienter med nativ klaffendokardit och protesendokardit [14/182 (7.7%) vs 8/72 (11.1%), (p=0.31)]. Trettionio procent av patienterna hade svåra komplikationer i samband med det kirurgiska ingreppet. Överlevnaden efter ett och fem år var 86% respektive 75%.

Delarbete II visade att EKG-styrd CT identifierade fler abscesser och högre antal patienter med förtjockad aortarotsvägg medan TEE var bättre än CT att identifiera tecken på klaffläckage och vegetationer. Det fanns en bra överensstämmelse bland de kirurgiska fynden (abscess, vegetation och klaffläckage) och CT respektive TEE. När man kombinerade resultaten efter TEE och ECG-styrd CT ökade överensstämmelsen med kirurgi ytterligare och blev mycket god med mätt med Kappastatistik till 0.88 (95% CI 0.74-1.0)

I delarbete III var den totala 30-dagarsdödligheten 15%. Trettiofem procent av patienterna hade svåra komplikationer i samband med det kirurgiska ingreppet. När båda grupperna sammanräknades var överlevnaden var 82%, 78%, 75%, and 67% efter ett, tre, fem respektive 10 år. Mätning av livskvalitet visar inte någon statistisk skillnad mellan patienter som blev opererade och en frisk kontrollgrupp.

I delarbete IV var 30-dagarsdödlighet 10 %. Fyrtioen procent av patienterna hade allvarliga komplikationer i samband med det kirurgiska ingreppet. Överlevnaden var 81% och 75% efter fem respektive 10 år. Det var färre patienter som blev opererade det första årtiondet och 30-dagarsdödligheten var högre under det första årtiondet [22 vs 3.6%, (p = 0.007)] och 5-åröverlevnaden var högre i det andra årtiondet (88% vs 66%, p = 0.013).

Slutsatser

Den kirurgiska behandlingen av patienter med endokardit är associerad med hög tidig dödlighet och hög incidens av komplikationer, men långsiktigt är resultaten efter kirurgi tillfredsställande. Det var ingen skillnad i sjuklighet och dödlighet efter kirurgi mellan de infekterade nativa klaffarna och protesendokarditerna. (Arbete I)

ECG-styrd CT har likvärdiga diagnostiska prestanda jämfört med TEE hos patienter med protesendokardit i aortaklaffen och kan vara ett komplement till TEE. CT tillför ytterligare information avseende existens och utsträckning av infektioner som engagerar aortaroten. (Arbete II)

Akut nativ aortaendokardit med abscess och protesendokardit i aortaklaff kan framgångsrikt behandlas med ett homograft som ersättning för den sjuka aortaklaffen men med en väsentlig tidig komplikationsgrad och dödlighet. Återfall av endokardit är ovanligt. Långtidsöverlevnad och livskvalitet är tillfredställande hos patienter som överlever den omedelbara postoperativa perioden. (Arbete III)

Vid operation av protesendokardit i aortaklaffen är tidiga komplikationer vanliga och dödligheten hög, men långtidsöverlevnaden är tillfredsställande. Överlevnad efter kirurgi har ökat markant under det senaste årtiondet. (Arbete IV)

9. Acknowledgments

My heartfelt thanks and gratitude to all those who in various ways helped, guided and supported me in completing my thesis. I wish to express my sincere appreciation to all of you.

I wish to express special thanks to:

My supervisor, Associate Professor Gunnar Svensson, for his enthusiasm and support.

My co-supervisor, Professor Anders Jeppsson, for his constructive criticism.

My co-authors: Obaid Aljassim, Odd Bech-Hanssen, Erika Fagman, Agneta Flinck, Victoria Fröjd, Carl Lamm, and Lars Olaison for fruitful cooperation.

Research secretary, Caroline Ivarsson, for much needed support.

Research assistants: Linda Thimour-Bergström, Pernilla Lyckner and Erica Backlund for valuable help.

My colleagues and friends at work.

