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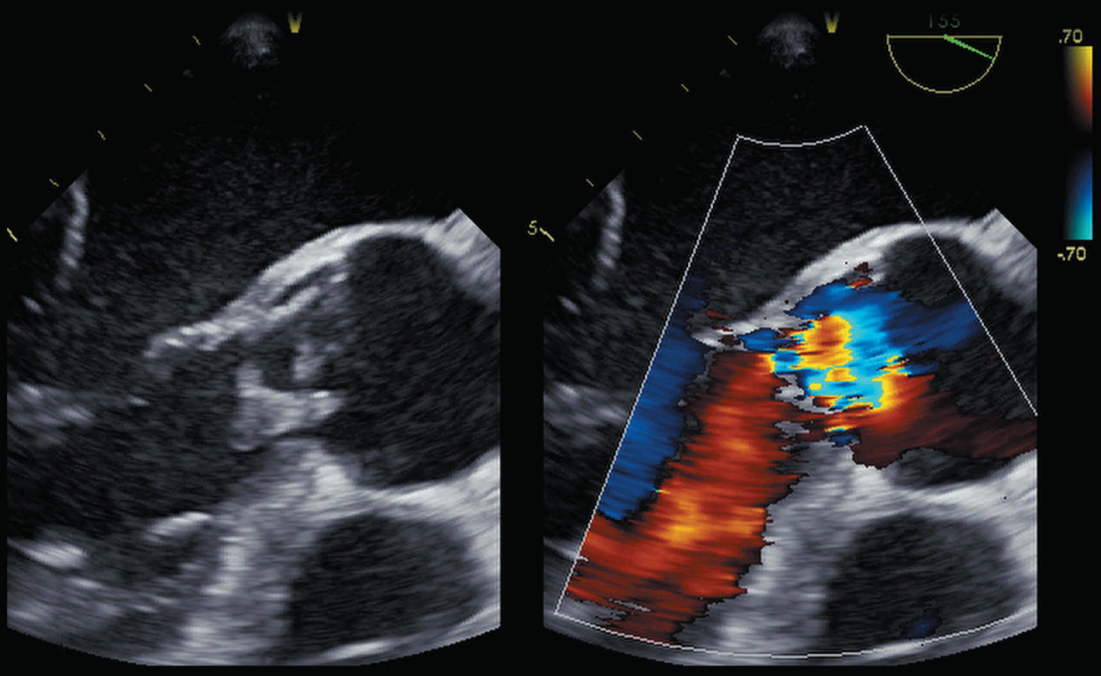

INFECTIVE ENDOCARDITIS IN FINLAND

Elina Ahtela

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1680 | MEDICA – ODONTOLOGICA | TURKU 2022

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To my family

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ELINA AHTELA: Infective Endocarditis in Finland
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ABSTRACT

Infective endocarditis (IE) is a severe disease associated with several complications, and despite advanced treatment methods, mortality remains high. Population-based epidemiology and trends of IE are, however, insufficiently understood, and knowledge on the long-term mortality of IE patients is scarce. Furthermore, more data evaluating the characteristics of the different microbiological etiologies and the factors associated with embolic events in IE patients are needed. In this thesis, the sex- and age-specific epidemiology and temporal trends of IE were investigated in a population-based setting in Finland. Moreover, the population-based epidemiology of fatal IE was studied. Additionally, the characteristics of the different microbiological etiologies and the factors associated with embolic events were assessed in IE patients in a tertiary care hospital.

The incidence of IE increased in young adults but not in the older population. Men, particularly at middle-age, were at a higher risk of IE than women. In men, the length of stay (LOS) in hospital due to IE was longer than in women, and LOS remained stable over time. Short-term all-cause mortality was similar in both sexes, whereas five- and ten-year mortality was higher in women. Mortality did not change over the years. Men were at a two-fold risk of fatal IE compared to women. The incidence of fatal IE increased progressively with age from 50 years of age onwards, but the proportion of IE-related deaths of all deaths was the highest in the youngest population. The incidence of fatal IE remained stable over time. Enterococcal IE was often associated with a previous healthcare procedure or hospital admission and heart failure. Furthermore, *Staphylococcus aureus* etiology and IE of the multiple valves were related to a higher rate of all embolic events but not cerebral embolisms in IE patients. Detected vegetation was associated with the occurrence of both all embolic events and cerebral embolisms.

This thesis provides novel information on the epidemiology and clinical characteristics, especially regarding the etiology and embolic events, of IE in Finland.

KEYWORDS: infective endocarditis, epidemiology, incidence, mortality, length of stay, embolic event, cerebral embolism

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TIIVISTELMÄ

Infektiivinen endokardiitti on vakava, useita komplikaatioita aiheuttava sairaus, ja huolimatta kehittyneistä hoitomenetelmistä kuolleisuus siihen on pysynyt korkeana. Väestöpohjaisista epidemiologisista tutkimuksista saatua tietoa endokardiitista on rajatusti. Pitkän aikavälin kuolleisuudesta on vain vähän aiempaa tietoa. Lisää tietoa tarvitaan myös eri mikrobien aiheuttamista erilaisista taudinkuvista ja embolioiden esiintyvyyteen yhteydessä olevista tekijöistä. Tämän väitöskirjan väestöpohjaisessa tutkimuksessa selvitettiin sukupuoli- ja ikäspesifisiä eroja ja muutoksia endokardiitin epidemiologiassa Suomessa. Lisäksi tutkittiin kuolemaan johtaneen endokardiitin epidemiologiaa. Eri mikrobietiologioiden erityispiirteitä ja embolioihin yhteydessä olevia tekijöitä selvitettiin yliopistollisessa keskussairaalassa hoidetuilla endokardiittipotilailla.

Tutkimuksessa todettiin, että endokardiitin ilmaantuvuus kasvoi nuorilla aikuisilla mutta ei vanhemmalla väestöllä. Miehillä, erityisesti keski-iässä, oli suurempi riski sairastua endokardiittiin naisiin verrattuna. Endokardiittihoidon kesto sairaalassa oli miehillä pidempi kuin naisilla, eikä hoidon kestossa tapahtunut muutosta ajan kuluessa. Lyhyen aikavälin kokonaiskuolleisuudessa ei ollut eroa sukupuolten välillä, mutta viiden ja kymmenen vuoden kuolleisuus oli naisilla korkeampi. Miehillä oli kaksinkertainen riski kuolemaan johtaneeseen endokardiittiin naisiin verrattuna. Kuolemaan johtaneen endokardiitin ilmaantuvuus kasvoi 50 ikävuodesta eteenpäin, mutta endokardiittiin liittyvien kuolemien osuus kaikista kuolemista oli suurin nuorimmassa ikäryhmässä. Kuolleisuudessa tai kuolemaan johtaneen endokardiitin ilmaantuvuudessa ei tapahtunut muutosta ajan kuluessa. Enterokokin aiheuttaman endokardiitin havaittiin olevan usein yhteydessä aiempaan terveydenhuollon toimenpiteeseen tai sairaalahoitoon sekä sydämen vajaatoimintaan. Lisäksi *Staphylococcus aureuksen* aiheuttama endokardiitti sekä useamman kuin yhden läpän endokardiitti olivat yhteydessä kaikkien embolioiden mutta eivät erikseen tutkittujen aivoembolioiden esiintyvyyteen. Todettu vegetaatio oli yhteydessä sekä kaikkien embolioiden että aivoembolioiden esiintyvyyteen.

Tämä väitöskirja tarjoaa uutta tietoa endokardiitin epidemiologiasta sekä kliinisistä erityispiirteistä Suomessa.

AVAINSANAT: endokardiitti, epidemiologia, ilmaantuvuus, kuolleisuus, hoidon kesto, embolia, aivoembolia

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Abbreviations

AHA	American Heart Association
AIDS	Acquired immunodeficiency syndrome
APTT	Activated partial thromboplastin time
BCNIE	Blood culture-negative infective endocarditis
BNP	B-type natriuretic peptide
CI	Confidence interval
CCI	Charlson comorbidity index
CHD	Congenital heart disease
CoNS	Coagulase-negative staphylococci
CRHC	Care Register for Health Care
CRP	C-reactive protein
CT	Computed tomography
ESC	European Society of Cardiology
^{18}F-FDG	Fluorodeoxyglucose F 18
HACEK	*Haemophilus* spp., *Aggregatibacter* spp. (previously *Actinobacillus*), *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp.
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICD-10	International Classification of Diseases, Tenth Revision
IE	Infective endocarditis
IQR	Interquartile range
IRR	Incidence rate ratio
IVDU	Intravenous drug user or intravenous drug use
LOS	Length of stay
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
NICE	National Institute for Health and Clinical Excellence
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
NVIE	Native valve infective endocarditis
OR	Odds ratio

PCR	Polymerase chain reaction
PCT	Procalcitonin
PET/CT	Positron emission tomography with computed tomography
PVIE	Prosthetic valve infective endocarditis
RR	Risk ratio
SD	Standard deviation
SPECT/CT	Single photon emission computed tomography
spp.	Species
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
UK	United Kingdom
US	United States
WBC	White blood cell count
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Ahtela E., Oksi J., Porela P., Ekström T., Rautava P., Kytö V. Trends in occurrence and 30-day mortality of infective endocarditis in adults: population-based registry study in Finland. *BMJ Open*, 2019; 9(4): e026811.

II Ahtela E., Oksi J., Sipilä J., Rautava P., Kytö V. Occurrence of fatal infective endocarditis: a population-based study in Finland. *BMC Infectious Diseases*, 2019; 19(1): 987.

III Ahtela E., Oksi J., Vahlberg T., Sipilä J., Rautava P., Kytö V. Short- and long-term outcomes of infective endocarditis admission in adults: A population-based registry study in Finland. *PLOS ONE*, 2021; 16(7): e0254553.

IV Ahtela E., Kytö V., Vahlberg T., Hohenthal U., Ekström T., Porela P., Oksi J. Infective endocarditis in a Finnish tertiary care hospital: from etiology to embolic events. Manuscript.

1 Introduction

Infective endocarditis (IE) is an infection of the endocardium of the heart, mainly the valves. It is a severe disease, and despite advances in the treatment, the mortality of IE remains high. The epidemiologic profile of IE is changing due to longer life expectancy, developments in diagnostic methods, and changes in risk factors. In addition, exposure to healthcare procedures is increasing, and a notable proportion of IE today is healthcare-associated (Cresti et al., 2017; G. Habib et al., 2019; Halavaara et al., 2020; Holland et al., 2020; Kiriyama et al., 2020; Selton-Suty et al., 2012; Sy & Kritharides, 2010). The number of cardiac operations conducted with implanted prosthetic material is growing, and the incidence and proportion of IE related to prosthetic material is increasing (Carrasco et al., 2016; Cresti et al., 2017; Greenspon et al., 2011; Keller et al., 2017; Kurtz et al., 2010; Toyoda et al., 2017). Furthermore, the improved survival of patients with predisposing factors to IE, such as congenital heart disease or prosthetic heart valves, may also have an impact on IE incidence.

The incidence of IE has been described as 3–8 cases per 100,000 person-years (Duval et al., 2012; Jordal et al., 2018; Ternhag et al., 2013; Thornhill, Jones, et al., 2018; Toyoda et al., 2017). European studies have found increasing incidence (Cresti et al., 2017; Erichsen et al., 2016; Jensen et al., 2021; Jordal et al., 2018; Ternhag et al., 2013; Van Den Brink et al., 2017), whereas studies in the United States (US) have found both increasing (Bor et al., 2013; Pant et al., 2015) and stable (Bikdeli et al., 2013; Toyoda et al., 2017) incidence. Short-term mortality (i.e. within 30 days of or during a hospital stay) has been reported as 6–24% (Cresti et al., 2017; Erdem et al., 2019; G. Habib et al., 2019; Jordal et al., 2018; Keller et al., 2017; Morita et al., 2019; Sunder et al., 2019; Sy & Kritharides, 2010; Ternhag et al., 2013) and longer-term (i.e. within six months–one year of the diagnosis) mortality as 18–37% (Cresti et al., 2017; Fedeli et al., 2011; Hill et al., 2007; Jordal et al., 2018; Sunder et al., 2019; Sy & Kritharides, 2010; Toyoda et al., 2017) after IE diagnosis. Mortality has not decreased in recent years (Bor et al., 2013; Cresti et al., 2017; Fedeli et al., 2011; Jordal et al., 2018; Keller et al., 2017; Ternhag et al., 2013), the reason for which remains unclear.

Today, the most common pathogen causing IE is *Staphylococcus aureus* accounting for up to 30% of all IE cases (Cresti et al., 2017; Erdem et al., 2019; G. Habib et al., 2019; Jordal et al., 2018; Selton-Suty et al., 2012). *Staphylococcus aureus* has also been found to be a major causative agent in healthcare-associated IE (Fernández-Hidalgo et al., 2008; Kiriyama et al., 2020; Selton-Suty et al., 2012) and in a currently more prevalent group of IE patients, intravenous drug users (IVDUs) (Halavaara et al., 2020; Hilbig & Cheng, 2020; Lawrence et al., 2021; Murdoch et al., 2009; Thalme et al., 2007). However, especially in cases of healthcare-associated IE, enterococci have emerged as significant causing pathogens (Chirouze et al., 2013; Fernández-Hidalgo et al., 2008; Halavaara et al., 2020; Leone et al., 2012; Pericàs et al., 2020; Sy & Kritharides, 2010).

Common complications of IE include heart failure, which is found in up to 55% of IE cases (Cresti et al., 2017; Heiro et al., 2006; Holland et al., 2020; Kiefer et al., 2013), uncontrolled infection with persisting infection and perivalvular complications, and embolic events (G. Habib et al., 2015). Embolic events occur in approximately 34–55% of IE patients (Di Salvo et al., 2001; Erdem et al., 2019; Holland et al., 2020; Rizzi et al., 2014; Selton-Suty et al., 2012; Thuny et al., 2005). *Staphylococcus aureus* etiology has been found to be associated with embolic events (Fabri et al., 2006; G. Habib et al., 2019; Miro et al., 2005; Rizzi et al., 2014; Tascini et al., 2020; Thuny et al., 2005), but the existing data on the association between an affected valve and embolic events are contradictory.

Population-based sex- and age-specific epidemiology and trends of IE are insufficiently understood, and the knowledge on long-term mortality of more than one year is scarce. Furthermore, more data evaluating the characteristics of the different microbiological etiologies of IE and the factors associated with embolic events are needed.

The main objective of this thesis was to examine the age and sex differences, temporal trends, and factors associated with the incidence, short-term, one-, five-, and ten-year mortality of IE, and length of stay (LOS) in hospital due to IE. Sex- and age-specific differences and the temporal trends in the occurrence of fatal IE were also investigated. Moreover, the current clinical profile of IE, the characteristics of the different microbiological etiologies, and the factors associated with embolic events in IE patients were evaluated.

2 Review of the Literature

2.1 Definition and different types of IE

Infective endocarditis is defined as an infection of the endocardium of the heart, usually the valves. The endocardium consists of endothelium and connective tissue, and the normal endothelium of the heart valves is resistant to pathogens. However, any endothelial lesion initiates a healing reaction in the tissue resulting in ideal circumstances for pathogen adherence. Valve colonization may also occur in an intact endothelium due to particularly virulent, invasive pathogens. (Moreillon et al., 2002). Infective endocarditis usually affects the valves of the left side of the heart, the mitral and aortic valves (Cresti et al., 2017; Erdem et al., 2019; G. Habib et al., 2019; Murdoch et al., 2009). This is believed to be due to the higher pressure in the left side of the heart and the consequently turbulent flow through the left-sided valves, causing endothelial damage that predisposes to IE (Sullam et al., 1985). Furthermore, the higher oxygen content in the circulation of the left side may offer a more favorable environment for bacteria to grow. Finally, acquired valve abnormalities, which may predispose to IE, occur more frequently in the left side of the heart (Iung et al., 2003). Some previous studies have found that the aortic valve is more often affected than the mitral valve (G. Habib et al., 2019; Halavaara et al., 2020; Heiro et al., 2006; Hubert et al., 2013; Thuny et al., 2005), whereas others have found that the mitral valve is more commonly affected (Hill et al., 2007; Holland et al., 2020; Murdoch et al., 2009; Selton-Suty et al., 2012).

The valves of the right side of the heart, usually the tricuspid valve and rarely the pulmonary valve, are infected in 12–15% of IE cases (Cresti et al., 2017; Erdem et al., 2019; G. Habib et al., 2019; Holland et al., 2020; Jordal et al., 2018). Right-sided IE is often associated with intravenous drug use (IVDU) (Colville et al., 2016; Halavaara et al., 2020; Holland et al., 2020; Leahey et al., 2019). It has been suggested that the particles in the injected material may damage the valves, particularly those in the right side of the heart, as the injected particles first encounter with the tricuspid valve. In addition, drug-induced pulmonary hypertension can cause turbulent blood flow and consequently damage the valves. A previously damaged valve is more susceptible to IE. (Frontera & Gradon, 2000). Furthermore, right-sided IE can occur if intracardiac devices, such as pacemakers and implantable

automatic defibrillators, become infected, as the leads of these devices are situated in the right side of the heart (Carrasco et al., 2016; Cresti et al., 2017; Urien et al., 2021).

Prosthetic valve IE (PVIE) accounts for 12–30% of all IE cases (Erdem et al., 2019; G. Habib et al., 2019; Holland et al., 2020; Sunder et al., 2019; Ternhag et al., 2013). Previous studies have found IE to be equally common in mechanical and biological valves (Brown et al., 2008; Kulik et al., 2006; Stassano et al., 2009) or to more frequently affect biological valves (Brennan et al., 2013; Kytö et al., 2020). A recent meta-analysis of 12 studies published in 1991–2017 found that patients with bioprosthetic valves were at a higher risk of IE than patients with mechanical valves (Anantha-Narayanan et al., 2020). Early PVIE occurs within one year of the prosthetic valve being implanted and late PVIE more than one year after the procedure, as the causative pathogens differ notably before and after this time point (G. Habib et al., 2015; López et al., 2007). In cases of PVIE and when IE is associated with intracardiac devices, diagnosis and treatment are particularly challenging (G. Habib et al., 2015). Most studies have found that around 30% of IE cases are healthcare-associated (Cresti et al., 2017; Fernández-Hidalgo et al., 2008; G. Habib et al., 2019; Halavaara et al., 2020; Holland et al., 2020; Kiriyama et al., 2020; Selton-Suty et al., 2012; Sy & Kritharides, 2010). However, one US study investigating 75,829 IE patients during 1998–2013 reported that around half of the IE cases were healthcare-associated (Toyoda et al., 2017).

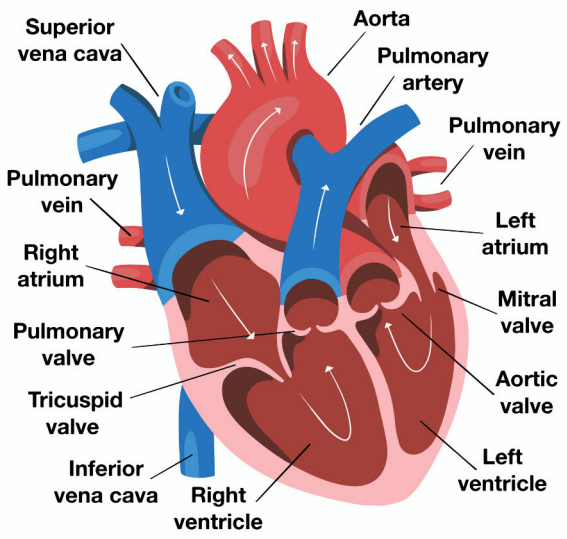

Figure 1. Normal heart anatomy including the valves. Picture by Katalin Macevics/Shutterstock.com.

2.2 Population at risk

Patients at the highest risk of IE can be divided into three groups (Table 1) (G. Habib et al., 2015). The first group consists of patients with prosthetic valves or prosthetic material used for cardiac valve repair (Lalani et al., 2013). The second group includes patients with untreated cyanotic congenital heart disease (CHD) and patients with CHD who have postoperative shunts or other prostheses (Baumgartner et al., 2010; Knirsch & Nadal, 2011). The third group consists of patients with previous IE (Chu et al., 2005).

Table 1. Patients at the highest risk of infective endocarditis (IE) (G. Habib et al., 2015).

1)	Patients with prosthetic valves or prosthetic material used for cardiac valve repair
2)	Patients with untreated cyanotic congenital heart disease (CHD) and patients with CHD who have postoperative shunts or other prostheses
3)	Patients with previous IE

2.3 Antibiotic prophylaxis for IE

Antibiotic prophylaxis for IE has undergone major changes in recent years. Initially, antibiotic prophylaxis was based on the idea that dental procedures and different operations may cause bacteremia leading to IE. However, it has now been demonstrated that repeated low-grade bacteremia occur in everyday life, such as toothbrushing (Lockhart et al., 2008), and might be associated with a higher risk of IE than a single dental procedure with transient high-grade bacteremia (Veloso et al., 2011). It has also been demonstrated that the risk of IE after a dental procedure is low (Strom et al., 1998), and consequently the impact of antibiotic prophylaxis on reducing the emergence of IE after dental procedures is also low (Duval et al., 2006). Moreover, a substantial proportion of IE cases occur in individuals with no previously known heart disease (Castillo et al., 2002; Duval et al., 2012; Olmos et al., 2014; B. J. Sun et al., 2015). Furthermore, the extensive use of antibiotics is associated with the increase in the number of antibiotic resistant bacteria (Willemsen et al., 2009). These findings have led to restrictions in prophylaxis guidelines.

2.3.1 When is antibiotic prophylaxis needed?

The prophylaxis guidelines published in 2007 (American Heart Association (AHA)) (Wilson et al., 2007), 2008 (United Kingdom (UK), The National Institute for Health and Clinical Excellence (NICE)) (Stokes et al., 2008), and 2009 (European Society of Cardiology (ESC)) (G. Habib et al., 2009) restricted significantly pre-procedural antibiotic usage for the prevention of IE. The AHA recommended prophylaxis in

dental procedures only for patients with cardiac conditions associated with the highest risk of the adverse effects of IE (Wilson et al., 2007). Furthermore, the NICE guidelines abolished all antibiotic prophylaxis (Stokes et al., 2008). According to the current ESC guidelines, which follow the 2009 ESC guidelines on antibiotic prophylaxis, prophylaxis is recommended for patients at the highest risk of IE (Table 1). Prophylaxis is not recommended for patients with, for example, a bicuspid aortic valve or mitral regurgitation. (G. Habib et al., 2015). The AHA also recommends prophylaxis for patients with cardiac transplants who develop valvulopathy, whereas the ESC does not (G. Habib et al., 2015; Wilson et al., 2007).

Prophylaxis of primarily 2 grams of amoxicillin 30–60 minutes before a procedure is recommended in dental procedures involving the manipulation of the gingival or periapical region or the perforation of the oral mucosa. When performing other operations in sites with an established infection, the antibiotic regimen should contain an agent against possible IE-causing pathogens in that particular site. Perioperative antibiotic prophylaxis should be considered when prosthetic valves or other prosthetic material is implanted in the heart. Furthermore, maintaining good oral and cutaneous hygiene is essential, especially in the highest risk groups. (G. Habib et al., 2015).

Despite the restrictions in the prophylaxis guidelines, there is evidence that excessive antibiotic prophylaxis is still applied in dental procedures. A study in the US that examined 168,420 dental visits with an antibiotic prophylaxis prescribed before the visit from 2011 to 2015 found that more than 80% of the prophylaxis was unnecessary (Suda et al., 2019). Furthermore, surveys evaluating the knowledge and use of prophylactic antibiotics for IE among dentists and dental hygienists have revealed that the knowledge of and compliance with the prophylaxis guidelines is heterogenous (Cloitre et al., 2018; Jain et al., 2015).

2.3.2 Effects of restrictions to antibiotic prophylaxis

Studies have been conducted on the possible effects of the restricted prophylaxis policy. After the guideline changes, the increased occurrence of IE has been found in the UK (Dayer et al., 2015), the Netherlands (Van Den Brink et al., 2017), and Germany (Keller et al., 2017). A recent study in the UK, however, found no evidence that the restricted prophylaxis policy would have affected the incidence of IE (T. P. Quan et al., 2020). A study in the US, published in 2018, found a decrease in the number of prescriptions for prophylactic antibiotics and a concomitant increase in IE incidence in a high-risk population after the guideline changes (Thornhill, Gibson, et al., 2018). Previous North American studies, however, have found no association between the new IE prophylaxis guidelines and hospital admissions due to IE (Mackie et al., 2016; Toyoda et al., 2017). Accordingly, a study conducted in Canada

reported that antibiotic prophylaxis for IE decreased significantly in the moderate-risk group with only a minor change in the high-risk group after the guideline changes by the AHA in 2007 (Garg et al., 2019). Hospital admissions related to IE increased since 2010, however, in both the moderate- and high-risk groups, indicating that the increase was not likely due to antibiotic prophylaxis changes. A recent study in Sweden found no increase in the incidence of IE caused by viridans group streptococci or *S. aureus* after the recommended cessation of antibiotic prophylaxis for IE in dentistry in Sweden in 2012 (Vähäsarja et al., 2020). However, it should be noted that these studies described the incidence of IE before and after the guideline changes, and the actual causality could not be proven.

2.4 Diagnosis of IE

2.4.1 Clinical findings

The substantial variation in the clinical profile of IE makes it a diagnostic challenge. Infective endocarditis can manifest as a rapidly progressing fulminant infection as well as a subacute or chronic disease with non-specific symptoms. Up to 90% of IE patients present with fever (Cecchi et al., 2015; Duval et al., 2012; G. Habib et al., 2019; Heiro et al., 2006). A new or worsening heart murmur is common and has been found in more than 50% of IE cases (Cecchi et al., 2015; Heiro et al., 2006). Emboli occur in 34–55% of IE patients and are found in, for example, the brain, lungs, or spleen (Di Salvo et al., 2001; Erdem et al., 2019; Holland et al., 2020; Rizzi et al., 2014; Selton-Suty et al., 2012; Thuny et al., 2005). Patients may also have manifestations on the skin, such as Osler's nodes, Splinter hemorrhages, or Janeway lesions, but these are no longer common (Cecchi et al., 2015; G. Habib et al., 2019; Murdoch et al., 2009). Systemic symptoms, such as fatigue and weight loss, are possible.

2.4.2 Imaging

2.4.2.1 Echocardiography

Echocardiography, either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), is the main imaging technique for diagnosing IE and plays a major role in monitoring IE patients. Echocardiography should be performed without delay when IE is suspected. Transesophageal echocardiography must be performed if TTE yields no findings and if a suspicion of IE is substantial, if the quality of TTE is suboptimal, or if PVIE or IE affecting intracardiac device is

suspected. Furthermore, TEE should be considered to rule out paravalvular complications if IE is found in TTE. (G. Habib et al., 2015). Transthoracic echocardiography has a sensitivity of 70% and 50% to detect vegetations on native and prosthetic valves, respectively, whereas TEE's sensitivity is 96% and 92%, respectively (G. Habib et al., 2015). Detecting vegetations may be challenging in the case of pre-existing valvular disease, prosthetic valves, or an IE affecting intracardiac device (G. Habib et al., 2010).

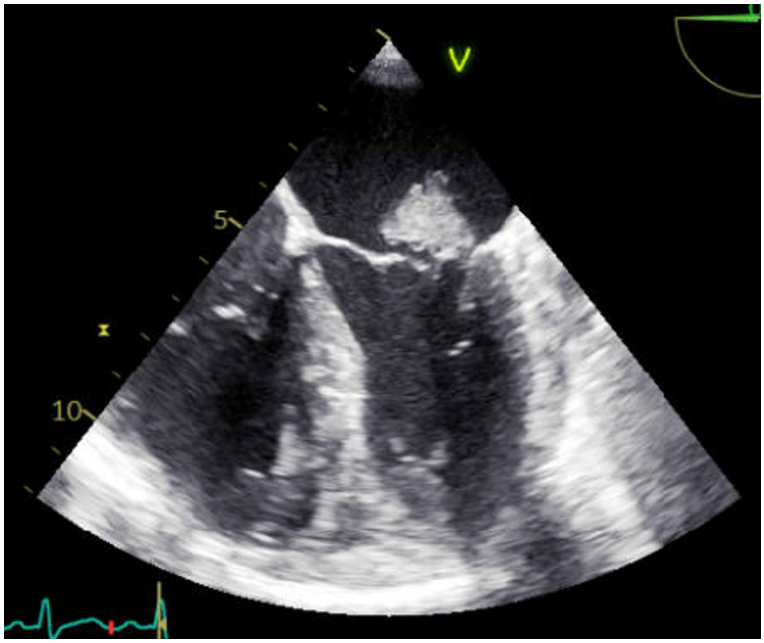

Figure 2. Echocardiography image of a vegetation on the mitral valve. Photo by Sanna Laurila and published with her permission.

2.4.2.2 Nuclear imaging

Positron emission tomography with fluorodeoxyglucose F 18 integrated with computed tomography (^{18}F-FDG PET/CT) can be used as a supplementary imaging method for suspected IE and diagnostic difficulties, especially in patients with a prosthetic valve or intracardiac device. The use of ^{18}F-FDG PET/CT is based on ^{18}F-FDG being actively incorporated into activated leukocytes, macrophages, and CD4-positive T cells that are present in the infected area (Ishimori et al., 2002; Kubota et al., 1992). Particularly in the diagnosis of PVIE or IE affecting intracardiac device, ^{18}F-FDG PET/CT can play an important role (de Camargo et al., 2020; Granados et al., 2016; Saby et al., 2013; Sarrazin et al., 2012; Swart et al., 2018). Some studies suggest that ^{18}F-FDG PET/CT might be useful for detecting infectious emboli or

other extra-cardiac infectious findings in IE patients (Holle et al., 2020; Kestler et al., 2014; Orvin et al., 2015). Furthermore, San et al. found in their recently published study that positive findings of ^{18}F-FDG PET/CT in PVIE patients predict major cardiac and new embolic events within the first year of IE (San et al., 2019). In their study, findings consistent with IE were observed in ^{18}F-FDG PET/CT in 83% of the patients with definite PVIE. Moreover, a recent study involving 70 PVIE and 70 native valve IE (NVIE) patients found that ^{18}F-FDG PET/CT modified the classification and/or care of IE in 40% of the patients (Duval et al., 2021).

A recent meta-analysis of 13 studies in different countries reported the sensitivity and specificity of PET/CT for diagnosis of IE to be 76.8% and 77.9%, respectively (Mahmood et al., 2019). Sensitivity for PVIE was higher, 80.5%, whereas specificity was 73.1%. Additional extra-cardiac infectious foci were detected in 17% of patients in whole body PET/CT. A Finnish study investigating patients with suspected PVIE and NVIE with ^{18}F-FDG PET/CT found strong ^{18}F-FDG uptake in the affected valve area in all six cases of definite PVIE according to the modified Duke criteria, in three of five possible PVIE cases, and in two of five rejected cases (Salomäki et al., 2017). However, in four PVIE cases, time since the prosthetic valve operation was less than three months, which is the time limit of the imaging criterion of the ESC guidelines discussed later (G. Habib et al., 2015). Contrary to PVIE, only one of seven NVIE patients had ^{18}F-FDG uptake in the area of the valve. Embolic infectious foci were found in 58% of the definite IE cases.

Radiolabeled leukocyte single photon emission computed tomography (SPECT/CT) is one option for detecting IE and metastatic infectious foci (Erba et al., 2012; Rouzet et al., 2014), but it is currently rarely used in Finland because other imaging methods, such as PET, are more frequently used.

2.4.2.3 Computed tomography

Multislice computed tomography (CT) of the heart has been shown to be comparable to TEE or surgical findings for detecting valvular abnormalities (Fagman et al., 2012; Feuchtner et al., 2009). However, the advantage of TEE over CT is that in can visualize blood flow. An important role of cardiac CT is the non-invasive assessment of the coronary arteries before heart surgery (Meijboom et al., 2006). Cardiac CT may be particularly considered in patients with vegetations of the aortic valve, who are consequently at a high risk of systemic embolism in invasive coronary angiography (Bruun et al., 2014; G. Habib et al., 2015). Moreover, CT can be used to evaluate perivalvular complications, such as abscesses (G. Habib et al., 2015). Computed tomography can also be utilized to detect extra-cardiac manifestations of IE, such as emboli in the lungs or the spleen.

2.4.2.4 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is primarily used to detect cerebrovascular complications of IE, such as clinical and subclinical embolic events or cerebral microbleeds. Embolic events are manifested as ischemic or hemorrhagic strokes, embolic abscesses, or infrequently mycotic aneurysms. By systematic use of MRI, cerebrovascular complications have been found in 65–82% of IE cases (Duval et al., 2010; Snygg-Martin et al., 2008). Silent events without neurological symptoms can occur in 30–70% of IE patients (Cooper et al., 2009; Duval et al., 2010; Grabowski et al., 2011; Hess et al., 2013; Snygg-Martin et al., 2008).

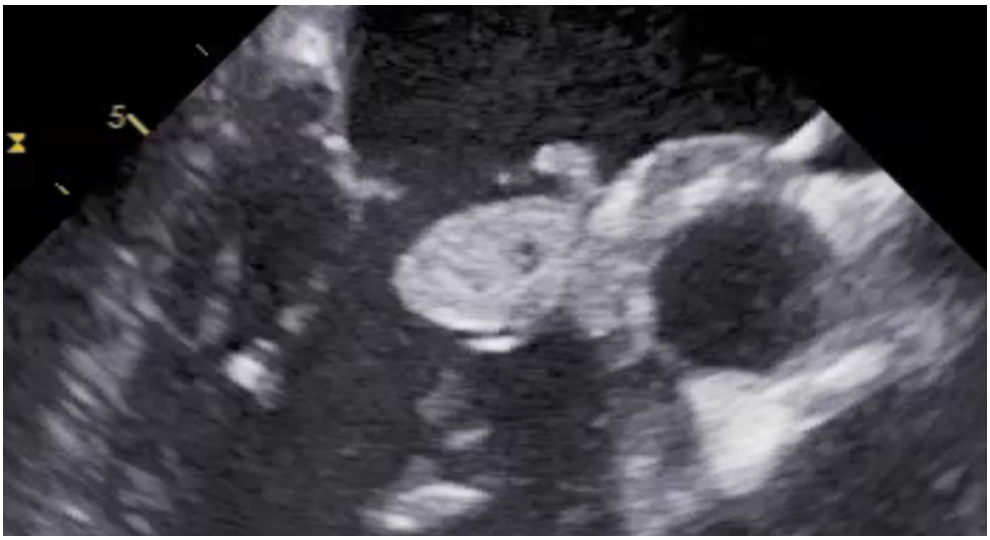

Figure 3. Echocardiography image of a vegetation on the mitral valve. Photo by Ville Kytö and published with his permission.

2.4.3 Microbiological findings

Positive blood cultures are essential for the diagnosis of IE. At least three sets of blood cultures (aerobic + anaerobic) should be taken at 30 minutes intervals. Cultures should be taken from a peripheral vein rather than a central venous catheter to avoid the risk of contamination. In IE, the bacteremia is nearly constant, and there is no need to time the cultures with the peaks of fever. (G. Habib et al., 2015). Blood cultures should be obtained before antibiotic administration, but taking the cultures must not delay the rapid onset of antibiotic treatment of a septic patient.

Positive blood cultures are present in more than 85% of IE cases (Cresti et al., 2017; Erdem et al., 2019; Halavaara et al., 2020; Muñoz et al., 2015; Van Den Brink et al., 2017). Blood culture-negative IE (BCNIE) is a diagnostic and therapeutic

challenge and is most commonly due to prior antibiotic administration. The cause of BCNIE can be fungi or fastidious bacteria, for example intracellular bacteria. Cultivating these bacteria requires special media, and their growth is slow. (Brouqui & Raoult, 2001; Houpikian & Raoult, 2005). Systematic serological testing has proven to be useful for investigating the causative agent of BCNIE (Fournier et al., 2010; Raoult et al., 2005). In cases of BCNIE, the ESC recommends serological testing for *Coxiella burnetii*, *Bartonella* spp., *Aspergillus* spp., *Mycoplasma pneumoniae*, *Brucella* spp., and *Legionella pneumophila*, followed by specific bacterial polymerase chain reaction (PCR) assays for *Tropheryma whipplei*, *Bartonella* spp., and fungi (*Candida* spp., *Aspergillus* spp.) from the blood (G. Habib et al., 2015).

Histological and microbiological examination (culture, staining, and PCR) of the resected valvular tissue or embolic material after surgery for IE to find evidence of microbes and infection is essential for the diagnosis of IE (Fournier et al., 2010; Kotilainen et al., 2006; Liesman et al., 2017). However, the impact of pre-operative antibiotic treatment should be taken into account. Halavaara et al. investigated 87 patients who had undergone cardiac surgery due to IE in Helsinki University Hospital in Finland (Halavaara et al., 2019). They found that in patients with less than two weeks of antibiotic administration before the operation, PCR was positive in 91% and valve culture in 41% of cases. Nevertheless, in patients with two weeks or longer pre-operative antibiotic treatment, PCR was positive in 53% and all valve cultures were negative. Their study also highlighted the importance of PCR in BCNIE. In 13 BCNIE cases, PCR was able to find the causative agent in ten patients.

2.4.4 Laboratory findings

Due to the poor predictive value and specificity in diagnosis of IE, laboratory parameters and biomarkers are not part of the diagnostic criteria of IE. However, some interesting findings have been made regarding the association between IE and certain parameters.

Heiro et al. found in their study in Turku University Hospital in Finland of 134 IE episodes that the serum C-reactive protein (CRP) and white blood cell count (WBC) fell faster in cases of uncomplicated recovery from IE than in cases with complications or death (Heiro et al., 2005). Other studies have also found increased levels of CRP and WBC, as well as procalcitonin (PCT), to be associated with death or serious complications in IE patients (Cornelissen et al., 2013; Tascini et al., 2020; Verhagen et al., 2008).

Thrombocytopenia is common in septicemia and is associated with increased mortality (Larkin et al., 2016; Xie et al., 2019). A multihospital Finnish study of 495 patients with *S. aureus* bacteremia discovered that thrombocytopenia (thrombocytes

less than 150 x 10^9/L) was associated with IE (Forsblom et al., 2017). An association between thrombocytopenia and IE in patients with *S. aureus* bacteremia was also found in a study in Israel (Gafter-Gvili et al., 2011). Studies investigating the prognostic role of the thrombocyte level in IE have found mortality to be higher in patients with thrombocytopenia (Ferrera et al., 2014; Sy et al., 2008). Furthermore, it has been reported that an increased D-dimer level is associated with mortality in IE patients (Lin et al., 2021; Turak et al., 2014).

Elevated levels of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), which are markers of cardiac load in heart failure or sepsis, have been found by several previous studies to be associated with a worse outcome in IE patients (Kahveci et al., 2007; Shiue et al., 2010; Siciliano et al., 2014, 2020; Wei et al., 2017). Comparably, increased levels of cardiac troponins reflecting damage in the myocardial cells have been reported to associate with poor clinical outcome in IE (Gucuk Ipek et al., 2015; Purcell et al., 2008; Siciliano et al., 2020; Stancoven et al., 2011; Thoker et al., 2016; Tsenovoy et al., 2009).

In Helsinki University Hospital in Finland, a study of patients with non-fatal methicillin-sensitive *S. aureus* bacteremia investigated changes in the hemostasis parameters of patients with IE or thromboembolic events (Forsblom et al., 2019). The patients were divided into two groups: an IE group and a thromboembolic events group. Both groups had age- and sex-adjusted control groups. The study found that patients with IE had increased hemostatic activity at an early time point with decreased levels of antithrombin III and higher levels of thrombin-antithrombin and prolonged activated partial thromboplastin time (APTT) compared to the control group. Patients with thromboembolic events had elevated levels of thrombin-antithrombin at an early time point compared to the controls. Hemostasis parameter changes in the early phase also seemed to predict IE or thromboembolic events. The results of the study suggest that patients with non-fatal *S. aureus* bacteremia have minor hemostasis parameter changes that might have predictive value for IE or thromboembolic events.

2.4.5 Diagnostic criteria

The diagnosis of IE is based on the modified Duke criteria and the 2015 ESC guidelines for the management of IE (G. Habib et al., 2015; Li et al., 2000). Three new diagnostic criteria were introduced by ESC in 2015 regarding the identification of abnormal findings in cardiac CT, ^{18}F-FDG PET/CT, or radiolabeled leukocyte SPECT/CT, and vascular phenomena observed by imaging only (silent events) (G. Habib et al., 2015).