10. References

1. Major RH. Notes on the history of endocarditis. Bull Hist Med. 1945;17:351-359.
2. Covisart dM, Nicolas J. Essai sur les maladies et les lesions organique du coeur et des gros vaisseaux. Paris: Migneret, 1806.
3. Bertil RJ, Bouilland J. Trait s des maladies du coeur. Paris; Bailliere 1824.
4. Osler W. The Gulstonian lectures on malignant endocarditis. Br Med J. 1885;1:467-470 522-6, 577-9.
5. Orth J. Ueber die aetiologie der esperimentellen Myocotischem endocarditis. Arch Pathol Anat 1886; 103:23.
6. Wyssokowitch W. Beatrage zur lehre von der endocarditis. Arch Patholo Anat 1886; 103:21.
7. Chamoun AJ, Conti V, Lenihan DJ. Native valve infective endocarditis: what is the optimal timing for surgery? Am J Med Sci. 2000 Oct;320(4):255-62.
8. Kay JH, Bernstein S, Feinstein D, Biddle M. Surgical cure of Candida albicans endocarditis with open-heart surgery. N Engl J Med. 1961 May 4;264:907-10.
9. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? Circulation. 2010 Mar 9;121(9):1141-52.
10. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Aug 29.
11. Weinstein LW, Brusch JL. Infective Endocarditis. New York, NY: Oxford University Press; 1996.
12. Hoen B, Alla F, Selton-Suty C, Beguinot I, Bouvet A, Briancon S, Casalta JP, Danchin N, Delahaye F, Etienne J, Le Moing V, Leport C, Mainardi JL, Ruimy R, Vandenesch F. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA 2002;288:75-81.
13. Aksoy O, Meyer LT, Cabell CH, Kourany WM, Pappas PA, Sexton DJ. Gender differences in infective endocarditis: pre- and co-morbid conditions lead to different management and outcomes in female patients. Scand J Infect Dis 2007;39:101-107.
14. Thuny F, Grisoli D, Cautela J, Riberi A, Raoult D, Habib G. Infective endocarditis: prevention, diagnosis, and management. Can J Cardiol. 2014 Sep;30(9):1046-57.

15. Wang A, Athan E, Pappas PA, Fowler VG Jr, Olaison L, Paré C, Almirante B, Muñoz P, Rizzi M, Naber C, Logar M, Tattevin P, Iarussi DL, Selton-Suty C, Jones SB, Casabé J, Morris A, Corey GR, Cabell CH. International Collaboration on Endocarditis-Prospective Cohort Study Investigators. Contemporary clinical profile and outcome of prosthetic valve endocarditis. JAMA. 2007 Mar 28;297(12):1354-61.
16. Miró JM, del Río A, Mestres CA. Infective endocarditis in intravenous drug abusers and HIV-1 infected patients. Infect Dis Clin North Am. Jun 2002;16(2):273-95, vii-viii.
17. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Stoner S, Baddour LM. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol. 2007 May 8;49(18):1851-9.
18. Gotz F. Staphylococcus and biofilms. Mol. Microbiol., 2002, 436, 1367-1378.
19. Von Eiff C; Peters G; Heilmann C. Pathogenesis of infections due to coagulase-negative staphylococci. Lancet Infect. Dis., 2002, 2(11), 677-685.
20. Keynan Y, Rubinstein E. Pathophysiology of infective endocarditis. Curr Infect Dis Rep. 2013 Aug;15(4):342-6.
21. Kloos WE; Bannerman TL. Update on clinical significance of coagulase-negative staphylococci. Clin. Microbiol. Rev., 1994, 7(1), 117-140.
22. Crawford MH, Durack DT. Clinical presentation of infective endocarditis. Cardiol Clin. May 2003;21(2):159-66.
23. Eknoyan G, Lister BJ, Kim HS, Greenberg SD. Renal complications of bacterial endocarditis. Am J Nephrol. 1985;5(6):457-69.
24. Pruitt AA, Rubin RH, Karchmer AW, Duncan GW. Neurologic complications of bacterial endocarditis. Medicine (Baltimore). Jul 1978;57(4):329-43.
25. Snygg-Martin U, Gustafsson L, Rosengren L, Alsiö A, Ackerholm P, Andersson R, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. Clin Infect Dis. Jul 1 2008;47(1):23-30.
26. Sexton DJ, Spelman D. Current best practices and guidelines. Assessment and management of complications in infective endocarditis. Cardiol Clin. May 2003;21(2):273-82, vii-viii.
27. Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, Casalta JP, Gouvernet J, Derumeaux G, Iarussi D, Ambrosi P, Calabró R, Riberi A, Collart F, Metras D, Lepidi H, Raoult D, Harle JR, Weiller PJ, Cohen A, Habib G. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation. 2005 Jul 5;112(1):69-75.
28. Cunha BA, Gill MV, Lazar JM. Acute infective endocarditis. Diagnostic and therapeutic approach. Infect Dis Clin North Am. Dec 1996;10(4):811-34.

29. Terpenning MS, Buggy BP, Kauffman CA. Infective endocarditis: clinical features in young and elderly patients. Am J Med. Oct 1987;83(4):626-34.
30. Bansal RC. Infective endocarditis. Med Clin North Am. Sep 1995;79(5):1205-40.
31. Weinstein L. Life-threatening complications of infective endocarditis and their management. Arch Intern Med. May 1986;146(5):953-7.
32. Weinstein L, Schlesinger JJ. Pathoanatomic, pathophysiologic and clinical correlations in endocarditis (first of two parts). N Engl J Med. Oct 17 1974;291(16):832-7.
33. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med. 1994;96:200-209.
34. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633-638.)
35. Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG Jr, Bayer AS, Karchmer AW, Olaison L, Pappas PA, Moreillon P, Chambers ST, Chu VH, Falco V, Holland DJ, Jones P, Klein JL, Raymond NJ, Read KM, Tripodi MF, Utili R, Wang A, Woods CW, Cabell CH. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169: 463-473.
36. Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS, Figueredo VM. Infective endocarditis epidemiology over five decades: a systematic review. PLoS One. 2013 Dec 9;8(12):e82665.
37. Chu VH Jr., Woods CW, Miro JM, Hoen B, Cabell CH, Pappas PA, Federspiel J, Athan E, Stryjewski ME, Nacinovich F, Marco F, Levine DP, Elliott TS, Fortes CQ, Tornos P, Gordon DL, Utili R, Delahaye F, Corey GR, Fowler VG Jr. Emergence of coagulase-negative staphylococci as a cause of native valve endocarditis. Clin Infect Dis 2008;46:232-242.
38. Revilla A, San Roman JA, Lopez J, Vilacosta I, Luaces M, Fernandez-Aviles F. Current profile of left-sided native valve endocarditis caused by coagulase negative Staphylococcus. Rev Esp Cardiol 2005;58:749-752.
39. Fournier PE, Thuny F, Richet H, Lepidi H, Casalta JP, Arzouni JP, Maurin M, Célard M, Mainardi JL, Caus T, Collart F, Habib G, Raoult D. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. Clin Infect Dis. 2010 Jul 15;51(2):131-40.
40. Heidenreich PA, Masoudi FA, Maini B, Chou TM, Foster E, Schiller NB, Owens DK. Echocardiography in patients with suspected endocarditis: a cost-effectiveness analysis. Am J Med. 1999;107:198-208.
41. Lindner JR, Case RA, Dent JM, Abbott RD, Scheld WM, Kaul S. Diagnostic value of echocardiography in suspected endocarditis: an evaluation based on the pretest probability of disease. Circulation. 1996;93:730-736.