The diagnosis consists of both major and minor criteria (Table 2). The major criteria are blood cultures and imaging positive for IE. The first criterion is a finding

of typical microorganisms consistent with IE in two separate blood cultures or microorganisms consistent with IE from persistently positive blood cultures. Alternatively, the criterion can be met with a finding of *Coxiella burnetii* in a single blood culture or serological test. The primary imaging method is TTE or TEE. Findings associated with IE are vegetation, abscess, pseudoaneurysm, intracardiac fistula, valvular perforation or aneurysm, or new partial dehiscence of the prosthetic valve. Furthermore, abnormal activity around the site of the prosthetic valve detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted >3 months ago) or radiolabeled leukocyte SPECT/CT is considered positive for IE. The final imaging criterion is the detection of definite paravalvular lesions by cardiac CT.

The minor criteria are predisposition (e.g. predisposing heart condition or IVDU), fever of >38 ˚C, vascular phenomena (e.g., emboli, mycotic aneurysms, Janeway's lesions), including those detected by imaging only, immunological phenomena (e.g. glomerulonephritis, Osler's nodes), and positive blood culture but does not meet a major criterion or serological signs of active IE with a microorganism consistent with IE.

For definite clinical diagnosis of IE according to the modified Duke and ESC criteria, either a pathological criterion or two major criteria, one major criterion and three minor criteria, or five minor criteria must be met (Table 2). For possible IE diagnosis, either one major criterion and one minor criterion, or three minor criteria must be fulfilled. Pathological criteria consist of microbes found in the cultivation or histological examination of a vegetation or an abscess of the heart, or a vegetation or an intracardiac abscess confirmed by histological examination.

Table 2. Definition of infective endocarditis according to the modified Duke criteria and ESC guidelines (2015) (G. Habib et al., 2015; Li et al., 2000). Clinical criteria are defined in the text.

Definite IE
Pathological criteria
Microbes found in culture or histological examination of a vegetation or an intracardiac abscess
Vegetation or intracardiac abscess confirmed by histological examination
Clinical criteria
2 major criteria; or
1 major criterion and 3 minor criteria; or
5 minor criteria
Possible IE
1 major criterion and 1 minor criterion; or
3 minor criteria

2.5 Pathogens causing IE

The main causative microorganisms of IE are staphylococci, viridans group streptococci, and enterococci.

2.5.1 Staphylococci

Staphylococci are part of the normal microbiome of the human skin (Byrd et al., 2018). The most common pathogen causing IE today is *S. aureus*, which accounts for approximately 30% of IE cases (Cresti et al., 2017; Erdem et al., 2019; G. Habib et al., 2019; Jordal et al., 2018; Selton-Suty et al., 2012). The emergence of *S. aureus* is caused at least in part by increasing exposure to healthcare procedures, as *S. aureus* has been found to be the major causative agent in healthcare-associated IE (Fernández-Hidalgo et al., 2008; Kiriyama et al., 2020; Selton-Suty et al., 2012). Previous studies in Europe and Australia have found methicillin-resistant *S. aureus* (MRSA) to be present in 4–7.5% of IE cases (Ferraris et al., 2018; Hill et al., 2007; Holland et al., 2020; Motoc et al., 2021; Selton-Suty et al., 2012; Sy & Kritharides, 2010). A multicenter study involving 41 hospitals in 13 countries, which examined IE patients during 2015–2018, found the prevalence of MRSA to be 8.4% (Erdem et al., 2019). In previous studies of patients with blood culture positive for *S. aureus*, IE was detected in 4–29% of the cases (Forsblom et al., 2018; Incani et al., 2013; Kobayashi et al., 2014; Rasmussen et al., 2011; Rieg et al., 2009; Saunderson et al., 2015).

In IVDUs, *S. aureus* is the most prevalent microbe causing IE (Hilbig & Cheng, 2020; Lawrence et al., 2021; Murdoch et al., 2009; Thalme et al., 2007). Halavaara et al. found in their study of IE patients in the Helsinki University Hospital Area between 2013 and 2017 that 74.2% of IVDUs' IE was caused by *S. aureus* (Halavaara et al., 2020). Furthermore, another Finnish study of 430 patients with *S. aureus* bacteremia found IE to be more common in IVDUs (46%) than in non-addicts (14%) (Ruotsalainen et al., 2006). *Staphylococcus aureus* IE is known for a potentially fulminant course of disease and is associated with increased mortality (Bor et al., 2013; Cresti et al., 2017; Jordal et al., 2018; Leone et al., 2012; Miro et al., 2005; Olmos et al., 2017; Selton-Suty et al., 2012; Sunder et al., 2019).

Coagulase-negative staphylococci (CoNS) (e.g. *S. epidermidis*, *S. lugdunensis*, *and S. hominis*) have been reported to cause 4–12% of IE cases (Bourget et al., 2022; Erdem et al., 2019; Halavaara et al., 2020; Jordal et al., 2018; J. H. Kim et al., 2021). Traditionally, CoNS were mainly responsible for PVIE, but *S. aureus* has emerged as a significant causative agent for PVIE (Lalani et al., 2013; Luehr et al., 2020; A. Wang et al., 2007). *Staphylococcus epidermidis* accounts for the majority of IE cases caused by CoNS (Bourget et al., 2022; Chu et al., 2008; Chu, Cabell, Abrutyn, et al., 2004; De La Mària et al., 2015). Native valve IE caused by CoNS is often healthcare-associated (Chu et al., 2008; Chu, Cabell, Abrutyn, et al., 2004; De La Mària et al., 2015).

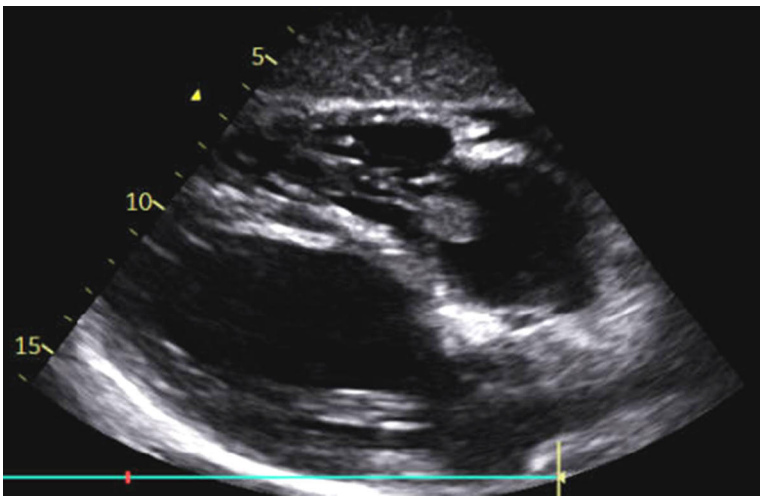

Figure 4. Echocardiography image of a vegetation on the tricuspid valve of an intravenous drug user. Photo by Emily Pan and published with her permission.

2.5.2 Streptococci

Streptococci account for 20–30% of IE cases (Fernández Hidalgo et al., 2020; Hill et al., 2007; Keller et al., 2017; Pant et al., 2015; Sy & Kritharides, 2010). Viridans group streptococci are present in 10–30% (Correa De Sa et al., 2010; Cresti et al., 2017; Erdem et al., 2019; Fernández Hidalgo et al., 2020; Halavaara et al., 2020; Heiro et al., 2006; Hill et al., 2007; Jordal et al., 2018) and *S. bovis* (or *S. gallolyticus*) in around 7–11% of IE patients (Cecchi et al., 2015; G. Habib et al., 2019; Hill et al., 2007). The most common viridans group streptococci that cause IE are *S. sanguinis*, *S. oralis (mitis)*, *S. salivarius*, and *S. mutans* (Baddour et al., 2015). A recent study in Denmark, which investigated 6506 cases with bloodstream infections caused by streptococci, found the IE prevalence with different viridans group streptococci to be high, up to 47.9% (Chamat-Hedemand et al., 2020). Viridans group streptococci are abundant in the mouth cavity, and poor dental hygiene is associated with IE-related bacteremia with viridans group streptococci (Lockhart et al., 2009). *Streptococcus bovis* is associated with colon cancer, and thus colonoscopy should be considered in cases of *S. bovis* IE (Corredoira et al., 2015; Lazarovitch et al., 2013; Zarkin et al., 1990). *Streptococcus pneumoniae* is a rare cause of IE today (De Egea et al., 2015; Fernández Hidalgo et al., 2020; Martínez et al., 2002). Beta-hemolytic streptococci (e.g. *S. agalactiae*, *S. dysgalactiae*, and *S. pyogenes*) can also infrequently cause IE (El Rafei et al., 2016; Fernández Hidalgo et al., 2020).

2.5.3 Enterococci

Enterococci account for 10–20% of IE cases, (Cecchi et al., 2015; Erdem et al., 2019; Ferraris et al., 2018; G. Habib et al., 2019; Hill et al., 2007; Jordal et al., 2018; Limonta et al., 2020; Motoc et al., 2021; Sy & Kritharides, 2010). *Enterococcus faecalis* accounts for the majority of enterococcal IE cases (Cecchi et al., 2015; Chirouze et al., 2013; Erdem et al., 2019; Hill et al., 2007; Pericàs et al., 2020). Infective endocarditis has been found in 17–26% of patients with *E. faecalis* septicemia (Dahl et al., 2019; Østergaard et al., 2019). Enterococci inhabit the gastrointestinal tract in humans, and *E. faecalis* IE has been shown to be associated with colorectal neoplasms (Corredoira et al., 2015; Pericàs et al., 2021). The origin of enterococcal IE may also be, for example, in the genitourinary tract (Fernández Guerrero et al., 2007; Pericàs et al., 2020). Studies have found patients with enterococcal IE to be older than patients with IE caused by other pathogens (McDonald et al., 2005; Olaison & Schadewitz, 2002; Pericàs et al., 2020). Community-acquired enterococci detected in two separate blood cultures is a major criterion of the diagnosis of IE (G. Habib et al., 2015). However, it has been found that a significant proportion of enterococcal IE cases are healthcare-associated (Chirouze et al., 2013; Pericàs et al., 2020; Sy & Kritharides, 2010).

2.5.4 Fungi

Fungi are rare causes of IE and typically present in PVIE, patients with central venous catheters, or IE of IVDUs and immunodeficient patients (Baddley et al., 2008; Pierrotti & Baddour, 2002; Tattevin et al., 2014). *Candida* and *Aspergillus* spp. are the most common fungi causing IE (Meshaal et al., 2018; Siciliano, Gualandro, et al., 2018; X. L. Sun et al., 2013; Tattevin et al., 2014). The mortality of fungal IE is very high (Baddley et al., 2008; Falcone et al., 2009; Lefort et al., 2012; Siciliano, Gualandro, et al., 2018; Sunder et al., 2019).

2.5.5 Other pathogens

A rare cause of IE is the fastidious and slow-growing HACEK-group of bacteria (*Haemophilus* spp., *Aggregatibacter* spp. (previously *Actinobacillus*), *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp.) (Chambers et al., 2013; Limonta et al., 2020). In BCNIE, *Coxiella burnetii*, *Bartonella* spp., *Aspergillus* spp., *Candida* spp., *Mycoplasma pneumoniae*, *Brucella* spp., *Legionella pneumophila*, and *Tropheryma whipplei* should be suspected and considered to investigate (Fournier et al., 2010; Raoult et al., 2005; Tattevin et al., 2014).

2.5.6 Pathogens in NVIE and PVIE

In PVIE, staphylococci and fungi have been described as more common causative agents and streptococci less common than in NVIE (G. Habib et al., 2015; Hill, Herregods, et al., 2008; Pierrotti & Baddour, 2002; Siciliano, Randi, et al., 2018; Tattevin et al., 2014). In early and late PVIE, the pathogens that cause IE are different (Castillo et al., 2004; Hill, Herregods, et al., 2008; López et al., 2007). Pathogens may be acquired perioperatively or later when transmission may be healthcare-associated or community-acquired. The majority of healthcare-associated PVIE cases likely occur during the first year after valve implantation (A. Wang et al., 2007). The principal causes of early PVIE are staphylococci, fungi, enterococci, and Gram-negative bacilli. In cases of late PVIE, the pathogens are similar to NVIE, suggesting that late PVIE is more likely community-acquired. (Castillo et al., 2000; Hill, Herregods, et al., 2008; López et al., 2007; Siciliano, Randi, et al., 2018).

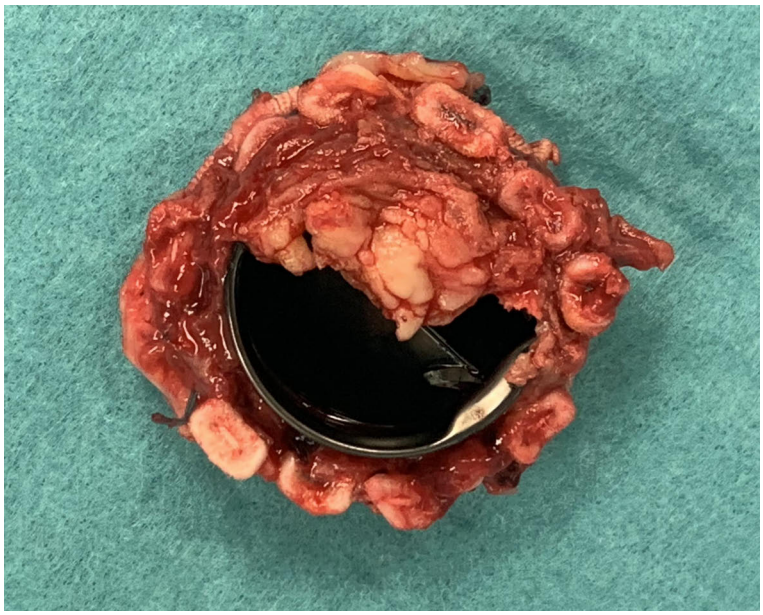

Figure 5. Infected mechanical aortic valve after surgical resection. Photo by Markus Malmberg and published with his permission.

2.6 Complications of IE

2.6.1 Heart failure

The most significant complication of IE is heart failure, which is also the most common indication for heart surgery (G. Habib et al., 2015; Iung et al., 2016; Lalani

et al., 2013; Murdoch et al., 2009; Nadji et al., 2009; Tornos et al., 2005). Heart failure is found in 33–55% of IE cases (Cresti et al., 2017; Heiro et al., 2006; Holland et al., 2020; Kiefer et al., 2013). Heart failure in IE is most commonly caused by new or worsening severe aortic or mitral regurgitation (G. Habib et al., 2015; Nadji et al., 2009). Valvular regurgitation can be caused by a rupture of the mitral chordae, a perforation of the cusp, or interference of the vegetation with the cusp (G. Habib et al., 2015). Clinical signs of heart failure may include dyspnea, pulmonary edema, and cardiogenic shock (Gelsomino et al., 2012; Nadji et al., 2009). Heart failure in IE patients is associated with increased mortality (Cresti et al., 2017; G. Habib et al., 2019; Leone et al., 2012; Olmos et al., 2017).

2.6.2 Uncontrolled infection

In IE, infection is considered uncontrolled if there are signs of persisting infection and locally uncontrolled infection. In a persisting infection, blood cultures remain positive, and the patient is still febrile 7–10 days after the initiation of effective antibiotic therapy. Perivalvular complications are the most common cause of uncontrolled infection and are often associated with high mortality and a need for surgery. (G. Habib et al., 2015). Perivalvular complications include abscesses, pseudoaneurysms, and fistulae (Anguera et al., 2006; G. Habib et al., 2015). Perivalvular extension of IE should be suspected if the patient presents with continuous fever or new atrioventricular block, and in these cases repeated TTE/TEE should be performed. In addition to perivalvular complications, increasing vegetation size is a sign of a locally uncontrolled infection. (G. Habib et al., 2015).

2.6.3 Embolic events

Embolic events in IE are due to the migration of material from cardiac vegetations and may cause infarcts or abscesses in different organs. Embolisms are frequent and occur in approximately 34–55% of IE patients (Di Salvo et al., 2001; Erdem et al., 2019; Holland et al., 2020; Rizzi et al., 2014; Selton-Suty et al., 2012; Thuny et al., 2005). In left-sided IE, the embolisms are most often found in the brain and spleen, whereas in right-sided IE, the lungs are the most common site for embolisms (G. Habib et al., 2015). Often, embolisms due to IE are already present at admission (Arregle et al., 2021; Cabell et al., 2001; Fabri et al., 2006; Hubert et al., 2013), and the risk of embolism notably decreases after the initiation of antibiotic therapy (Dickerman et al., 2007; Fabri et al., 2006; Hubert et al., 2013; Rizzi et al., 2014; Vilacosta et al., 2002). Previous studies have found *S. aureus* etiology to be associated with embolic events (Fabri et al., 2006; G. Habib et al., 2019; Miro et al., 2005; Rizzi et al., 2014; Tascini et al., 2020; Thuny et al., 2005). Vegetation size has

also been found to correlate with the risk of embolism (García-Cabrera et al., 2013; Iung et al., 2013; Mohananey et al., 2018; Thuny et al., 2005). Embolisms are associated with the need for intensive care and increased mortality (Fabri et al., 2006; Olmos et al., 2017; Rizzi et al., 2014; Sonneville et al., 2011).

Cerebral embolisms are detected in 16–26% of IE cases (Erdem et al., 2019; Holland et al., 2020; Rizzi et al., 2014; Selton-Suty et al., 2012; Thuny et al., 2005). Clinically silent cerebral complications may be present in 30–70% of IE cases (Cooper et al., 2009; Duval et al., 2010; Grabowski et al., 2011; Hess et al., 2013; Snygg-Martin et al., 2008).

According to previous studies, pulmonary embolism is detected in 4–19% of IE cases (Di Salvo et al., 2001; Erdem et al., 2019; Holland et al., 2020; Rizzi et al., 2014; Selton-Suty et al., 2012; Thuny et al., 2005). Pulmonary embolisms have been found to be frequent in cases of IE in IVDUs (Halavaara et al., 2020; Holland et al., 2020) and to be associated with IE of the tricuspid valve and *S. aureus* etiology (Clarelin et al., 2021; Erdem et al., 2019; Miro et al., 2005; Rizzi et al., 2014).

2.6.4 Other complications

Infective endocarditis can cause cerebral microhemorrhages, mycotic aneurysms (infection of the wall of the vessel and dilatation of the lumen), or subarachnoid hemorrhage (Duval et al., 2010; García-Cabrera et al., 2013; Hess et al., 2013). *Staphylococcus aureus* etiology has been found to be associated with a higher rate of cerebral complications in IE patients (Arregle et al., 2021; Dickerman et al., 2007; García-Cabrera et al., 2013; Iung et al., 2013; Xu et al., 2020). Neurologic complications are associated with increased mortality (Bor et al., 2013; García-Cabrera et al., 2013; Heiro et al., 2000). Acute renal failure is a fairly common complication of IE (Ferraris et al., 2013; Olmos et al., 2013; Zencirkiran Agus et al., 2019). Renal failure in IE patients may have numerous causes, such as immune complex and vasculitic glomerulonephritis, unstable hemodynamics, or toxicity of administered antibiotics (Mahr et al., 2014; Majumdar et al., 2000).

Septic infection and bacteremia itself can cause various complications, such as abscesses, septic shock (Georges et al., 2018; Mourvillier et al., 2004; Olmos et al., 2013), spondylodiscitis, or vertebral osteomyelitis (Behmanesh et al., 2019; Pigrau et al., 2005; Tamura, 2010). According to previous studies, vertebral osteomyelitis is found in 5–19% of IE cases (Murillo et al., 2018; Pigrau et al., 2005; Tamura, 2010) and IE in 13–31% of vertebral osteomyelitis cases (Koslow et al., 2014; Pigrau et al., 2005; Tamura, 2010). Consequently, imaging, preferably MRI, should be performed in IE patients with back pain and echocardiography in patients with vertebral osteomyelitis/spondylodiscitis and cardiac condition predisposing to IE (G. Habib et al., 2015).