42. San Roman JA, Vilacosta I, Zamorano JL, Almeria C, Sanchez- Harguindey L. Transesophageal echocardiography in right-sided endocarditis. J Am Coll Cardiol. 1993;21:1226 –1230.
43. Reynolds HR, Jagen MA, Tunick PA, Kronzon I. Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. J Am Soc Echocardiogr. 2003;16:67-70.
44. Daniel WG, Mugge A, Grote J, Hausmann D, Nikutta P, Laas J, Lichtlen PR, Martin RP. Comparison of transthoracic and transesophageal echocardiography for detection of abnormalities of prosthetic and bioprosthetic valves in the mitral and aortic positions. Am J Cardiol. 1993;71: 210-215.
45. Bayer AS. Infective endocarditis. Clin Infect Dis. 1993;17:313-320.
46. Daniel WG, Mugge A, Martin RP, Lindert O, Hausmann D, Nonnast- Daniel B, Laas J, Lichtlen PR. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. N Engl J Med. 1991;324:795-800.
47. Sanfilippo AJ, Picard MH, Newell JB, Rosas E, Davidoff R, Thomas JD, Weyman AE. Echocardiographic assessment of patients with infectious endocarditis: prediction of risk for complications. J Am Coll Cardiol. 1991;18:1191-1199.
48. Rohmann S, Erbel R, Gorge G, Makowski T, Mohr-Kahaly S, Nixdorff U, Drexler M, Meyer J. Clinical relevance of vegetation localization by transoesophageal echocardiography in infective endocarditis. Eur Heart J. 1992;13:446-452.
49. Mugge A, Daniel WG, Frank G, Lichtlen PR. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. J Am Coll Cardiol. 1989;14:631- 638.
50. Steckelberg JM, Murphy JG, Ballard D, Bailey K, Tajik AJ, Taliercio CP, Giuliani ER, Wilson WR. Emboli in infective endocarditis: the prognostic value of echocardiography. Ann Intern Med. 1991;114: 635-640.
51. Bruun NE, Habib G, Thuny F, Sogaard P. Cardiac imaging in infectious endocarditis. Eur Heart J 2014;35:624-632.
52. Grob A, Thuny F, Villacampa C, Flavian A, Gaubert JY, Raoult D, Casalta JP, Habib G, Moulin G, Jacquier A. Cardiac multidetector computed tomography in infective endocarditis: a pictorial essay. Insights Imaging. 2014 Oct;5(5):559-70. doi: 10.1007/s13244-014-0353-1.
53. Goddard AJ, Tan G, Becker J. Computed tomography angiography for the detection and characterization of intra-cranial aneurysms: current status. Clin Radiol 2005;60:1221-1236.
54. Goulenok T, Klein I, Mazighi M, Messika-Zeitoun D, Alexandra JF, Mourvillier B,Laissy JP, Leport C, Iung B, Duval X. Infective endocarditis with symptomatic cerebral complications: contribution of cerebral magnetic resonance imaging. Cerebrovasc Dis 2013;35:327-336.

55. Jamar F, Buscombe J, Chiti A, Christian PE, Delbeke D, Donohoe KJ, Israel O, Martin-Comin J, Signore A (2013) EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. J Nucl Med 54 (4):647-658.
56. Pizzi MN, Roque A, Fernandez-Hidalgo N, Cuellar-Calabria H, Ferreira-Gonzalez I, Gonzalez-Alujas MT, Oristrell G, Gracia-Sanchez L, Gonzalez JJ, Rodriguez-Palomares J, Galinanes M, Maisterra-Santos O, Garcia-Dorado D, Castell-Conesa J, Almirante B, Aguade-Bruix S, Tornos P (2015) Improving the Diagnosis of Infective Endocarditis in Prosthetic Valves and Intracardiac Devices with 18F-FDG-PET/CT-Angiography: Initial Results at an Infective Endocarditis Referral Center. Circulation. doi:10.1161/circulationaha.115.015316
57. Kwan-Leung C. & Embli, J.M. (2006). Endocarditis: diagnosis and management, Springer, ISBN 978-1-84625-452-6, London, UK.
58. Tornos P, Iung B, Permanyer-Miralda G, Baron G, Delahaye F, Gohlke-Barwolf C, Butchart EG, Ravaud P, Vahanian A. Infective endocarditis in Europe: lessons from the Euro heart survey. Heart 2005;91:571-575.
59. Thuny F, Avierinos JF, Tribouilloy C, Giorgi R, Casalta JP, Milandre L, Brahim A, Nadji G, Riberi A, Collart F, Renard S, Raoult D, Habib G. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J 2007;28:1155-1161.
60. Ruttmann E, Willeit J, Ulmer H, Chevtchik O, Hofer D, Poewe W, Laufer G, Muller LC. Neurological outcome of septic cardioembolic stroke after infective endocarditis. Stroke 2006;37:2094-2099.
61. Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, Song JM, Choo SJ, Chung CH, Song JK, Lee JW, Sohn DW. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012;366:2466-2473.
62. Yoshioka D, Sakaguchi T, Yamauchi T, Okazaki S, Miyagawa S, Nishi H, Yoshikawa Y, Fukushima S, Saito S, Sawa Y. Impact of early surgical treatment on postoperative neurologic outcome for active infective endocarditis complicated by cerebral infarction. Ann Thorac Surg 2012;94:489-495.
63. Chang HW, Kim KH, Hwang HY, Kim JS. Role of mitral valve repair in infective endocarditis. J Heart Valve Dis. 2014 May;23(3):350-9.
64. Chen X, Chen X, Gu F, Xie D. (2009). An alternative surgical approach for aortic infective endocarditis: vegetectomy. Eur. J. Cardiothorac. Surg., Vol.35, No.6, pp. 1096-1098, ISSN 1010-7940.
65. Moon MR, Miller DC, Moore KA, Oyer PE, Mitchell RS, Robbins RC, Stinson EB, Shumway NE, Reitz BA. Treatment of endocarditis with valve replacement: the question of tissue versus mechanical prosthesis. Ann Thorac Surg. 2001 Apr;71(4):1164-71.
66. Nguyen DT, Delahaye F, Obadia JF, Duval X, Selton-Suty C, Carteaux JP, Hoen B, Alla F. (2010) Aortic valve replacement for active infective endocarditis: 5-year survival comparison of bioprostheses, homografts and mechanical pros-