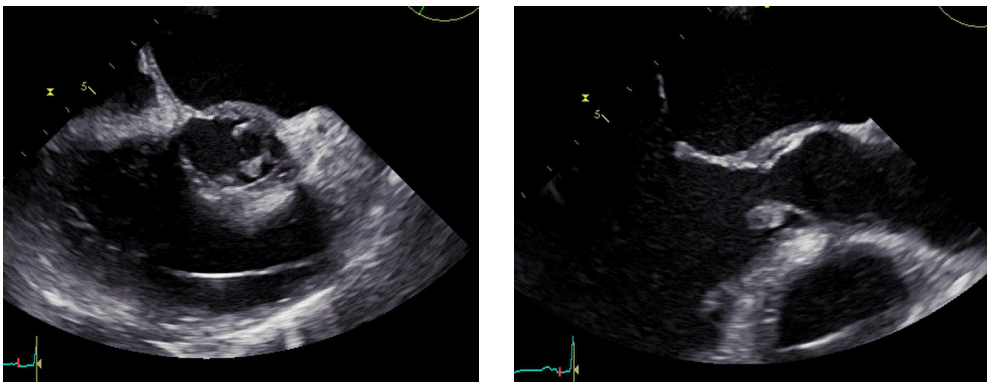

Figure 6. Two echocardiography images of the same patient showing vegetations on the aortic valve. Photos by Ville-Veikko Hynninen and published with his permission.

2.7 Treatment of IE

2.7.1 Antibiotic treatment

The purpose of antibiotic administration is to eradicate the microorganisms causing IE. According to the etiology of IE, antibiotic treatment should be continued in cases of NVIE for two to six weeks and in cases of PVIE for at least six weeks. The duration of the antibiotic treatment is based on the first day of effective antibiotic administration. However, if the culture of the surgically resected valves is positive, a new complete antibiotic course must be initiated. (G. Habib et al., 2015). In the future, the duration of intravenous treatments may decrease. A recent study randomized patients in a stable condition with left-sided IE caused by streptococci, *E. faecalis*, *S. aureus*, or CoNS after initial intravenous antibiotic administration for at least ten days to either continue with intravenous treatment or switch to oral treatment (Iversen et al., 2019). The groups did not differ significantly in terms of primary composite outcome, which consisted of all-cause mortality, unplanned cardiac surgery, embolic events, or a relapse of bacteremia with the primary pathogen, until six months after antibiotic treatment was completed. However, a limitation of this study was the investigation of only left-sided IE and patients with certain pathogens limiting the applicability of the study results.

2.7.2 Surgical treatment

2.7.2.1 Indications for surgery

The need for surgical intervention should be evaluated at the beginning of the treatment of IE (G. Habib et al., 2015). The purpose of surgery is to remove infected tissue, material, and abscesses and to replace or repair the valves destroyed by infection. Heart failure is the most common indication for heart surgery (Iung et al., 2016; Tornos et al., 2005). As mentioned before, heart failure in IE is most commonly caused by new or worsening severe aortic or mitral regurgitation (G. Habib et al., 2015; Nadji et al., 2009). Other indications for surgical treatment are severe valvular regurgitation without heart failure, uncontrolled infection, such as perivalvular complications, enlarging vegetation, or infection caused by multiresistant organisms or fungi, or prevention of embolisms if, for example, the vegetation is large (G. Habib et al., 2015; Iung et al., 2016; Tornos et al., 2005).

Currently, according to studies in referral centers, in 34–51% of IE cases, surgical intervention is performed during hospital admission (G. Habib et al., 2019; Lalani et al., 2010, 2013; Murdoch et al., 2009; Nadji et al., 2009). However, in population-based settings, the percentages of surgery are lower (Cresti et al., 2017; Halavaara et al., 2020; Sunder et al., 2019). Emergency surgery is indicated if the patient presents with cardiogenic shock or deterioration of heart failure despite medical therapy, unless there are contraindications to surgery, such as severe comorbidities (G. Habib et al., 2015; Matsuura et al., 2018). Surgery is also indicated with persisting vegetation of >10 mm and one or more clinical or silent embolism despite appropriate antibiotic treatment (G. Habib et al., 2015).

2.7.2.2 Surgery and mortality

Surgery for IE has been found to be associated with lower mortality than medical treatment alone (Aksoy et al., 2007; Lalani et al., 2010; Leone et al., 2012; Vikram et al., 2003), but some studies have found similar mortality between patients treated surgically or medically only (García-Cabrera et al., 2013; Lalani et al., 2013). Whether the operation should be in the active or later phase of IE has been debated. In the active phase, uncontrolled sepsis and impaired hemodynamic might worsen the outcome of surgery and increase the rate of IE relapse (Thuny et al., 2011). However, when an operation is performed later, the risk of embolic events and extensive damage to cardiac tissue might increase (D. H. Kim et al., 2010).

There is evidence that early surgery, performed during the active phase of IE, i.e. 7–14 days after diagnosis or during admission or antibiotic treatment, more effectively reduces mortality than surgery performed after the acute phase (Liang et

al., 2016). However, some studies have demonstrated that mortality is similar in patients operated on urgently or electively (D. H. Kim et al., 2010; Revilla et al., 2007). In the early-surgery group, patients might be more likely to have several complications of IE, but on the other hand, patients who are operated on are generally likely to be younger and have less co-morbidities (Cabell et al., 2005; Funakoshi et al., 2011; Lalani et al., 2010; Tleyjeh et al., 2007; Tornos et al., 2005).

A randomized trial with 76 patients compared patients with left-sided IE, severe valve disease, and large vegetations undergoing surgery as urgently as within 48 hours after randomization (n=37) to those receiving conventional treatment (surgery during hospital admission or follow-up (n=39) (Kang et al., 2012). The study found no difference between these groups in six-month all-cause mortality, but the rate of composite end point (death from any cause, embolic events, or recurrence of IE at six months) was 3% in the early-surgery group and 28% in the conventional-treatment group, p=0.02.

2.7.2.3 Role of surgery in preventing embolic events

Kang et al. found in their randomized trial that there were no embolic events in the early-surgery group, whereas there were eight events among those conventionally treated (p=0.005) (Kang et al., 2012). Accordingly, Kim et al. found early surgery to be associated with fewer embolic events than late surgery or no surgery (D. H. Kim et al., 2010). However, other studies have found no difference between the number of embolic events in surgically or only medically treated patients (Cabell et al., 2005; A. Wang et al., 2019).

2.7.2.4 Choice of prosthetic valve

In surgical operation for IE, infected valves may be repaired or most commonly replaced with either a mechanical or biological prosthetic valve. The choice of either valve remains controversial. A mechanical valve tends to be chosen more often in younger IE patients (Kytö et al., 2019; Nguyen et al., 2010; Toyoda et al., 2018). Some studies have found equal long-term mortality after the implantation of a mechanical or biological valve due to IE (Said et al., 2018; Toyoda et al., 2018), whereas others have described increased mortality after the implantation of a biological valve (Kytö et al., 2019; Nguyen et al., 2010; Tao et al., 2017). The risk of recurrent IE after the implantation of a prosthetic valve due to IE has been found to be similar for both mechanical and biological valves (Fedoruk et al., 2009; Toyoda et al., 2018) or higher for biological prostheses (Havers-Borgersen et al., 2020; Tao et al., 2017). However, there are no specific guidelines for the choice of prosthetic valve in IE.

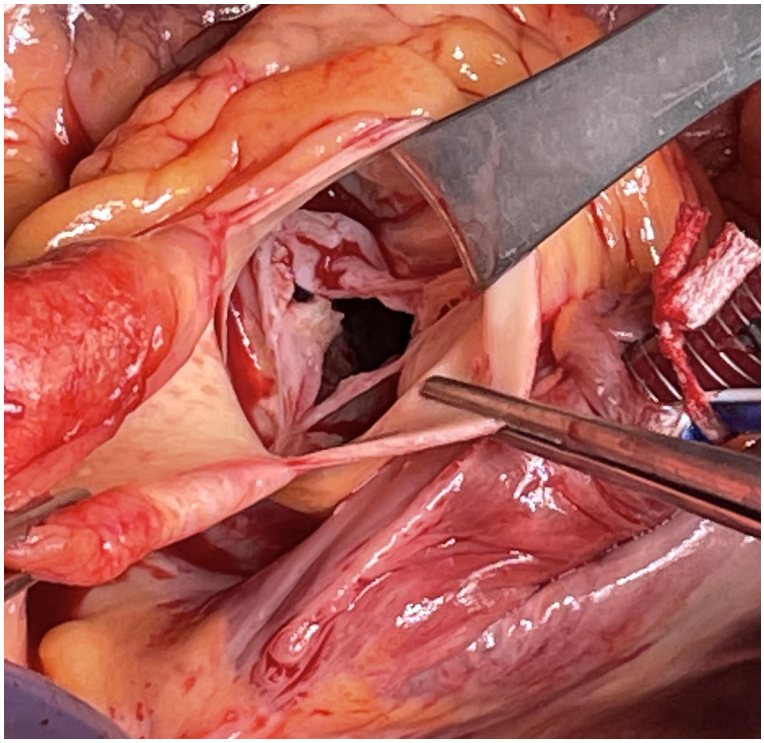

Figure 7. Infective endocarditis of the aortic valve. Vegetations on the left coronary cusp of the valve. Echocardiography images of the same patient are in Figure 6. Photo by Elina Ahtela.

2.7.3 Length of hospital stay

Previous studies have found substantial variation in LOS due to IE, from 7 to 43 days (Fedeli et al., 2011; Morita et al., 2019; Olmos et al., 2017; Schranz et al., 2019; Selton-Suty et al., 2012; Sunder et al., 2019; Sy & Kritharides, 2010; Ternhag et al., 2013). Longer hospital stays have been reported in patients who have had surgery (Schranz et al., 2019; Slater et al., 2007), whereas shorter hospital stays have been reported in patients who have died during hospitalization (Muñoz et al., 2015; Selton-Suty et al., 2012). The possible transition to partial oral instead of full-length intravenous antibiotic treatment (Iversen et al., 2019) might shorten LOS in the future.

2.8 Epidemiology of IE

2.8.1 Age- and sex-specific epidemiology

The mean age of IE patients has been described as approximately 59–66 years (Bor et al., 2013; Cresti et al., 2017; G. Habib et al., 2019; Olmos et al., 2017; Ternhag et

al., 2013). Studies have demonstrated that the age of IE patients has increased over time (Erichsen et al., 2016; Fedeli et al., 2011; Sy & Kritharides, 2010). Moreover, the rate of IE has increased in the older population (Bor et al., 2013; Erichsen et al., 2016; Jensen et al., 2021; Olmos et al., 2017). According to studies, 59–74% of IE patients are men (G. Habib et al., 2019; Olmos et al., 2017; Selton-Suty et al., 2012; Sy & Kritharides, 2010; Ternhag et al., 2013; Varela Barca et al., 2021). One possible explanation for male predominance might be that men have more risk factors (Thornhill, Jones, et al., 2018) and medical conditions that predispose them to IE, such as degenerative valve disease, than women. It has previously been demonstrated that estrogen protects against endothelial damage (Bakir et al., 2000; Guo et al., 2010). Furthermore, a well-known risk factor of IE, IVDU, is more common in men (Degenhardt et al., 2017; Rönkä & Markkula, 2020).

2.8.2 Incidence

The incidence of IE has been found to be 3–8/100,000 person-years (Duval et al., 2012; Jordal et al., 2018; Ternhag et al., 2013; Thornhill, Jones, et al., 2018; Toyoda et al., 2017). European studies have demonstrated increasing IE incidence (Cresti et al., 2017; Erichsen et al., 2016; Jensen et al., 2021; Jordal et al., 2018; Ternhag et al., 2013; Van Den Brink et al., 2017), whereas studies in the US have found both increasing (Bor et al., 2013; Pant et al., 2015) and stable (Bikdeli et al., 2013; Toyoda et al., 2017) incidence. Growing IE rates have been discovered in the older age group in particular (Bor et al., 2013; Erichsen et al., 2016; Jensen et al., 2021; Olmos et al., 2017). Increasing incidence has been described in PVIE and in IE associated with intracardiac devices (Carrasco et al., 2016; Cresti et al., 2017; Greenspon et al., 2011). Most studies have found a similar increase in the incidence rate in men and women (Cresti et al., 2017; Olmos et al., 2017; Van Den Brink et al., 2017), whereas an increased rate in only women (Correa De Sa et al., 2010) or more pronounced increase in men (Erichsen et al., 2016) has also been described.

2.8.3 Mortality

2.8.3.1 Short-term mortality

Short-term mortality can be classified as in-hospital mortality or 30-day mortality. According to previous studies, in-hospital mortality is 6–24% (Bor et al., 2013; Cresti et al., 2017; Erdem et al., 2019; G. Habib et al., 2019; Keller et al., 2017; Morita et al., 2019; Sunder et al., 2019; Sy & Kritharides, 2010) and 30-day mortality 8–14% (Heiro et al., 2007; Jordal et al., 2018; Ternhag et al., 2013). Short-term

mortality has not changed significantly in recent years (Bor et al., 2013; Cresti et al., 2017; Jordal et al., 2018; Keller et al., 2017; Ternhag et al., 2013).

2.8.3.2 Long-term mortality

Previous studies have found one-year mortality to be 21–37% (Cresti et al., 2017; Fedeli et al., 2011; Jordal et al., 2018; Sunder et al., 2019; Toyoda et al., 2017) and five-year mortality 41–53% (Bannay et al., 2011; Toyoda et al., 2017). Studies have demonstrated both stable and increasing one-year mortality (Cresti et al., 2017; Fedeli et al., 2011). The reason why mortality has not decreased over time is unclear. Up-to-date evidence on long-term mortality over five years is scarce. A Finnish study in Turku University Hospital of IE patients treated between 1980 and 2004 found the overall survival to be 62% at five and 49% at ten years after IE admission (Heiro et al., 2008). Moreover, a study in Switzerland in a tertiary referral center between 1980 and 1995 discovered mortality of 42% and 50% at five and ten years (Netzer et al., 2002).

2.8.3.3 Age- and sex-specific differences in mortality

As expected, mortality of IE is higher in the older population (Armiñanzas et al., 2019; Cresti et al., 2017; Duval et al., 2012; Fedeli et al., 2011; Olmos et al., 2017). Most studies have found the mortality of IE to be similar in men and women (Chu, Cabell, Benjamin, et al., 2004; Cresti et al., 2017; G. Habib et al., 2019; Heiro et al., 2007, 2008; Hill et al., 2007; Murdoch et al., 2009; Netzer et al., 2002; Selton-Suty et al., 2012; Sunder et al., 2019), but some differences between the sexes have been described. Two Spanish studies (Olmos et al., 2017; Varela Barca et al., 2021) and one US study including only patients with NVIE (Khan et al., 2020) reported female sex to be an independent risk factor for in-hospital mortality, whereas a UK study found men to be at a significantly higher risk of dying during the IE admission (Thornhill, Jones, et al., 2018). Furthermore, women had higher long-term mortality in a previous study in the Netherlands (Van Den Brink et al., 2017).

2.8.3.4 Mortality in NVIE and PVIE

The differences in mortality between NVIE and PVIE patients have been investigated. Both increased and similar mortality in PVIE compared to NVIE have been discovered. Wang et al. found the in-hospital mortality of PVIE to be significantly higher than NVIE, 22.8% vs. 16.4% (A. Wang et al., 2007). A large prospective multicenter study including 25 countries (Murdoch et al., 2009) and an Italian study involving 24 centers (Leone et al., 2012) found prosthetic valve

involvement to be associated with increased in-hospital mortality. However, Selton-Suty et al. found in-hospital mortality to be similar between PVIE and NVIE (Selton-Suty et al., 2012), and furthermore Cabell et al. found that prosthetic valve infection was not a predictor of one-year mortality (Cabell et al., 2002). Abdallah et al. discovered the in-hospital mortality of left-sided PVIE caused by *S. aureus* to be as high as 48.5% and of left-sided PVIE caused by other pathogens 16.0% (Abdallah et al., 2016). Comparably, other studies have also found *S. aureus* to be a predictor of mortality in PVIE (G. Habib et al., 2005; A. Wang et al., 2007). Ternhag et al. found that the five-year mortality of patients with PVIE was higher than of NVIE patients, but one-year mortality was similar (Ternhag et al., 2013). Furthermore, Cresti et al. found no difference in either in-hospital or one-year mortality between NVIE and PVIE patients (Cresti et al., 2017).

2.8.3.5 Mortality in right-sided IE

As mentioned before, right-sided IE accounts for around 12–15% of all IE cases (Cresti et al., 2017; Erdem et al., 2019; G. Habib et al., 2019; Holland et al., 2020; Jordal et al., 2018) and is often associated with IVDU (Colville et al., 2016; Halavaara et al., 2020; Holland et al., 2020; Leahey et al., 2019) or intracardiac devices (Carrasco et al., 2016; Cresti et al., 2017; Urien et al., 2021). In IVDUs' IE, *S. aureus* is the most frequent microbe (Halavaara et al., 2020; Hilbig & Cheng, 2020; Lawrence et al., 2021; Murdoch et al., 2009; Thalme et al., 2007). Consequently, the majority of the mortality data on right-sided IE are based on previous studies that have investigated IVDUs' IE and IE caused by *S. aureus* or IE associated with intracardiac devices.

In their study of patients with IE caused by *S. aureus*, Asgeirsson et al. found lower in-hospital (2% vs. 13%) and one-year (7% vs. 27%) mortality in right-sided IE than left-sided IE. Left-sided IE was an independent risk factor for one-year mortality (Asgeirsson et al., 2015). In their study, 85% of the patients with right-sided IE were IVDUs. Guerrero et al. found in their study of patients with *S. aureus* IE in-hospital mortality to be 38% in left-sided IE and 17% in right-sided IE (Guerrero et al., 2009). The mortality of right-sided IE in IVDUs (n=53) was only 3.7%. Conversely, in the patients with right-sided IE associated with an infected intravenous catheter (n=11), the mortality was 82%. A study investigating *S. aureus* NVIE reported in-hospital mortality of 28.6% in left-sided IE and 5.9% in right-sided IE (Miro et al., 2005). According to these studies, patients with right-sided IE are notably younger than those with left-sided IE (Asgeirsson et al., 2015; Guerrero et al., 2009; Miro et al., 2005). A likely explanation for the lower mortality rates found in right-sided IE in these studies is the high proportion of IVDUs, who are usually young and have few comorbidities. Furthermore, in right-sided IE, mortality-

associated complications, such as heart failure or other embolisms than pulmonary, are less frequent than in left-sided IE (G. Habib et al., 2015).

It is known that IVDUs in general suffer from excessive mortality over time. Some studies have described the long-term mortality of IVDUs with IE. In their study of IVDUs with *S. aureus* IE, Asgeirsson et al. reported one-year mortality to be 4.1% in right-sided IE and 15% in left-sided IE (Asgeirsson et al., 2016). A study including all definite IE cases according to the modified Duke criteria found one-year mortality of 16% in IVDUs' IE cases and similar 13% in non-IVDUs' IEs (Leahey et al., 2019). However, in this study, only 35% of the IVDUs' IEs were right-sided. Thalme et al. found the mortality during a mean follow-up of 5.1 years in IVDUs with right-sided IE to be 34.6% and with left-sided 56.3% during a mean follow-up of 3.3 years (Thalme et al., 2007).

Ruotsalainen et al. investigated a potential explanation for lower mortality in IVDUs in *S. aureus* bacteremia and IE in their study on microbiological and serological characteristics and host factors (Ruotsalainen et al., 2008). Their prospective study included 44 IVDUs with *S. aureus* bacteremia and 44 controls. Twenty patients in both groups had IE according to the modified Duke criteria. No differences were found between IVDUs and non-addicts with *S. aureus* bacteremia in the percentage of patients with deep infection or thromboembolic complications. There were no significant differences in the bacterial strains and their virulence factors or host immune responses between the groups.

One study of different types of right-sided IE investigated the prognosis of isolated right-sided IE (Ortiz et al., 2014). In this study, right-sided IE was divided into three groups according to the patient: IVDUs (n=36), cardiac device carriers (n=65), and the "three noes" group: no left-sided, no IVDUs, and no cardiac devices (n=20). In-hospital mortality was 30% in the "three noes" group, 17% in IVDUs, and only 3% in the cardiac devices group. Other studies on intracardiac device-associated IE found similar short-term-mortality (in-hospital or 30-day mortality), 4–8% (Baman et al., 2009; Greenspon et al., 2011; A. Habib et al., 2013; Sohail et al., 2011).

3 Aims

The purpose of this study was to provide better understanding of the current epidemiology, clinical profile, etiology, and embolic complications of IE in Finland. The specific aims of the study are:

1. To investigate the temporal trends and sex- and age-specific differences in the incidence and 30-day mortality of IE in Finland.
2. To study the sex- and age-specific differences and temporal trends in the occurrence of fatal IE in Finland.
3. To evaluate the sex- and age-specific differences, temporal trends, and the factors affecting LOS and long-term mortality in IE patients in Finland.
4. To assess the current clinical profile of IE, the characteristics of the different microbiological etiologies, and the factors associated with embolic events in IE patients in a tertiary care hospital in Finland.