theses. Eur. J. Cardiothorac. Surg., Vol.37, No.5, pp. 1025-1032, ISSN 1010-7940.
67. Perrotta S, Aljassim O, Jeppsson A, Bech-Hanssen O, Svensson G. Survival and quality of life after aortic root replacement with homografts in acute endocarditis. Ann Thorac Surg. 2010 Dec;90(6):1862-7.
68. Sabik JF, Lytle BW, Blackstone EH, Marullo AG, Pettersson GB, Cosgrove DM. Aortic root replacement with cryopreserved allograft for prosthetic valve endocarditis. Ann Thorac Surg. 2002 Sep;74(3):650-9; discussion 659.
69. David TE, Regesta T, Gavra G, Armstrong S, Maganti MD. Surgical treatment of paravalvular abscess: long-term results. Eur J Cardiothorac Surg. 2007 Jan;31(1):43-8.
70. Perrotta S, Lentini S. (2010). In patients with severe active aortic valve endocarditis, is a stentless valve as good as the homograft? Interact. Cardiovasc. Thorac. Surg., Vol.11, No.3, pp. 309-313, ISSN 1569-9293.
71. Wilbring M, Tugtekin SM, Alexiou K, Matschke K, Kappert U. Composite aortic root replacement for complex prosthetic valve endocarditis: initial clinical results and long-term follow-up of high-risk patients. Ann Thorac Surg. 2012 Dec;94(6):1967-74.
72. Hagl C, Galla JD, Lansman SL, Fink D, Bodian CA, Spielvogel D, Griepp RB. Replacing the ascending aorta and aortic valve for acute prosthetic valve endocarditis: is using prosthetic material contraindicated? Ann Thorac Surg. 2002 Nov;74(5):S1781-5; discussion S1792-9.
73. Leyh RG, Knobloch K, Hagl C, Ruhparwar A, Fischer S, Kofidis T, Haverich A. Replacement of the aortic root for acute prosthetic valve endocarditis: prosthetic composite versus aortic allograft root replacement. J Thorac Cardiovasc Surg. 2004; 127(5): 1416-20.
74. Joyce F, Tingleff J, Pettersson G. The Ross operation: results of early experience including treatment for endocarditis. Eur J Cardiothorac Surg. 1995;9(7):384-91; discussion 391-2.
75. Pettersson G, Tingleff J, Joyce FS. Treatment of aortic valve endocarditis with the Ross operation. Eur J Cardiothorac Surg. 1998 Jun;13(6):678-84.
76. Prat A, Saez de Ibarra JI, Vincentelli A, Decoene C, Fabre OH, Jegou B, Savoye C. Ross operation for active culture-positive aortic valve endocarditis with extensive paravalvular involvement. Ann Thorac Surg. 2001 Nov;72(5):1492-5; discussion 1495-6.
77. Schmidtke C, Dahmen G, Sievers HH. Subcoronary Ross procedure in patients with active endocarditis. Ann Thorac Surg. 2007 Jan;83(1):36-9.
78. Wang A, Pappas P, Anstrom KJ, Abrutyn E, Fowler VG Jr, Hoen B, Miro JM, Corey GR, Olaison L, Stafford JA, Mestres CA, Cabell CH; International Collaboration on Endocarditis Investigators. The use and effect of surgical therapy for prosthetic valve infective endocarditis: a propensity analysis of a multicenter, international cohort. Am Heart J. 2005 Nov;150(5):1086-91.

79. Rekik S, Trabelsi I, Maaloul I, Hentati M, Hammami A, Frikha I, Ben Jemaa M, Kammoun S. Short- and long-term outcomes of surgery for active infective endocarditis: a Tunisian experience. Interact Cardiovasc Thorac Surg. 2009 Aug;9(2):241-5.
80. Musci M, Hübler M, Amiri A, Stein J, Kosky S, Meyer R, Weng Y, Hetzer R. Surgical treatment for active infective prosthetic valve endocarditis: 22-year single-centre experience. Eur J Cardiothorac Surg. 2010 Nov;38(5):528-38.
81. Habib G, Thuny F, Avierinos JF (2008) Prosthetic valve endocarditis: current approach and therapeutic options. Prog Cardiovasc Dis 50:274-281.
82. Chan KL (2002) Early clinical course and long-term outcome of patients with infective endocarditis complicated by perivalvular abscess. CMAJ 167:19-24.
83. Zoghbi WA, Chambers JB, Dumesnil JG et al. (2009) Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves. J Am Soc Echocardiogr 22:975-1014, quiz 1082-1014.
84. Birmingham GD, Rahko PS, Ballantyne F 3rd (1992) Improved detection of infective endocarditis with transesophageal echocardiography. Am Heart J 123:774-781.
85. Moreillon P, Que YA. Infective endocarditis. Lancet 2004;363: 139-49.
86. Alexiou C, Langley SM, Stafford H, Lowes JA, Livesey SA, Monro JL. Surgery for active culture-positive endocarditis: determinants of early and late outcome. Ann Thorac Surg 2000;69:1448-54.
87. Tornos P. Management of prosthetic valve endocarditis: a clinical challenge. Heart 2003;89:245-6.
88. Tugtekin S, Matschke K, Daubner D, et al. Prosthetic valve endocarditis: importance of surgical treatment. Thorac Cardiovasc Surg 2007;55:94-8.
89. Vogt PR, Turina MI. Management of infected aortic grafts: development of less invasive surgery using cryopreserved homografts. Ann Thorac Surg. 1999 Jun;67(6):1986-9; discussion 1997-8.
90. Niwaya K, Knott-Craig CJ, Santangelo K, Lane MM, Chandrasekaran K, Elkins RC. Advantage of autograft and homograft valve replacement for complex aortic valve endocarditis. Ann Thorac Surg. 1999 Jun;67(6):1603-8.
91. Koskas F, Goëau-Brissonnière O, Nicolas MH, Bacourt F, Kieffer E. Arteries from human beings are less infectible by Staphylococcus aureus than polytetrafluoroethylene in an aortic dog model. J Vasc Surg. 1996 Mar;23(3):472-6.
92. Prat A, Grandmougin D, Decoene C, Godart FR, Saez de Ibarra JI, Savoye C, Goffin Y, Stankowiak C. Aortic root replacement with a pulmonary autograft in young adults: medium-term results in 70 patients. Ann Thorac Surg. 1998 Dec;66(6 Suppl):S148-52.