4 Materials and Methods

4.1 Study design and data collection

4.1.1 Studies I and III

These population-based studies included adult patients (aged ≥18 years) admitted to hospital due to IE during 2005–2014. The data were obtained retrospectively from the nationwide Care Register for Health Care (CRHC) database maintained by the Finnish National Institute for Health and Welfare. This mandatory database collects hospital discharge data, including individual baseline data (e.g. age, sex, admission, surgery, and discharge dates), discharge diagnoses (International Classification of Diseases, Tenth Revision (ICD-10)), and operational codes (Nordic Classification of Surgical Procedures) of all hospital admissions in Finland.

Patients discharged from the medical or surgical care units of all 38 hospitals (including five university hospitals) treating acute IE between January 1, 2005, and December 31, 2014, were included. Operations of the heart or ascending aorta as well as pacemaker implantations or changes performed during one year prior to hospitalization due to IE during the study period were identified from the CRHC. Patients with a discharge diagnosis of IE (ICD-10 codes I33, I38, and I39) as the primary, secondary, or tertiary cause of admission were included in the study. Patients admitted for IE in 2004 were excluded from study III.

The specificity of the ICD-10 IE codes (I33, I38, or I39) was evaluated in a subgroup of patients admitted to Turku University Hospital. The patient data (e.g. laboratory, microbiology, pathology, and imaging data) of randomly selected patients (n=188; 74% male, mean age 59.7 years) admitted during 2005–2014 were analyzed to determine whether the modified Duke criteria for IE (G. Habib et al., 2015; Li et al., 2000) were fulfilled. Of the 188 analyzed patients, 182 fulfilled the criteria (definitive IE in 122 and possible IE in 60 patients) resulting in a specificity of 96.8%.

The Charlson comorbidity index (CCI) score, including baseline diabetes mellitus, congestive heart failure, peripheral vascular disease, myocardial infarction, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, hemi- or paraplegia, renal disease, malignancies,

and acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV), was calculated as previously described (H. Quan et al., 2005).

In study I, data on the Finnish population at risk (42,754,847 person-years) and the 30-day mortality data of patients with IE admission were acquired from Statistics Finland. The person-years of each study year were estimated by population at the end of the year. One IE admission per patient per year was included.

In study III, the survival data were obtained from the Cause of Death Registry held by Statistics Finland. The follow-up ended on December 31, 2016, or at ten years after discharge, whichever came first. Length of stay was defined as beginning days, and both the patients who were discharged alive and those who died during the hospitalization were included. Seasons were determined as winter: December–February; spring: March–May; summer June–August; autumn: September–November.

4.1.2 Study II

This study included adults (≥18 years of age) with IE-related death during 2004–2016. The deceased individuals with IE contributing to death recorded on death certificate were retrospectively identified from the nationwide Cause of Death Registry of Statistics Finland (Helsinki, Finland). Issuance of death certificate with determination of the causes of death and collection of death certificates into Statistics Finland database is required by law and covers the whole population. The physician issuing the death certificate determines one cause of death that they suspect is the underlying cause of death, and this is recorded as the official cause of death according to the World Health Organization (WHO) classification. Additionally, other causes contributing to death are recorded. All death certificates are verified by the competent authority in charge of forensic medicine.

Infective endocarditis was recognized by ICD-10 codes I33, I38, or I39. Age- and sex-specific population and the mortality data of the Finnish population from 2004 to 2016 were acquired from Statistics Finland. The study period included 28,657,870 person-years and 651,556 total deaths. The person-years of each study year were estimated by population at the end of the year. Seasons were defined as winter: December–February; spring: March–May; summer June–August; autumn: September–November.

4.1.3 Study IV

This study included patients (≥18 years of age) treated in Turku University Hospital due to IE between January 1, 2004, and June 31, 2017. The hospital has a cardiothoracic surgical unit and serves as a tertiary referral center in the southwestern

part of Finland, covering a population of approximately 870,000 individuals. Patients were identified retrospectively by discharge diagnosis (ICD-10 codes I33, I38, or I39), and detailed patient data were collected from the patient record system. Patients with definite or possible diagnosis of IE according to the modified Duke criteria and the ESC guidelines for the management of IE in 2015 were included (G. Habib et al., 2015; Li et al., 2000). Three IE cases were excluded because the IE could not be specified to any heart valve (two with a non-specific mass inside the atrium of the heart and one with a ventricular septal defect). The etiology of IE was obtained from the blood cultures. Embolic events were diagnosed by CT, MRI, PET/CT, or clinically. Certain information collected for the study was missing in the patient record as a result of, for example, a transfer from another hospital. The cases with missing information were excluded from the analyses that required the missing information. The number of cases with missing information were stated in the tables alongside the particular factor or in the text.

4.2 Statistical analyses

4.2.1 Study I

The age-, year-, and sex-specific population data were used to determine the annual incidence rate of admissions per calendar year. Incidence was standardized with the European 2013 standard population using the direct method. Chi-squared and t-tests were used to compare patient characteristics. To analyze the incidence rates negative binomial regression with logarithm of the corresponding population as an offset parameter was used. Regression models with the number of admissions as a dependent variable and sex, age, and year of admission as independent variables were used to determine incidence rate ratios (IRR). Cox regression modeling was performed to study the mortality of the first IE admission during the study period. Interaction analyses were utilized to detect the potential association modifications by age, sex, and study year. The variables associated with mortality with p-value of <0.2 in the univariable analysis were included in the multivariable Cox modeling. Otherwise, statistical significance was inferred at $p<0.05$. The SAS system version 9.4 was used for statistical analyses (SAS Institute Inc.).

4.2.2 Study II

Incidence was standardized with the direct method and the 2013 European standard population. Continuous variables were compared using a t-test. Poisson regression modeling was used to analyze the associations of age, sex, and study year with the incidence rate and proportion of deaths. The logarithm of the corresponding

population or number of deaths were used as an offset parameter in regression modeling. The potential influence of age on the associations with sex was analyzed using interaction analysis. Potential monthly and seasonal differences in the number of deaths due to IE were studied using the Chi-squared test. Ninety-five percent confidence intervals (95% CI) of the count variables were determined assuming Poisson distribution. P-values of <0.05 were considered statistically significant. Statistical analyses were performed using the SAS system version 9.4 (SAS Institute Inc).

4.2.3 Study III

Chi-squared and independent samples t-tests were used to study patient characteristics. The factors associated with LOS were analyzed using the independent samples t-test, one-way analysis of variance, and linear model. The Bonferroni method was utilized in pairwise comparisons between groups. Statistical analyses were performed with standardized logarithmically transformed values for LOS due to skewness. The factors associated with all-cause cumulative one-, five-, and ten-year mortality were analyzed using Cox regression and in-hospital mortality using logistic regression. Variables with a p-value of <0.1 in the univariable analysis were included in the multivariable models. The results were described as mean differences with a 95% CI, hazard ratios (HR) with a 95% CI, and odds ratios (OR) with a 95% CI. Kaplan-Meier estimates were used to determine the overall one-, five-, and ten-year mortality. Survival curves were drawn using the Kaplan-Meier method. P-values with significance level <0.05 were considered statistically significant. All p-values were two-sided. The SPSS version 25 (Armonk, NY: IBM Corp.) was used for statistical analyses.

4.2.4 Study IV

Chi-squared and independent samples t-test and Kruskal-Wallis one-way analysis of variance were utilized to evaluate the patient characteristics and the factors associated with the different etiologies and embolic events. Histograms were used to test normality visually. Mean and standard deviation (SD) were expressed for the normally distributed factors and for the non-normally distributed median and interquartile range (IQR), respectively. Logistic regression using generalized estimating equations was used to study the factors associated with embolic events to account for the possible correlations between the values of the different admissions of the same patients. Variables with a p-value of <0.1 in the univariable analysis and additionally the age group and sex were included in the multivariable models. The Phi coefficient in crosstabulation was used to analyze the correlations between the

clinical factors in the multivariable analysis to avoid multicollinearity problems, and values lower than 0.7 were included. The results were expressed as OR with 95% CI. P-values of <0.05 were considered statistically significant. Two-sided p-values were used. Statistical analyses were performed using the SPSS version 28 (Armonk, NY: IBM Corp.).

4.3 Ethical considerations

The studies were approved by the Hospital District of Southwest Finland (permission number TO2/015/17), the National Institute for Health and Welfare (THL/1349/5.05.00/2015 and THL/1484/5.05.00/2017), and Statistics Finland (TK53-1410-15). The legal basis for processing personal data is public interest and scientific research (EU General Data Protection Regulation 2016/679 (GDPR), Article 6(1)(e) and Article 9(2)(j); Data Protection Act, Sections 4 and 6). Due to the retrospective nature of the studies, informed consent was waived, and patients were not contacted.

5 Results

5.1 Characteristics of the study subjects

5.1.1 Study I

During 2005–2014 there were 2611 IE admissions in 2331 patients. Infective endocarditis was coded as the primary cause of admission in 66.3%, secondary in 24.1%, and tertiary in 9.6% of cases. The majority of the IE admissions (68.2%) were in men. The mean age of the IE patients was 60.0 years (SD 18.3, range 18–97) (Figure 8). The women were older than the men (mean age 62.0, SD 20.7 vs. 59.0, SD 17.1; p=0.0004) and had more comorbidities (CCI score ≥1 in 46.7% vs. 42.5% in men, p=0.047). During one year prior to hospitalization due to IE, 7.8% of patients had undergone open cardiac surgery, 0.8% coronary artery bypass grafting, and 5.5% prosthetic valve implantation. Pacemaker implantation or pacemaker generator change was performed in 1.5% of the patients during the year before IE hospitalization.

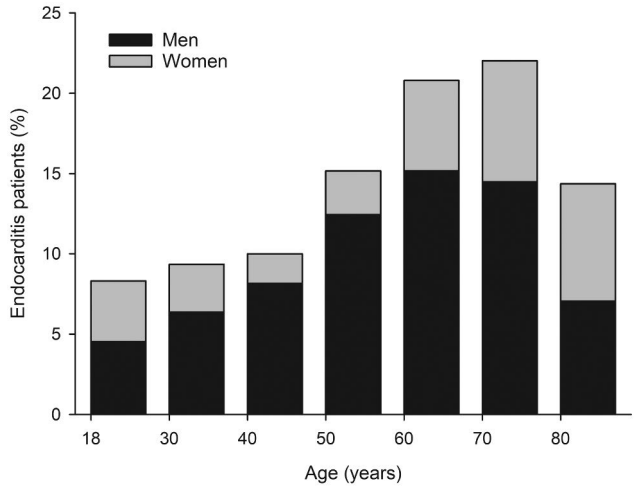

Figure 8. Age distribution of patients with infective endocarditis. Sex-specific distribution is presented as a relative proportion within bars. Reprinted from the original publication I with the permission of the copyright holders.

5.1.2 Study II

During 2004–2016 IE contributed to 754 deaths. The mean age of the individuals with an IE-associated death was 68.6 (SD 16.7 years, range 20–99 years). The women (n = 306) were older (mean age 73.1 years, SD 15.8) than the men (n = 448; mean age 65.6 years, SD 16.6; p<0.0001). Infective endocarditis-related death occurred in hospital or other healthcare facility in 89.5%, at home in 8.6%, and elsewhere in 1.6% of cases, whereas 0.3% of deaths occurred abroad.

5.1.3 Study III

Study included 2166 patients treated due to IE during 2005–2014. Men constituted 67.8% of the patients. The mean age of all the patients was 60.7 years (SD 18.2, range 18–97) and the women were older than the men (mean age 63.3, SD 20.3 vs. 59.5, SD 17.0; p<0.001). The CCI score was similar for both the sexes (p=0.078). Nearly half of the patients (49.1%) were treated in the university hospital. A prosthetic valve was implanted in 5.3% and a pacemaker was implanted or a pacemaker generator changed in 1.6% of the patients during the year prior to the IE hospitalization.

5.1.4 Study IV

During 2004–2017 there were 342 IE admissions in 320 patients. The majority of the cases were in men (75.1%). The mean age of the patients was 59.0 years (SD 19.1, range 18–97). The mean age of the sexes was similar (women 60.7 years, SD 22.4 vs. men 58.4 years, SD 17.9; p=0.379). Intravenous drug users accounted for 18.5% (n=63) of the patients. The mean age of the IVDUs was 30.4 years (SD 6.4, range 18–46) and 69.8% were men. Of the patients, 62 (18.1%) had a prosthetic valve.

A notable proportion (41.3%) of the patients had a history of a major healthcare procedure (cardiovascular, gastrointestinal, urological, or other major procedure) or hospital admission during six months or a central venous catheter (not dialysis-associated) during one month before IE hospitalization.

Transthoracic echocardiography had been performed in nearly all patients (99.4%) and TEE in 73.4%. Aortic valve IE accounted for 45.6% of the cases (n=156), mitral valve IE 27.8% (n=95), tricuspid valve IE 13.5% (n=46), and IE of the multiple valves 13.2% (n=45). In IVDUs, the tricuspid valve was infected in 57.1% of cases. Of the patients, 231 (67.5%) had a definite and 111 (32.5%) a possible IE diagnosis according to the modified Duke criteria. During the IE admission, 177 patients (53.8%) had heart failure.

5.2 Incidence

5.2.1 Study I

The standardized annual IE incidence was 6.33 cases per 100,000 person-years (95% CI: 6.09–6.57). In men, the standardized incidence was 9.46/100,000 person-years (95% CI: 9.04–9.89), and in women, 3.67/100,000 person-years (95% CI: 3.45–3.94). The youngest population had the lowest overall incidence rate, and the incidence increased progressively with age in the older population (Figure 9). Incidence increased more steadily with aging in men than in women. Increasing incidence was discovered from the age of 60 years in women (Figure 9). Men were at a significantly higher risk of IE than women (IRR 2.49; CI 2.22–2.79; $p<0.0001$). The sex difference in the IE risk was observed in patients aged ≥30 years, was most notable in the population aged 40–59 years (IRR 4.49; CI 3.68–5.48; $p<0.0001$), and decreased in older patients (Figure 10).

5.2.2 Study II

The standardized incidence of IE-related deaths was 1.42/100,000 person-years (95% CI: 1.32–1.52). Incidence depended significantly on age ($p<0.0001$), being lowest in the population aged 18–29 years, remaining similar in the population aged 30–49, and increasing progressively with age from 50 years onwards. The oldest population (≥90 years) were 37 times more likely to acquire IE severe enough to contribute to death (8.83 deaths/100,000) than the youngest population. In men, the risk of acquiring fatal IE was twice as high than in women (risk ratio (RR) 1.95; 95% CI: 1.71–2.22; $p<0.0001$). Association was not modified by age (interaction $p=0.102$). In men, the overall incidence was 1.95/100,000 person-years (95% CI: 1.79–2.13) and in women 0.99/100,000 (95% CI: 0.88–1.12). No monthly ($p=0.642$) differences were observed in the incidence of IE-related deaths.

The standardized incidence of deaths with IE as the underlying cause was 0.66/100,000 person-years (95% CI: 0.59–0.73). The age distribution of deaths with IE as the underlying cause was similar to all IE-related deaths. Furthermore, the sex difference (men vs. women RR 2.21; 95% CI: 1.72–2.83; $p<0.0001$) was also similar to all deaths related to IE.

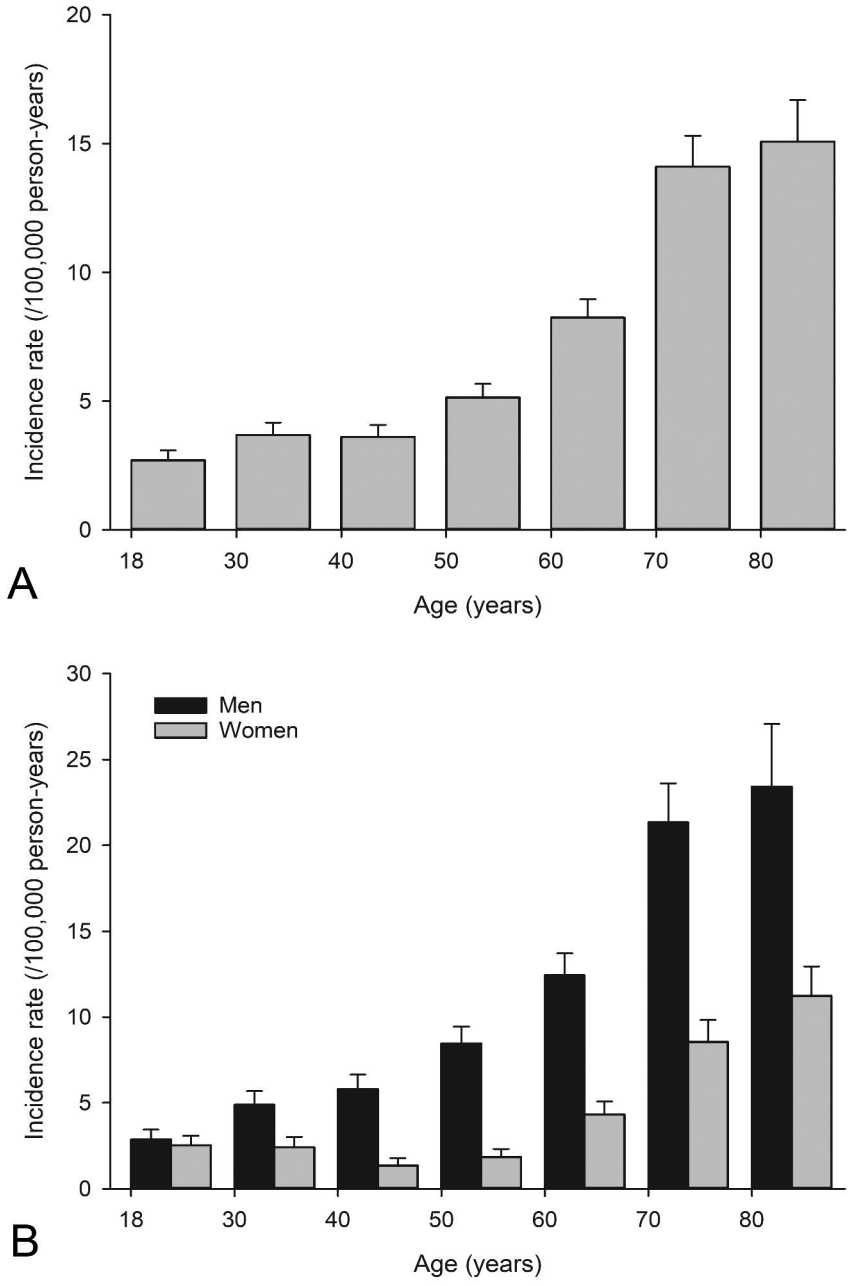

Figure 9. Incidence of infective endocarditis admissions in the general adult population. Total (A) and sex-specific (B) annual incidence rates (per 100,000 person-years) by age. Error bars represent the upper limits of 95% CI. Reprinted from the original publication I with the permission of the copyright holders.

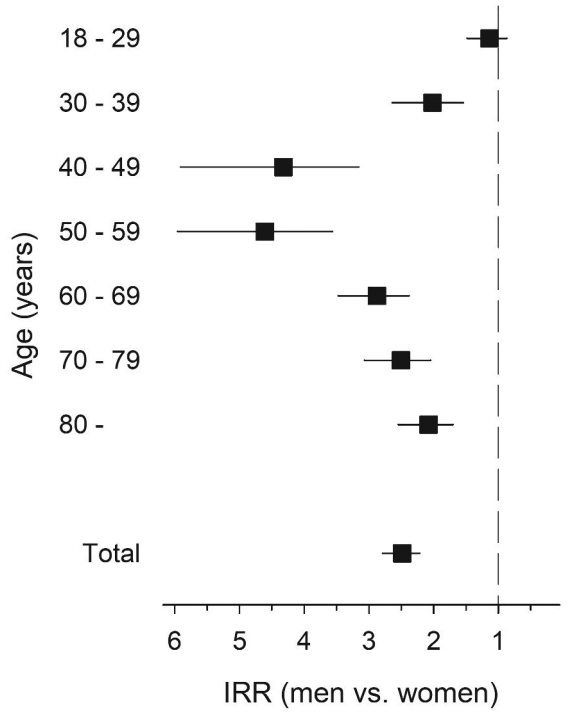

Figure 10. Sex differences in the relative risk of infective endocarditis by age in the general adult population. IRR=incidence rate ratio. Error bars represent 95% CI. Reprinted from the original publication I with the permission of the copyright holders.