93. David TE, Gavra G, Feindel CM, Regesta T, Armstrong S, Maganti MD. Surgical treatment of active infective endocarditis: a continued challenge. J Thorac Cardiovasc Surg 2007; 133:144-9.
94. Valencia Nuñez DM, Merino Cejas C, Alados Arboledas P, Muñoz Carvajal I. Heart transplantation in a patient with recurrent early extensive endocarditis. Interact Cardiovasc Thorac Surg. 2013 Aug;17(2):423-5.
95. Musci M, Hübler M, Amiri A, Stein J, Kosky S, Weng Y, Pasic M, Hetzer R. Repair for active infective atrioventricular valve endocarditis: 23-year single center experience. Clin Res Cardiol. 2011 Nov;100(11):993-1002.
96. de Kerchove L, Vanoverschelde JL, Poncelet A, Glineur D, Rubay J, Zech F, Noirhomme P, El Khoury G (2007) Reconstructive surgery in active mitral valve endocarditis: feasibility, safety and durability. Eur J Cardiothorac Surg 31:592-599
97. Gammie JS, O'Brien SM, Griffith BP, Peterson ED. (2005) Surgical treatment of mitral valve endocarditis in North America. Ann Thorac Surg 80:2199-2204.
98. Iung B, Rousseau-Paziaud J, Cormier B, Garbarz E, Fondard O, Brochet E, Acar C, Couetil JP, Hvass U, Vahanian A (2004) Contemporary results of mitral valve repair for infective endocarditis. J Am Coll Cardiol 43:386-392.
99. Podesser BK, Rodler S, Hahn R, Eigenbauer E, Vodrazka M, Moritz A, Laufer G, Simon P, Wolner E (2000) Mid-term follow up of mitral valve reconstruction due to active infective endocarditis. J Heart Valve Dis 9:335-340.
100. David TE, Feindel CM, Armstrong S, Sun Z. Reconstruction of the mitral anulus. A ten-year experience. J Thorac Cardiovasc Surg. 1995 Nov;110(5):1323-32.
101. Musci M, Weng Y, Hübler M, et al. Homograft aortic root replacement in native or prosthetic active infective endocarditis: twenty-year single-center experience. J Thorac Cardiovasc Surg 2010;139:665-73.
102. Glazier JJ, Verwilghen J, Donaldson RM, Ross DN. Treatment of complicated prosthetic aortic valve endocarditis with annular abscess formation by homograft aortic root replacement. J Am Coll Cardiol. 1991 Apr;17(5):1177-82.
103. Avierinos JF, Thuny F, Chalvignac V, Giorgi R, Tafanelli L, Casalta JP, Raoult D, Mesana T, Collart F, Metras D, Habib G, Riberi A. Surgical treatment of active aortic endocarditis: homografts are not the cornerstone of outcome. Ann Thorac Surg. 2007 Dec;84(6):1935-42.
104. Klieverik LM, Yacoub MH, Edwards S, Bekkers JA, Roos-Hesselink JW, Kappetein AP, Takkenberg JJ, Bogers AJ. Surgical treatment of active native aortic valve endocarditis with allografts and mechanical prostheses. Ann Thorac Surg. 2009 Dec;88(6):1814-21.
105. El-Hamamsy I, Clark L, Stevens LM, et al. Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial. J Am Coll Cardiol 2010;55:368-76.
106. O'Brien MF, Finney RS, Stafford EG, Gardner MA, Pohlner PG, Tesar PJ, Cochrane AD, Gall KL, Smith SE. Root replacement for all allograft aortic valves: preferred technique or too radical? Ann Thorac Surg. 1995 Aug;60(2 Suppl):S87-91.
107. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2015 Sep 1. pii: S0140-6736(15)00067-7.
108. E Durante-Mangoni, S Bradley, C Selton-Suty, the International Collaboration on Endocarditis Prospective Cohort Study Group, et al. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study Arch Intern Med, 168 (2008), pp. 2095-2103.
109. Lopez J, Revilla A, Vilacosta I, et al. Definition, clinical profile, microbiological spectrum, and prognostic factors of early-onset prosthetic valve endocarditis. Eur Heart J 2007; 28: 760-65.
110. Alonso-Valle H, Farinas-Alvarez C, Garcia-Palomo JD, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. J Thorac Cardiovasc Surg 2010; 139: 887-93.
111. Novick, R. P. et al. Synthesis of staphylococcal virulence factors is controlled by a regulatory RNA molecule. EMBO J. 12, 3967-3975 (1993).
112. Feuchtner GM, Stolzmann P, Dichtl W, Schertler T, Bonatti J, Scheffel H, Mueller S, Plass A, Mueller L, Bartel T, Wolf F, Alkadhi H. Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. J Am Coll Cardiol 2009;53:436-444.
113. Gahide G, Bommart S, Demaria R, Sportouch C, Dambia H, Albat B, Vernhet-Kovacsik H. Preoperative evaluation in aortic endocarditis: findings on cardiac CT. AJR Am J Roentgenol. 2010 Mar;194(3):574-8.
114. Falcoz PE, Chocron S, Mercier M, Puyraveau M, Etievent JP. Comparison of the Nottingham Health Profile and the 36-item health survey questionnaires in cardiac surgery. Ann Thorac Surg 2002;73:1222-8.
115. Nötzold A, Hüppe M, Schmidtke C, Blömer P, Uhlig T, Sievers HH. Quality of life in aortic valve replacement: pulmonary autografts versus mechanical prostheses. J Am Coll Cardiol 2001;37:1963-6.
116. Falcoz PE, Chocron S, Stoica L, et al. Open heart surgery: one-year self-assessment of quality of life and functional outcome. Ann Thorac Surg 2003;76:1598-604.
117. Perchinsky M, Henderson C, Jamieson WR, et al. Quality of life in patients with bioprostheses and mechanical prostheses: evaluation of cohorts of patients aged 51 to 65 years at implantation. Circulation 1998;98(19 suppl):II81-6.
118. Vicchio CM, Della Corte A, De Santo LS, et al. Prosthesis patient mismatch in the elderly: survival, ventricular mass regression, and quality of life. Ann Thorac Surg 2008;86:1791-7.