5.3 Length of stay

5.3.1 Study III

The median LOS was 20.0 (IQR 10.0–34.0) days. In the multivariable analysis, the men had longer median LOS than the women (20.0 vs. 18.0 days, p=0.015) (Table 3). Furthermore, the patients aged 18–39 years had a significantly longer median LOS than the oldest patients (≥80 years) (24.0 vs. 16.0 days, p=0.014). However, no difference was found in pairwise comparisons between the patients with different CCI scores. In the univariable analysis, no difference was found in LOS in patients with or without a prosthetic valve implantation (p=0.962) or pacemaker operation (0.395) during the year prior to IE admission. The patients who died during the admission (n=217) had significantly shorter median LOS, 12.0 (IQR 7.0–22.0) days, than the patients who survived (n=1949), 20.0 (IQR 11.0–35.0) days (p<0.001).

Table 3. Predictors of the length of stay in patients with infective endocarditis admission during 2005–2014 in the multivariable analysis. Modified from the original publication III.

Parameter	Median (IQR) hospital stay (days)	Adjusted mean difference (95% CI)	P value
Sex			
Female	18.0 (10.0–31.0)	Reference	
Male	20.0 (10.0–35.0)	0.11 (0.02–0.21)	0.015
Age group (years)			0.014
18–39	24.0 (12.0–40.0)	Reference	
40–59	21.0 (10.0–34.5)	-0.18 (-0.36–0.01)	0.067
60–79	19.0 (10.0–32.0)	-0.13 (-0.30–0.04)	0.239
≥80	16.0 (9.0–29.0)	-0.24 (-0.44–(-0.03))	0.014
CCI* score			0.030
0	21.0 (11.0–35.0)	Reference	
1	17.0 (9.0–32.0)	-0.12 (-0.25–0.01)	0.073
≥2	18.0 (9.0–31.0)	-0.11 (-0.25–0.03)	0.148

*Charlson comorbidity index

5.4 Mortality

5.4.1 Short-term mortality

5.4.1.1 Study I

Thirty-day all-cause mortality after IE admission was 11.3%. In the multivariable analysis, mortality increased significantly with age (Figure 11, Table 4) but was similar for both sexes (Table 4). Thirty-day mortality was 4.8% in patients <50 years, 10.9% in patients aged 50–69, increasing to 16.0% in the oldest (>70 years) patients ($p<0.0001$). The age difference was similar for men and women (interaction $p=0.145$). Thirty-day mortality increased with the comorbidity burden (CCI) (Table 4). A prosthetic valve implantation or pacemaker operation a year prior to IE did not affect 30-day mortality ($p=0.217$ and 0.993).

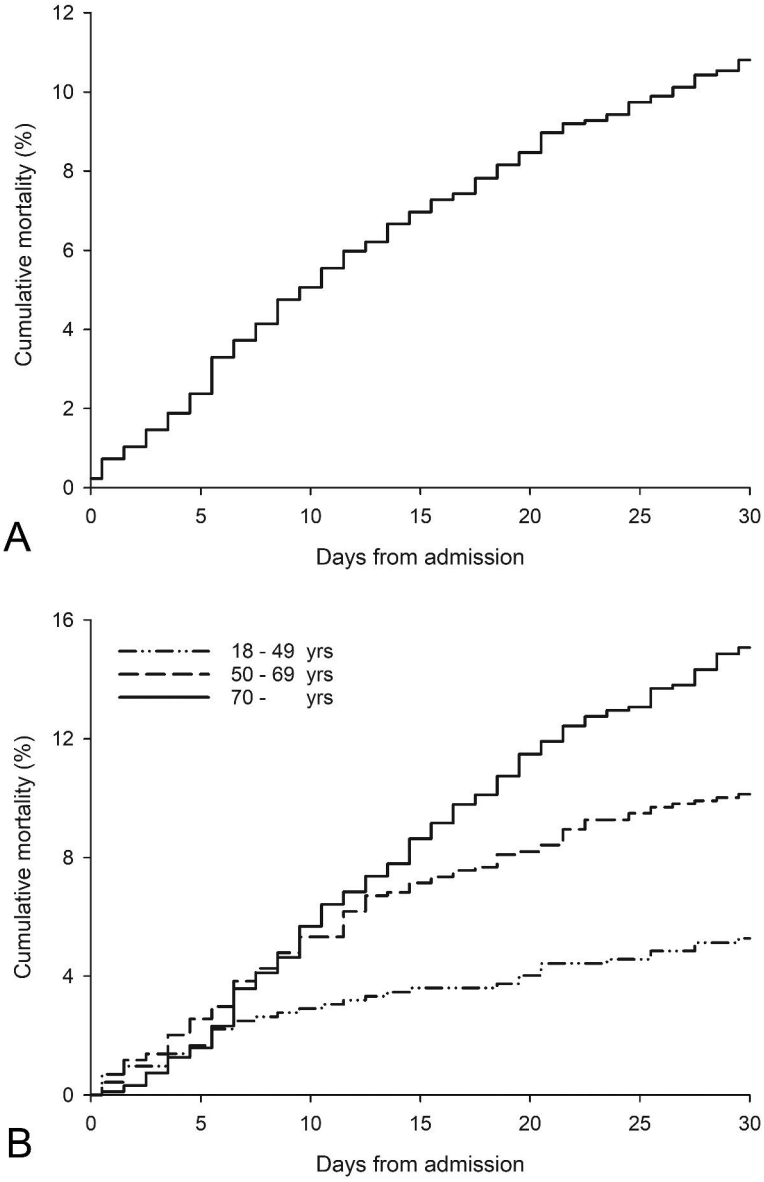

Figure 11. Cumulative total (A) and age-stratified (B) all-cause 30-day mortality after infective endocarditis admission. Reprinted from the original publication I with the permission of the copyright holders.

Table 4. Predictors of 30-day mortality after the first infective endocarditis admission during 2005–2014 in the multivariable analysis. Modified from the original publication I.

Parameter	HR (95% CI)	P value
Sex		
Male	Reference	
Female	1.09 (0.84–1.40)	0.532
Age group (years)		<0.0001
18–49	Reference	
50–69	2.05 (1.35–3.13)	0.001
≥70	2.83 (1.88–4.24)	<0.0001
CCI* score		<0.0001
0	Reference	
1	2.00 (1.49–2.70)	<0.0001
≥2	2.40 (1.79–3.23)	<0.0001

*Charlson comorbidity index

5.4.1.2 Study III

All-cause in-hospital mortality was 10% with no significant difference between men and women (9.3% vs. 11.5%, p=0.120). In-hospital mortality increased with aging and the comorbidity burden (CCI) in the multivariable analysis (Table 5) but was similar regardless of pacemaker operation (p=0.774) or prosthetic valve implantation (p=0.868) one year prior to IE admission. Furthermore, no seasonal variation was discovered (p=0.713).

5.4.2 Long-term mortality

5.4.2.1 Study III

One-year all-cause mortality was 22.7%, whereas five- and ten-year mortality was 37.5% and 48.5%, respectively (Figure 12). Median follow-up time after IE hospitalization was 4.0 years (range 0.0–10.0 years) for all patients, 5.9 years (range 2.0–10.0 years) for those who were alive by the end of follow-up time, and 0.58 years (range 0.0–9.8 years) for those who were not. In the multivariable analysis, the one-year mortality of women and men was similar (27.1% vs. 20.6%, p=0.075) (Table 5). However, five- and ten-year mortality was higher in women than in men (43.6% vs. 34.5%, p=0.034 and 55.7% vs. 45.1%, p=0.021) (Table 6, Figure 13).

Long-term mortality increased with age (Figure 13) and the comorbidity burden (CCI) (Table 6). Pacemaker operation or prosthetic valve implantation one year prior to IE admission did not affect long-term mortality. The underlying causes of deaths of the patients who died are listed in Table 7.

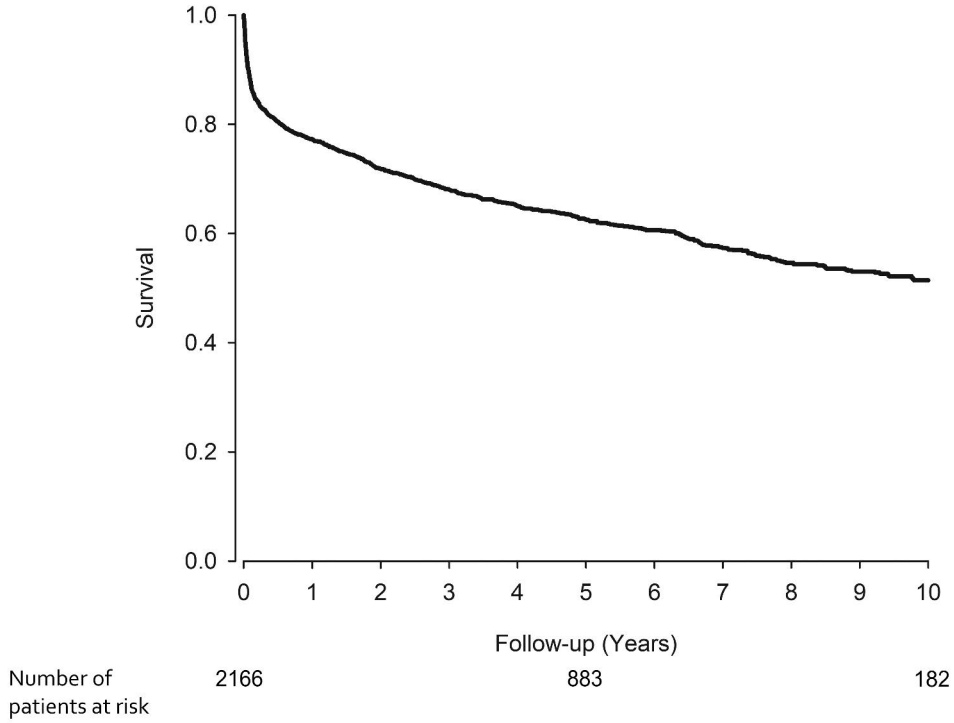

Figure 12. Overall ten-year survival of patients with infective endocarditis admission during 2005–2014. Reprinted from the original publication III with the permission of the copyright holders.

Table 5. Predictors of in-hospital and one-year mortality after infective endocarditis admission during 2005–2014 in the multivariable analysis. Modified from the original publication III.

	In-hospital mortality		**One-year mortality**	
Parameter	OR (95% CI)	P	HR (95% CI)	P
Sex				
Male	-		Reference	
Female	-	-	1.19 (0.98–1.43)	0.075
Age group (years)		0.006		<0.001
18–39	Reference		Reference	
40–59	1.47 (0.81–2.68)	0.203	1.80 (1.17–2.76)	0.008
60–79	2.24 (1.29–3.89)	0.004	2.85 (1.92–4.24)	<0.001
≥80	2.35 (1.28–4.32)	0.006	4.22 (2.79–6.39)	<0.001
CCI* score		<0.001		<0.001
0	Reference		Reference	
1	1.97 (1.39–2.80)	<0.001	2.06 (1.65–2.56)	<0.001
≥2	2.56 (1.81–3.63)	<0.001	2.63 (2.12–3.26)	<0.001

*Charlson comorbidity index

Table 6. Predictors of five- and ten-year mortality after infective endocarditis admission during 2005–2014 in the multivariable analysis. Modified from the original publication III.

	Five-year mortality		**Ten-year mortality**	
Parameter	HR (95% CI)	P	HR (95% CI)	P
Sex				
Male	Reference		Reference	
Female	1.18 (1.01–1.36)	0.034	1.18 (1.03–1.36)	0.021
Age group (years)		<0.001		<0.001
18–39	Reference		Reference	
40–59	1.88 (1.35–2.62)	<0.001	1.79 (1.32–2.43)	<0.001
60–79	2.90 (2.14–3.95)	<0.001	2.85 (2.16–3.78)	<0.001
≥80	4.96 (3.60–6.84)	<0.001	5.00 (3.72–6.71)	<0.001
CCI* score		<0.001		<0.001
0	Reference		Reference	
1	1.72 (1.44–2.05)	<0.001	1.60 (1.35–1.88)	<0.001
≥2	2.64 (2.23–3.12)	<0.001	2.47 (2.11–2.91)	<0.001

*Charlson comorbidity index

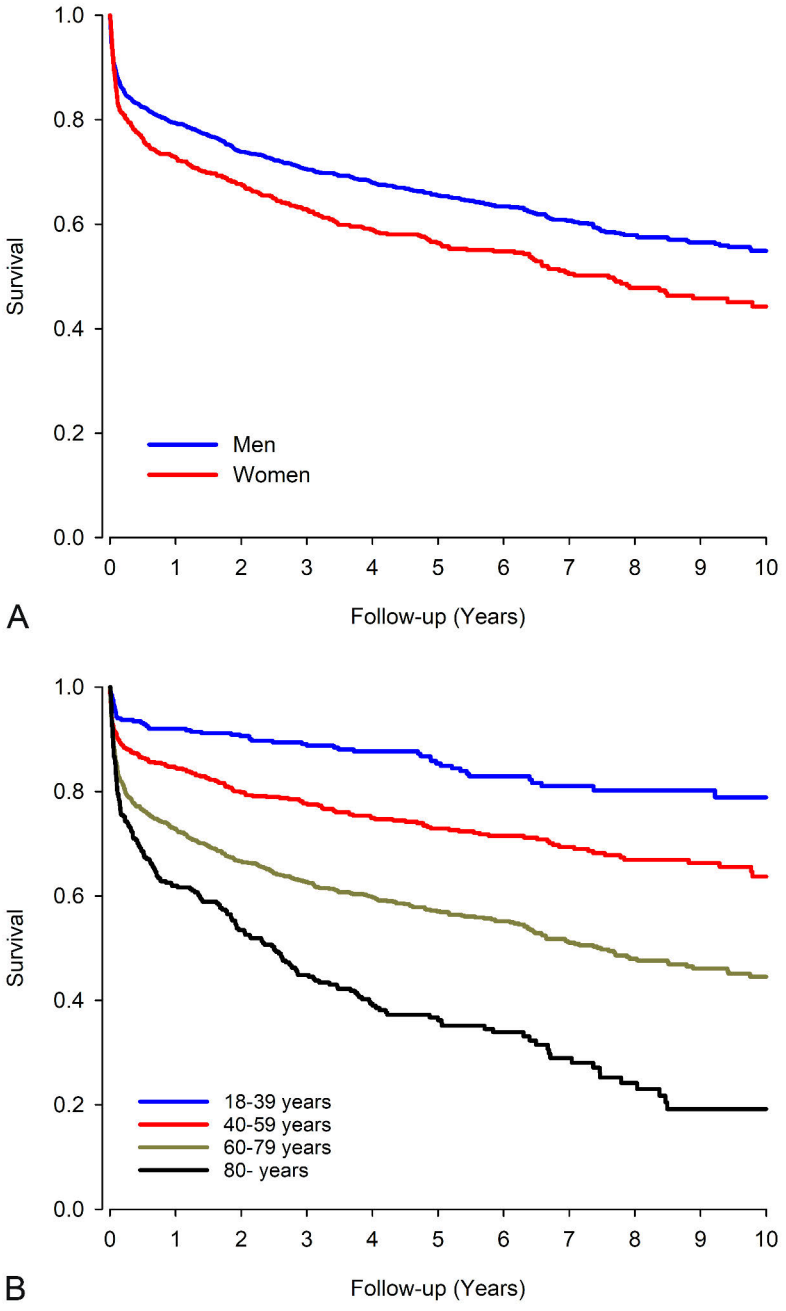

Figure 13. Ten-year survival of patients with infective endocarditis admission during 2005–2014 by A) sex and B) age group. Reprinted from the original publication III with the permission of the copyright holders.

Table 7. Underlying causes of deaths of infective endocarditis patients who died within ten years of the admission (n=878). Modified from the original publication III.

Underlying cause of death	N	**%**
Endocarditis	153	17.4
Septicemia	60	6.8
Other infection	28	3.2
Cardiovascular/circulatory disease*	329	37.5
Neoplasm/blood disease*	110	12.5
Digestive tract disease*	45	5.1
Accidents or violence	39	4.4
Endocrinological disease*	34	3.9
Psychiatric disease	22	2.5
Nervous system disease*	14	1.6
Congenital malformations	12	1.4
Musculoskeletal/connective tissue disease*	11	1.3
Genitourinary disease*	11	1.3
Respiratory tract disease*	7	0.8
Skin/subcutaneous tissue disease*	1	0.1
Unspecified	2	0.2

*Excluding infections

5.5 Temporal trends

5.5.1 Study I

The total incidence of IE hospitalizations ranged from 5.71/100,000 in 2005 to 7.08/100,000 in 2012, increasing on average by 2.13% per year (IRR 1.021; 95% CI: 1.002–1.042; p=0.035) (Figure 14). There was no difference in the overall incidence trend between men and women (interaction p=0.725). However, the incidence trends of the different age groups were significantly different (interaction p=0.003) (Table 8). In the population aged 18–39 years, IE incidence increased annually by 7.2%–7.6% (p=0.002). Furthermore, estimated 3.8% annual increase in incidence was found in the population aged 40–49, yet not reaching the significance level (p=0.084). In the older population, however, no clear incidence trend was observed

during the study period. The proportion of patients who had undergone a prosthetic valve or pacemaker operation during the year before IE admission varied by study year but had no significant trend. Furthermore, the comorbidity burden (CCI score) remained similar over the study period. Thirty-day mortality remained stable during the study period with a similar rate in both sexes and different age groups (interaction p>0.65 for both).

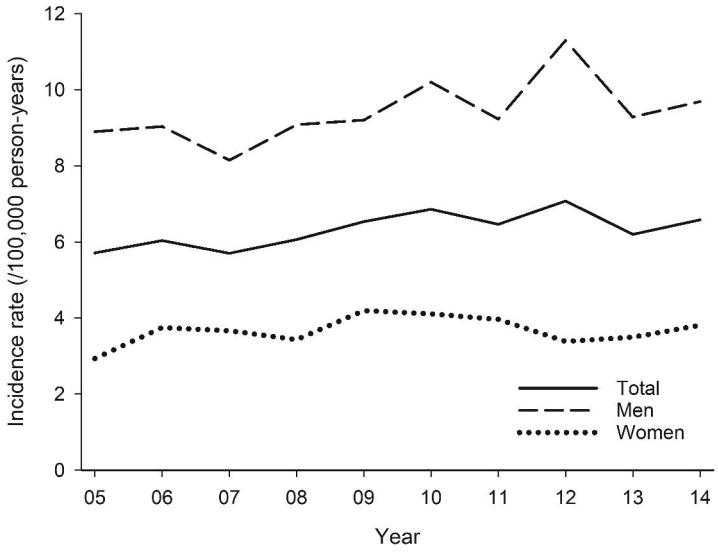

Figure 14. Trends in the annual incidence rate of infective endocarditis in the general adult population during 2005–2014. Reprinted from the original publication I with the permission of the copyright holders.

Table 8. Trends in the annual incidence rate of infective endocarditis hospitalizations during 2005–2014 by age. Modified from the original publication I.

Age (years)	Estimated annual change (%)	95% CI	P value
18–29	7.62	2.67–12.81	0.002
30–39	7.24	2.61–12.07	0.002
40–49	3.82	-0.50–8.32	0.084
50–59	0.52	-2.60–4.01	0.767
60–69	0.20	-2.75–3.18	0.910
70–79	-2.05	-5.39–1.42	0.244
80–	1.32	-2.23–5.00	0.470
Total*	2.13	0.15–4.15	0.035

* Adjusted for age

5.5.2 Study II

The incidence of IE-related deaths remained stable (p=0.994) during the study period (Figure 15). Furthermore, the proportion of deaths related with IE did not change significantly (p=0.465) over the study period (Figure 15).

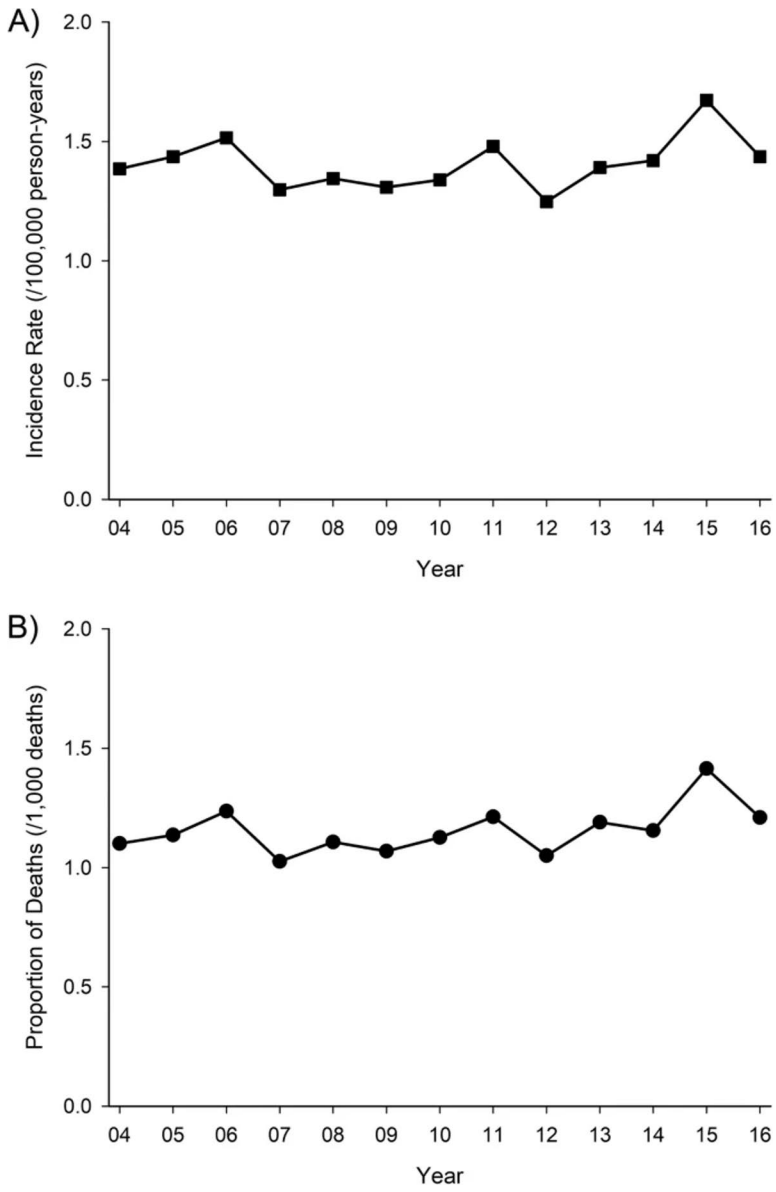

Figure 15. Occurrence of deaths associated with infective endocarditis in the adult population during 2004–2016. Standardized incidence rate (A) and proportion of deaths (B) associated with infective endocarditis of total deaths. Reprinted from the original publication II with the permission of the copyright holders.

5.5.3 Study III

Length of admission (p=0.726), in-hospital (p=0.054), or one-year mortality (p=0.081) did not change significantly between the study periods 2005–2009 and 2010–2014.

5.6 Proportion and causes of deaths

5.6.1 Study II

In the general adult population, IE contributed to an average of 1.16 out of 1000 deaths (95% CI: 1.08–1.24). The proportion of IE-associated deaths was highest in the population aged <40 years (4.42/1000; 95% CI: 3.41–5.64) and decreased thereafter with age to 0.39/1000 (95% CI: 0.28–0.53) in ≥90-year-olds (p<0.0001). Men had a higher proportion of IE-related deaths (1.38/1000; 95% CI: 1.25–1.51) than women (0.94/1000; 95% CI: 0.84–1.05) with a RR of 1.47 (95% CI: 1.17–1.84; p=0.0008). Association was not modified by age (interaction p=0.234).

Infective endocarditis was the underlying cause of death in 46.7% of deaths. The proportion of deaths with IE as the underlying cause was 0.54/1000 deaths (95% CI: 0.49–0.60), and the age and sex distribution was comparable to all IE-associated deaths. Septicemia was recorded as an underlying cause of death in 11.5% of cases and another infectious disease in 2.8% (Table 9). Staphylococci were recorded as having caused 62.1% of the septicemias as the underlying cause of death, streptococci 19.5%, and other or undetermined pathogens 18.4%. *Staphylococcus aureus* accounted for 91.3% of the staphylococcal septicemias. The most frequent non-infectious underlying causes of death were cardiovascular diseases (16.3%), of which coronary artery disease/myocardial infarction (39.8%) and cerebrovascular disease/stroke (18.7%) were the major contributors. In 46 cases (6.1%), the underlying cause of death was valvular stenosis or insufficiency: the aortic valve was affected in 60.9% (of which 89.2% were stenosis), the mitral valve in 23.9% (stenosis in 63.6%), and the tricuspid valve in 6.5% of the cases.

Table 9. Underlying causes of deaths associated with infective endocarditis during 2004–2016 (n=754). Modified from the original publication II.

Underlying cause of death	N	**%**
Endocarditis	352	46.7
Septicemia	87	11.5
Other infection	21	2.8
Cardiovascular/circulatory disease*	123	16.3
Neoplasm/blood disease*	48	6.4
Psychiatric disease	30	4.0
Digestive tract disease*	25	3.3
Endocrinological disease*	18	2.4
Musculoskeletal/connective tissue disease*	17	2.7
External causes/accidents	12	1.6
Congenital malformations	6	0.8
Respiratory tract disease*	6	0.8
Nervous system disease*	3	0.4
Skin/subcutaneous tissue disease*	3	0.4
Genitourinary disease*	3	0.4

*Excluding infections

5.7 Seasonal variation

5.7.1 Studies II and III

No seasonal (p=0.214) differences were observed in the incidence of IE-related deaths. Moreover, no seasonal variation was observed in LOS (p=0.829) or in five- and ten-year mortality (p=0.754 and 0.480). In the univariable analysis, the patients hospitalized due to IE in the summer had higher one-year mortality than the patients hospitalized in the winter (HR 1.30; 95% CI: 1.01–1.66; p=0.041). Nevertheless, in the overall comparison between the seasons, mortality was stable (p=0.199).

5.8 Microbial etiology

5.8.1 Study IV

Staphylococcus aureus was the most common etiology of IE accounting for 34.4% (n=116) of IE cases. Viridans group streptococci were the second most common etiology, accounting for 19.6% (n=66) of cases, and enterococci (8.9%, n=30) were third. Coagulase-negative staphylococci accounted for 6.2% (n=21) and the group Other (other microbe than *S. aureus*, viridans group streptococcus, enterococcus, CoNS; or two or more microbes from the different groups mentioned) for 16.9% (n=57) of cases. There was only one case of MRSA. Negative blood cultures were found in 13.9% of the patients.

The patients with IE caused by *S. aureus* were the youngest (median age 53.0 years, IQR 37), whereas the patients with IE caused by enterococci (median age 74.5 years, IQR 13) were the oldest ($p<0.001$ for overall comparison). The sex distribution was similar between the different etiologies ($p=0.636$ for overall comparison). In IE caused by *S. aureus* or the etiological group Other, the patients were more often IVDUs (35.3% and 22.8%) than in the other etiologies ($p<0.001$ for overall comparison). *Staphylococcus aureus* was the cause of IE in 66.1% of IVDUs' IEs. In IE caused by viridans group streptococci, none of the patients were IVDUs.

Enterococcal IE patients more often had a prosthetic valve (43.3%) than the patients with other etiologies ($p<0.001$ for overall comparison). Of the patients with *S. aureus* IE, only 9.5% had a prosthetic valve. There was no difference in the prevalence of coronary artery disease or diabetes between the patients with the different etiologies in the overall comparison ($p=0.279$ and 0.484 for overall comparison). The patients with enterococcal IE more frequently had a history of a previous healthcare procedure or hospital admission (67.9%) than those with other etiologies ($p<0.001$ for overall comparison). In IE caused by *S. aureus*, 35.3% of the patients had a history of a previous healthcare procedure or hospital admission. Of all patients with a previous healthcare procedure or hospital admission, 29.0% had IE caused by *S. aureus* and 15.3% by enterococci.

In *S. aureus* IE, the tricuspid valve was more commonly affected (27.6%) than in IE caused by other etiologies, whereas the aortic valve was more often affected in IE caused by CoNS (71.4%) ($p<0.001$ for overall comparison). Heart failure during IE admission was most frequent in the patients with enterococcal IE (74.1%) and least common in the patients with IE caused by viridans group streptococci (40.6%) ($p=0.026$ for overall comparison).

5.9 Embolic events

5.9.1 Study IV

Embolic event was diagnosed in 125 (39.1%) patients during the IE admission. The factors associated with all embolic events in the univariable analysis were the youngest age group vs. other age groups, IVDU, not having previous anticoagulation therapy, not having coronary artery disease or a prosthetic valve, definite diagnosis of IE according to the modified Duke criteria and the ESC guidelines, *S. aureus* etiology vs. other etiologies, IE of the tricuspid valve and multiple valves vs. the aortic valve, and a vegetation detected on echocardiography. In the multivariable analysis, *S. aureus* etiology vs. viridans group streptococci and enterococci, IE of the multiple valves vs. the aortic valve, and a detected vegetation were associated with all embolic events.

Cerebral embolism was detected in 51 (16.1%) patients during the IE hospitalization. An affected aortic valve vs. tricuspid valve was associated with cerebral embolisms in both the univariable and multivariable analysis and a detected vegetation in the multivariable analysis. Pulmonary embolism was diagnosed in 39 (12.4%) patients during the IE admission. Intravenous drug users consisted of 74.4% (n=29) of the patients with pulmonary embolism. Infective endocarditis was caused by *S. aureus* in 71.8% (n=28) and was located in the tricuspid valve in 74.4% (n=29) of the patients with pulmonary embolism.

6 Discussion

This thesis describes the sex- and age-specific differences, temporal trends, and factors associated with the incidence and mortality of IE in a population-based setting and clinical profile, the characteristics of the different microbiological etiologies, and the factors associated with embolic events in IE patients in a tertiary care hospital in Finland.

6.1 Incidence

In this study, the standardized incidence of IE admissions was 6.3 cases per 100,000 person-years. Comparably, other Western countries have reported incidence rates of 3–8/100,000 person-years (Duval et al., 2012; Jordal et al., 2018; Ternhag et al., 2013; Thornhill, Jones, et al., 2018; Toyoda et al., 2017). According to this study, the youngest population had the lowest probability of IE and the probability increased progressively with age in the older population. One likely explanation is that older patients have more predisposing conditions to severe bacterial infections, such as degenerative valve diseases and other comorbidities (Croft et al., 2004; Nkomo et al., 2006; H. E. Wang et al., 2012).

One of the main findings of this thesis was the rising IE incidence in adults aged <40 years. However, no significant trend was discovered in the older population. These findings differ from those of previous studies. For example, studies in the US, Denmark, and Spain have found increasing IE incidence in the older population (Bor et al., 2013; Erichsen et al., 2016; Olmos et al., 2017). A recent study in Denmark investigating changes in IE incidence from 1997 to 2017 found not only the incidence in the oldest age groups to increase but also in the youngest age group to decline (Jensen et al., 2021). One likely explanation for the increasing IE incidence in the younger population found in this study is the increasing intravenous drug abuse among young Finnish adults (Kankaanpää et al., 2016; Rönkä & Markkula, 2020). According to this study, a notable proportion, 18.5%, of the IE patients treated in Turku University Hospital were IVDUs. A previous study by Heiro et al. of IE patients admitted to Turku University Hospital between 1980 and 2004 found that the proportion of IVDUs increased significantly after 1996 (from 0 to 20%) (Heiro et al., 2006). A recent Finnish study of IE patients by Halavaara et al. in the Helsinki

University Hospital Area between 2013 and 2017 found the proportion of IVDU-related IE cases to be higher than in this study, 31% (Halavaara et al., 2020). Furthermore, studies in other countries in recent years have found substantial variation in the prevalence of IVDU. Two multinational studies, including countries also from outside Europe, found the proportion of IVDUs to be 6.1–6.9% (Erdem et al., 2019; G. Habib et al., 2019), whereas studies in Norway and Sweden described the proportion as considerably higher, 24–32% (Damlin & Westling, 2021; Jordal et al., 2018). Moreover, two of the studies that found increasing IE incidence in the older population also found that the proportion of IVDUs decreased over time (Bor et al., 2013; Olmos et al., 2017). In addition to IVDU, another likely contributor to the increased IE incidence are improved diagnostic methods, for example better availability and advanced technology in echocardiography, especially TEE. The variation in the socioeconomic factors and in, for example, the prevalence of IVDU between the countries and even within a particular country might contribute to the different incidence rates found in different studies.

In this study, the incidence of IE was found to be increasing at a stable rate during 2005–2014, suggesting that the guideline changes restricting antibiotic prophylaxis for IE published in 2007–2009 (G. Habib et al., 2009; Stokes et al., 2008; Wilson et al., 2007) did not remarkably affect the overall incidence of IE in the adult Finnish population. Similar findings have been found in some previous studies (Mackie et al., 2016; T. P. Quan et al., 2020; Toyoda et al., 2017), whereas others have described increasing IE incidence after the restrictions (Dayer et al., 2015; Keller et al., 2017; Van Den Brink et al., 2017). However, although antibiotic prophylaxis prescriptions have been found to be decreasing after the guideline changes (Dayer et al., 2015; Garg et al., 2019; T. P. Quan et al., 2020; Thornhill, Gibson, et al., 2018), it can be speculated that antibiotic prophylaxis is still somewhat widely used despite the restrictions.

According to this study, men were at a 2.5-fold risk of IE compared to women. This is in concordance with a study by Thornhill et al., which found men to have 2.2-fold odds of IE compared to women (Thornhill, Jones, et al., 2018). Other studies have also reported that IE is more common in men (G. Habib et al., 2019; Olmos et al., 2017; Selton-Suty et al., 2012; Sy & Kritharides, 2010; Ternhag et al., 2013; Varela Barca et al., 2021). Male predominance might be explained by the higher burden of risk factors (Thornhill, Jones, et al., 2018) and predisposing medical conditions, such as degenerative valve disease, for IE in men than in women. Moreover, estrogen has been found to protect against endothelial damage (Bakir et al., 2000; Guo et al., 2010). Another important contributor to male overrepresentation is the well-known risk factor for IE, IVDU, which is more common in men (Degenhardt et al., 2017; Rönkä & Markkula, 2020). In this study, the overall incidence trend was similar between men and women, which is in line

with previous studies (Cresti et al., 2017; Olmos et al., 2017; Van Den Brink et al., 2017). However, increased incidence in only women (Correa De Sa et al., 2010) or a more pronounced increase in men (Erichsen et al., 2016) has also been observed.

Interestingly, according to this study, the proportion of patients who had a prosthetic valve or pacemaker implanted or generator changed during the year prior to IE admission was found to remain stable over the years. Previously, an increasing incidence and proportion of all IE has been found in PVIE and in IE associated with intracardiac devices (Carrasco et al., 2016; Cresti et al., 2017; Greenspon et al., 2011; Toyoda et al., 2017). Thus, as the overall number of the operations related to prosthetic material of the heart is increasing, the finding of this study might reflect a low IE rate in these operations in Finland.

6.2 Mortality

According to this study, the in-hospital mortality of IE patients was 10%. Interestingly, the majority of previous studies have reported higher in-hospital mortalities, 14–24% (Bor et al., 2013; Cresti et al., 2017; Erdem et al., 2019; G. Habib et al., 2019; Keller et al., 2017; Olmos et al., 2017; Sunder et al., 2019; Sy & Kritharides, 2010). In most of these studies, the mean age was similar to the finding of 60.7 years in this study, but the higher mean age (63.8–69 years) of the IE patients in three of these studies (Cresti et al., 2017; Olmos et al., 2017; Sunder et al., 2019) might contribute to the higher mortality. However, this study's finding of 30-day mortality being 11.3% is comparable to the 10.4% found in a Swedish study investigating IE patients during 1997–2007 (Ternhag et al., 2013). Furthermore, a study in Norway by Jordal et al. found the 30-day mortality of IE patients to be 12.0% during 1996–2005 and 13.6% during 2006–2015 (Jordal et al., 2018). The lower short-term mortality than in several studies in other countries found in this study and, furthermore, in studies in our neighboring countries might reflect the high standard of care of IE patients in Scandinavia.

In this study, one-year mortality was 22.7% and five-year mortality 37.5%. Previous studies have found somewhat higher rates, 25–37% for one-year (Cresti et al., 2017; Fedeli et al., 2011; Sunder et al., 2019; Toyoda et al., 2017) and 41–53% for five-year mortality (Bannay et al., 2011; Toyoda et al., 2017). However, Jordal et al. found one-year mortality to be 21.1% between 1996 and 2005 and 22.8% between 2006 and 2015 (Jordal et al., 2018), which is comparable to the finding of this study. Nevertheless, age and comorbidities influence long-term mortality, and in three of these previous studies, the mean age of the IE patients was higher than in this study (Cresti et al., 2017; Sunder et al., 2019; Toyoda et al., 2017).

An important and worrying finding of this thesis was the stable mortality over time. Similar findings have been made by other studies (Bor et al., 2013; Cresti et

al., 2017; Keller et al., 2017; Ternhag et al., 2013). In the study by Jordal et al., both 30-day and one-year mortality remained stable (Jordal et al., 2018). The reason for the mortality not declining, despite improved diagnostic and treatment methods, is unclear. The possibilities to diagnose and treat more severely ill patients today might reduce the positive impact of advanced treatment methods on mortality rates. However, in this study, the comorbidity burden (CCI score) of the IE patients remained similar during the study period. In the future, it would be of particular interest to investigate the possible reasons for non-decreasing IE mortality and to attempt to improve the prognosis of IE.

Recent and population-based data on over five-year mortality after IE hospitalization are scarce. This study provided novel information on ten-year mortality after IE admission. According to this study, the ten-year mortality was 48.5%. Heiro et. al reported in their study of IE patients in Turku University Hospital between 1980 and 2004 the overall survival to be 62% at five and 49% at ten years after IE admission (Heiro et al., 2008). Moreover, a study of IE patients in a tertiary referral center in Switzerland during 1980–1995 found the mortality to be 42% at five and 50% at ten years (Netzer et al., 2002). The long-term mortalities reported in these studies from decades ago are comparable to the results of this study. One potential explanation for the non-improving long-term mortality rates found in this study might be the increasing proportion of IVDUs of IE patients and their impaired long-term survival.

According to this study, short-term and one-year mortality was similar between the sexes, whereas five- and ten-year mortalities were higher in women. Previously, similar short-term (G. Habib et al., 2019; Murdoch et al., 2009; Selton-Suty et al., 2012; Sunder et al., 2019) and longer-term mortality (Hill et al., 2007; Netzer et al., 2002; Sunder et al., 2019) between men and women has been reported. Furthermore, Heiro et al. found no difference in short- or long-term mortality between the sexes (Heiro et al., 2007, 2008). However, some differences between sexes have also been reported. Two studies in Spain (Olmos et al., 2017; Varela Barca et al., 2021) and one in the US including only patients with NVIE (Khan et al., 2020) found female sex to be an independent risk factor for in-hospital mortality, whereas in a UK study men were at a significantly higher risk of dying during IE admission (Thornhill, Jones, et al., 2018). Furthermore, in a study in the Netherlands, women had higher long-term mortality (Van Den Brink et al., 2017). The reason why short-term and one-year mortality was similar between the sexes but longer-term mortality higher in women in this study is not clear. Short-term mortality likely better describes the actual mortality of IE, and other causes of death emerge in longer-time mortality. The results of this study were adjusted by the CCI score, but it can be speculated that CCI score might not have taken into account all the comorbidities possibly affecting mortality. Furthermore, previous studies have reported women to undergo surgery

due to IE less often than men (G. Habib et al., 2019; Sunder et al., 2019; Van Den Brink et al., 2017; Varela Barca et al., 2021). This might contribute to the higher mortality in women. In this study, unfortunately, information on surgery rates due to IE was not available. In the future, the mortality differences between the sexes need to be examined further.

6.3 Deaths associated with IE

To better assess the deaths specifically associated with IE, the occurrence of fatal IE was studied in this thesis. This study was the first one to describe the population-based epidemiology of fatal IE. According to this study, the incidence of IE-associated deaths was the lowest in the youngest population and increased progressively with age from 50 years onwards. This is in line with the findings of the other studies of this thesis, which found that the incidence and all-cause mortality of IE increased with age. Accordingly, other studies have also found both the incidence (Erichsen et al., 2016; Jensen et al., 2021; Toyoda et al., 2017) and mortality (Armiñanzas et al., 2019; Cresti et al., 2017; Duval et al., 2012; Fedeli et al., 2011; Olmos et al., 2017) of IE to increase with age. In this study, the proportion of IE-related deaths of all deaths was the highest in the youngest population. This represents a lower number of comorbidities leading to death in this age group.