119. Que YA, Moreillon P. Staphylococcus aureus (including Staphylococcal toxic shock). In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed. Philapelphia: Elsevier/Saunders; 2015. p. 2237-71.
120. Verkaik NJ, van Wamel WJ, van Belkum A. Immunotherapeutic approaches against Staphylococcus aureus. Immunotherapy 2011;3:1063-73.
121. Jansen KU, Girgenti DQ, Scully IL, Anderson AS. Vaccine review: Staphylococcus aureus vaccines: problems and prospects. Vaccine 2013;31:2723-30.
122. Proctor RA. Challenges for a universal Staphylococcus aureus vaccine. Clin Infect Dis 2012;54:1179-86.
123. Veloso TR, Mancini S, Giddey M, Vouillamoz J, Que YA, Moreillon P, Entenza JM. Vaccination against Staphylococcus aureus experimental endocarditis using recombinant Lactococcus lactis expressing ClfA or FnbpA. Vaccine. 2015 Jul 9;33(30):3512-7.
124. Monaghan MJ. Role of real time 3D echocardiography in evaluating the left ventricle. Heart. 2006 Jan;92(1):131-6.
125. Mollet NR, Cademartiri F, Nieman K et al. Multislice spiral computed tomography coronary angiography in patients with stable angina pectoris. J Am Coll Cardiol 2004; 43: 2265-70.
126. Yamamuro M, Tadamura E, Kubo S et al. Cardiac functional analysis with multi-detector row CT and segmental reconstruction algorithm: comparison with echocardiography, SPECT, and MR imaging. Radiology 2005; 234: 381-90.
127. Ryan R, Abbara S, Colen RR, Arnous S, Quinn M, Cury RC, Dodd JD. Cardiac valve disease: spectrum of findings on cardiac 64-MDCT. AJR Am J Roentgenol. 2008 May;190(5):W294-303.
128. Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier L, Casalta JP, Gouriet F, Riberi A, Avierinos JF, Collart F, Mundler O, Raoult D, Thuny F (2013) Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol 61 (23):2374-2382.
129. Ricciardi A, Sordillo P, Ceccarelli L, Maffongelli G, Calisti G, Di Pietro B, Caracciolo CR, Schillaci O, Pellegrino A, Chiariello L, Andreoni M, Sarmati L (2014) 18-Fluoro-2-deoxyglucose positron emission tomography-computed tomography: an additional tool in the diagnosis of prosthetic valve endocarditis. Int J Infect Dis. doi:10.1016/j.ijid.2014.04.028.
130. Rouzet F, Chequer R, Benali K, Lepage L, Ghodbane W, Duval X, Iung B, Vahanian A, Le Guludec D, Hyafil F (2014) Respective Performance of 18F-FDG PET and Radiolabeled Leukocyte Scintigraphy for the Diagnosis of Prosthetic Valve Endocarditis. J Nucl Med 55 (12):1980-1985.

Appendix I–IV