According to this study, the incidence of fatal IE and the proportion of deaths related to IE remained stable during the study period. This is in concordance with the finding of this study of stable all-cause mortality and the findings of other studies of stable IE mortality over time (Bor et al., 2013; Cresti et al., 2017; Jordal et al., 2018; Keller et al., 2017; Ternhag et al., 2013). However, in the study of fatal IE of this thesis, only deaths that were related to IE were assessed, whereas in other mortality studies all causes of deaths were included.

It was found in this study that IE-associated death occurred in hospital or other healthcare facility in 89.5% and at home in 8.6% of cases. Individuals who were not diagnosed with IE prior to death most likely died elsewhere than in hospital. In this thesis, the incidence of IE was found to be 6.3/100,000 and in-hospital and 30-day mortality 10% and 11.3%, respectively. The finding of the incidence of fatal IE to be 1.42/100,000 therefore suggests that a significant proportion of IE-associated deaths occur later than a month after IE admission or to patients with no IE diagnosis prior to death. One likely contributor are IVDUs, who might not seek help for their IE.

In this study, men were at a two-fold risk of fatal IE compared to women. In another study of this thesis, men were at a 2.5-fold relative risk of IE compared to women. Therefore, when comparing these two studies, in men the risk of IE was found to be slightly higher than the risk of fatal IE when compared to women.

Furthermore, all-cause five- and ten-year mortality was found to be higher in women, although shorter-term mortality was similar between the sexes. It can be speculated that most deaths coded as IE-related occur rather within one year after admission than later. Thus, these results might suggest that in all-cause shorter-term mortality, the cause of death in men might have been other than IE more often than in women. However, as these results are derived from two different studies with different settings, such speculations should be interpreted with caution.

Interestingly, in IE-related deaths, IE was coded as the underlying cause of death in only 46.7% of the cases. Considering the severity of the disease, a higher percentage would have been presumable. Again, one plausible explanation might be that a notable proportion of IE-associated deaths occur after the acute phase of the disease. The age distribution of the cases with IE as the underlying cause of death was similar to all IE-associated deaths. Thus, the comorbidities of the elderly often coded as the underlying cause of death do not directly explain the somewhat low percentage. Septicemia was the underlying cause of death in 11.5% of the cases. Of septicemias, 62.1% were recorded as having been caused by staphylococci and of these, 91.3% were *S. aureus.* The rather high percentage of septicemia as the underlying cause of death might reflect the frequency of uncontrolled infection and complications of sepsis (e.g. septic shock) in IE patients. The finding of *S. aureus* causing more than half of septicemias is in concordance with previous studies that have found *S. aureus* etiology to be associated with increased mortality (Bor et al., 2013; Cresti et al., 2017; Jordal et al., 2018; Miro et al., 2005; Olmos et al., 2017; Selton-Suty et al., 2012; Sunder et al., 2019).

6.4 Length of stay

In this study, the median LOS due to IE was 20.0 days. Previously, a substantial variation in LOS due to IE between studies in different countries has been found, 7–43 days (Fedeli et al., 2011; Morita et al., 2019; Olmos et al., 2017; Schranz et al., 2019; Selton-Suty et al., 2012; Sunder et al., 2019; Sy & Kritharides, 2010; Ternhag et al., 2013). A study in Sweden found similar median LOS to this study, 23 days (Ternhag et al., 2013). A notably shorter median LOS was reported in two different studies in the US: seven days (Schranz et al., 2019) and ten days (Morita et al., 2019), whereas a French study found median LOS to be 43 days (Selton-Suty et al., 2012). A possible explanation for the shorter admissions found in some countries might be the wider use of outpatient clinics and quicker transfer to other healthcare facilities. However, in an Australian study, similar median LOS to this study (20 days) was found in patients enrolled in an outpatient parenteral antimicrobial therapy program, whereas the LOS of the patients receiving regular therapy was significantly longer, 45 days (Holland et al., 2020).

According to this study, the LOS of patients who died during the admission was shorter than of patients who survived. Similar findings have been described in studies in Spain and France (Muñoz et al., 2015; Selton-Suty et al., 2012). Thus, these results suggest that if the LOS of only survived patients is investigated, the admissions are likely longer. However, the previously mentioned US study included only the patients who survived until hospital discharge and reported median LOS to be only ten days (Morita et al., 2019). Nevertheless, a significant proportion of the discharged patients, 24.8%, were readmitted within 30 days, which might be associated with the short initial LOS.

Curiously, in this study, the LOS remained stable over time. Previously, an Italian study found median LOS to increase from 30 to 35 days between 2000 and 2008 (Fedeli et al., 2011). However, a US study including only patients with NVIE found the mean LOS to decrease from 17.4 to 13.4 days between 2002 and 2016 (Khan et al., 2020). It would be of common interest to shorten hospital stays for financial reasons. The utilization of a new regimen with partial oral antibiotic treatment replacing the full-time intravenous treatment might shorten LOS in IE patients in the future (Iversen et al., 2019). However, considering the often-severe course of the disease, shortening of LOS due to IE might be challenging.

Little is known about the factors associated with LOS in IE patients. Curiously, according to this study, the youngest patients had longer admissions than the oldest. One plausible explanation might be that young IE patients are more often IVDUs as was found in this study (mean age of the IVDUs was 30.4 years) and in other studies (Gray et al., 2018; Leahey et al., 2019; Thakarar et al., 2019). Furthermore, IVDUs' IE hospitalizations have been reported to be longer than non-IVDUs' (Gray et al., 2018; Schranz et al., 2019). Intravenous drug users' IE is more often caused by *S. aureus* as was found in this study (66.1% of IVDUs' IEs were caused by *S. aureus*) and, furthermore, in other studies (Halavaara et al., 2020; Leahey et al., 2019; Murdoch et al., 2009). In *S. aureus* IE, complications are frequent and potentially require operative treatment and consequently longer hospitalization (Rizzi et al., 2014; Thuny et al., 2005). Moreover, it has previously been found that surgically treated patients are younger (Cabell et al., 2005; Heiro et al., 2007; Tleyjeh et al., 2007; Tornos et al., 2005) and have longer hospitalizations than only medically treated patients (Schranz et al., 2019; Slater et al., 2007). Additionally, older IE patients might be more likely to be transferred to other healthcare facilities, such as health center wards, to continue their treatment. Previously, one study of patients treated for IE during 1987–1996 reported similar LOS between the different age groups (Peled et al., 2006). However, in recent years, no other studies have examined the association of age with LOS due to IE. In LOS studies, it should be considered that the differences between healthcare systems, for example the availability of health center wards, in different countries might affect results.

6.5 Seasonal variation

In this study, no seasonal variation was found in the occurrence of fatal IE or in in-hospital, five-, or ten-year mortality. Furthermore, no seasonality was found in LOS. These findings suggest that the severity of IE is not associated with the timing of the disease. Moreover, the quality of care in IE or LOS is not affected by, for example, the holiday seasons, when experienced healthcare staff are limited, and wards are temporarily closed. Accordingly, a previous study in Finland found no difference in LOS or mortality during internal medicine ward admissions between July and November (Sipilä et al., 2014). Previously, seasonal variation in mortality has been reported in sepsis (Danai et al., 2007), but data on the seasonality of IE are limited. A French study reported the incidence of cardiac implantable device infections to be positively associated with high temperature and precipitation (Maille et al., 2019).

6.6 Microbial etiology

In this study, *S. aureus* was the most common microbial etiology of IE (34.4% of the cases), which is in concordance with previous studies (Cresti et al., 2017; Erdem et al., 2019; G. Habib et al., 2019; Hill et al., 2007; Jordal et al., 2018; Selton-Suty et al., 2012). Halavaara et al. found *S. aureus* to be the cause of IE in 36.1% of the cases comparative to this study (Halavaara et al., 2020). Moreover, Heiro et al. stated in their study of IE patients during 1980–2004 that after 1994 *S. aureus* was the most common causative pathogen for IE (30.0–32.6% of the cases) (Heiro et al., 2006). The virtually unchanged proportion of *S. aureus* IE in Turku University Hospital between 1994 and 2017 might contribute to the stable mortality found in this study, as *S. aureus* etiology has been found to be associated with increased mortality (Bor et al., 2013; Cresti et al., 2017; Jordal et al., 2018; Leone et al., 2012; Miro et al., 2005; Olmos et al., 2017; Selton-Suty et al., 2012; Sunder et al., 2019).

Considering the alarming global antibiotic resistance problem, interestingly, only one case of MRSA (0.3% of IE patients) was found in this study. Halavaara et al. reported the proportion of IE patients with MRSA to be 2.2% (Halavaara et al., 2020). Previously, studies in Europe and Australia have found higher proportions of MRSA, 4–7.5% (Ferraris et al., 2018; Hill et al., 2007; Holland et al., 2020; Motoc et al., 2021; Selton-Suty et al., 2012; Sy & Kritharides, 2010). Furthermore, in a multicenter study including 41 hospitals in 13 countries investigating IE patients during 2015–2018, the prevalence of MRSA was 8.4% (Erdem et al., 2019). The finding of this study might reflect a rather good antibiotic resistance situation in Turku University Hospital. Furthermore, the proportion of MRSA of all *S. aureus* bacteremias in Turku University Hospital between 2005–2017 was only 1.2% (Turku University Hospital SAI-register (Sairaalan Antibiootti- ja Infektioseurantajärjestelmä, Hospital Antibiotic and Infection Monitoring System,

Neotide Oy), searched April 7, 2022), which is similar to the proportion of MRSA of all *S. aureus* bacteremias found in the IE patients in this study (0.8%).

In this study, enterococci caused 8.9% of the IE cases. Accordingly, Halavaara et al. described the proportion of enterococci as 9.9% (Halavaara et al., 2020) and Heiro et. al the proportion of *E. faecalis* 8.6% (Heiro et al., 2006). Recent studies in other countries have reported slightly higher proportions of enterococcal IE, 11.5–18% (Erdem et al., 2019; Ferraris et al., 2018; G. Habib et al., 2019; Motoc et al., 2021). According to the findings of this study, patients with IE caused by enterococci more often had heart failure (74.1%) during IE hospitalization than those with other etiologies. However, the patients with enterococcal IE were also older, as has also been reported by other studies (McDonald et al., 2005; Olaison & Schadewitz, 2002; Pericàs et al., 2020). Moreover, similarly to this study, a recent prospective study in Spain including 35 centers reported that enterococcal IE patients have heart failure more often than patients with other etiologies (Pericàs et al., 2020). Furthermore, in the study of Heiro et al., the proportion of *E. faecalis* IE patients with heart failure was high, 68% (Heiro et al., 2007). In this study, the enterococcal IE patients more often had a prosthetic valve (43.3%) than those with other etiologies. In previous studies, patients with enterococcal IE were found to have a prosthetic valve slightly less frequently, in 29–39% of patients (Anderson et al., 2005; Chirouze et al., 2013; Fernández Guerrero et al., 2007; Pericàs et al., 2020; Selton-Suty et al., 2012).

According to this study, a considerable proportion of the patients (41.3%) had a history of a significant healthcare procedure or hospital admission during six months before the IE hospitalization. Previously, approximately 30% of IE cases have been found to be healthcare-associated (Cresti et al., 2017; Fernández-Hidalgo et al., 2008; G. Habib et al., 2019; Halavaara et al., 2020; Holland et al., 2020; Kiriyama et al., 2020; Selton-Suty et al., 2012; Sy & Kritharides, 2010). However, a US study of 75,829 IE patients between 1998 and 2013 stated that around half of the IE cases were healthcare-associated (Toyoda et al., 2017). Nevertheless, the definition of healthcare-associated IE differs between studies and therefore affects the determined proportions.

Previously, *S. aureus* has been found to be the most common etiology of healthcare-associated IE (Fernández-Hidalgo et al., 2008; Kiriyama et al., 2020; Selton-Suty et al., 2012). However, enterococci have also emerged as prominent causative pathogens in healthcare-associated IE (Fernández-Hidalgo et al., 2008; Halavaara et al., 2020; Leone et al., 2012; Sy & Kritharides, 2010). In this study specifically investigating the characteristics of the different etiologies, a significant proportion, 67.9%, of the patients with IE caused by enterococci had a history of a previous healthcare procedure or hospital admission, and the proportion was higher than in other etiologies. Two previous studies examining enterococcal IE reported

the proportion of healthcare-associated IE to be lower than in this study, 23.4% (Chirouze et al., 2013) and 42.4% (Pericàs et al., 2020).

In this study, the proportion of IVDUs was found to be the highest in *S. aureus* IE (35.3%). Accordingly, previous studies have found 21–49% of *S. aureus* IE to be in IVDUs (Asgeirsson et al., 2015; Fowler et al., 2005; Miro et al., 2005; Ruotsalainen et al., 2006). The proportion of the young group of IVDUs likely explains why in this study the patients with *S. aureus* IE were the youngest. Furthermore, according to this study, the tricuspid valve was more frequently infected in *S. aureus* IE (27.6%) than in other etiologies, which is likely related to IVDUs' IE found to affect the tricuspid valve in 57.1% of the cases in this study. Correspondingly, right-sided IE has previously been reported to be associated with IVDU (Colville et al., 2016; Halavaara et al., 2020; Holland et al., 2020; Leahey et al., 2019), and the right-sided valves of the heart to be infected in 8–37% of *S. aureus* IE (Asgeirsson et al., 2015; Fowler et al., 2005; Le Moing et al., 2015; Nadji et al., 2005; Rasmussen et al., 2011; Ruotsalainen et al., 2006).

6.7 Embolic events

According to this study, 39.1% of the IE patients had an embolic event during hospitalization. This is in concordance with previous studies reporting that embolic events are detected in 34–55% of IE cases (Di Salvo et al., 2001; Erdem et al., 2019; Holland et al., 2020; Rizzi et al., 2014; Selton-Suty et al., 2012; Thuny et al., 2005). Furthermore, in this study, cerebral embolism was present in 16.1% of the patients during admission. Accordingly, cerebral embolism has previously been found in 16–26% of IE patients (Erdem et al., 2019; Holland et al., 2020; Rizzi et al., 2014; Selton-Suty et al., 2012; Thuny et al., 2005). Furthermore, Heiro et al. found that 31.3% of the IE patients in their study had embolisms outside the central nervous system and 8.3% had an embolic brain infarction (Heiro et al., 2006). Therefore, the overall rate of embolisms was comparable to the finding of this study, but embolic brain infarctions were detected less frequently than cerebral embolisms in this study. The improved availability and accuracy of cerebral imaging over the years has likely contributed to the higher rates of embolisms observed.

In this study, IE of the multiple valves vs. the aortic valve was associated with embolic events. Previous studies have found contradictory results regarding the association between the valve localization of IE and embolic events. Some studies have reported the mitral valve to be associated with embolic events (Berdejo et al., 2014; Yang et al., 2019). Nevertheless, an Italian multicenter study of 1456 IE episodes found right-sided IE to be an independent predictor of embolic events, but IE of the mitral vs. the aortic valve or IE of both the mitral and aortic valve were not predictors of embolisms (Rizzi et al., 2014). Moreover, a prospective cohort study

including 156 hospitals in 40 countries found right-sided IE to be independently associated with new embolic events under therapy (G. Habib et al., 2019). Aortic valve IE was reported to be an independent predictor of embolic events in a recent study in Belgium (Motoc et al., 2021). However, several other studies have found no association between the valve localization of IE and embolic events (Deprèle et al., 2004; Di Salvo et al., 2001; Hill, Herijgers, et al., 2008; Hubert et al., 2013; Mangoni et al., 2003; Pepin et al., 2009; Thuny et al., 2005; Vilacosta et al., 2002).

Previously, *S. aureus* etiology of IE has been found to be related to an increased risk of embolic events (Fabri et al., 2006; G. Habib et al., 2019; Miro et al., 2005; Rizzi et al., 2014; Tascini et al., 2020; Thuny et al., 2005). Moreover, *S. aureus* etiology has been reported to be associated with a higher rate of overall cerebral complications (Arregle et al., 2021; Dickerman et al., 2007; García-Cabrera et al., 2013) and ischemic cerebral lesions in IE patients (Iung et al., 2013; Xu et al., 2020). Interestingly, in this study, *S. aureus* vs. viridans group streptococci and enterococci was associated with any embolic event, but in cerebral embolisms no association with the etiology was detected. Similarly, Heiro et al. found peripheral emboli to be more frequent in patients with IE caused by *S. aureus* than other etiologies, but no significant difference was found in the rate of cerebral embolisms in the overall comparison between the different etiologies (Heiro et al., 2007). Nevertheless, a multivariable analysis was not performed in their study.

According to this study, pulmonary embolism was detected in 12.4% of the patients. Several studies have found lower rates of pulmonary embolism, 4–9%, (Di Salvo et al., 2001; Erdem et al., 2019; Rizzi et al., 2014; Selton-Suty et al., 2012; Thuny et al., 2005), likely due to the lower proportions of IVDUs (3–9%) in these studies than in this study. However, in a recent study in Australia, pulmonary embolism was found in 19% of IE cases, and accordingly the proportion of IVDUs was higher than in this study, 23% (Holland et al., 2020). Previously, pulmonary embolisms have been described as occurring frequently in IVDUs' IEs (Halavaara et al., 2020; Holland et al., 2020) and as being related to the tricuspid valve IE and *S. aureus* etiology (Clarelin et al., 2021; Erdem et al., 2019; Miro et al., 2005; Rizzi et al., 2014). Accordingly, in this study, 74.4% of the patients with pulmonary embolism were found to be IVDUs and the majority had IE of the tricuspid valve and *S. aureus* etiology. The significant role of *S. aureus* in the occurrence of all embolic events found in several studies might be at least partly due to the proportion of pulmonary embolisms. Furthermore, the association between the valve localization of IE and all embolic events might be affected by the proportion of pulmonary embolism if not taken into account. In this study, this was taken into consideration in the multivariable analysis. The youngest age group vs. other age groups, IVDU, and IE of the tricuspid valve vs. the aortic valve were related to embolic events in the univariable but not in the multivariable analysis. However, *S.*

aureus etiology vs. viridans group streptococci and enterococci was associated with embolic events also in the multivariable analysis.

In this study, CoNS were not less frequently associated with embolic events in IE than *S. aureus.* Correspondingly, a recent study investigating IE caused by CoNS or *S. aureus* found the rate of embolic events to be similar between the two groups (Bourget et al., 2022). However, a study involving patients with NVIE found that the occurrence of systemic emboli other than stroke was higher in patients with IE caused by *S. aureus* vs. CoNS (Chu et al., 2008).

According to this study, a vegetation detected on echocardiography was related to a higher occurrence of all embolic events and cerebral embolisms. This is in line with previous studies (G. Habib et al., 2019; Heiro et al., 2007; Yang et al., 2019). Interestingly, a detected vegetation was the only factor associated with both all embolic events and cerebral embolisms. In addition to the vegetation, the only factor related to cerebral embolisms was IE of the aortic valve vs. the tricuspid valve. Previously, several studies have reported that an affected mitral valve in IE patients is associated with cerebral complications (Cabell et al., 2001; Cao et al., 2019; Dickerman et al., 2007; Selton-Suty et al., 2016; Valenzuela et al., 2018; Xu et al., 2020). However, some studies have made contradictory findings. An affected mitral valve or mitral and aortic vs. aortic valve were not associated with a higher risk of ischemic neurological complications in a Spanish multicenter study examining neurologic complications of IE (García-Cabrera et al., 2013). Moreover, a recent study in France stated that IE affecting the aortic or mitral valve was not related to neurological complications (Arregle et al., 2021). Furthermore, Heiro et al. found no difference in the valve involvement of IE in the rate of cerebral embolisms (Heiro et al., 2007).

The explanation for why *S. aureus* etiology was related to a higher rate of any embolic events but not cerebral embolisms in this study is unclear. Furthermore, the reason for the contradictory findings regarding the association of valve involvement in IE with embolic events in different studies remains to be examined. Naturally, if a vegetation is located on the tricuspid valve, it cannot pass through to the brain to cause cerebral embolisms. However, it is possible that simultaneously there is a vegetation on the left-sided valve, but it has not been detected. This can affect the results of studies of embolisms. On the mitral valve, the vegetations might grow larger as the pressure gradients are not as high as in the aortic location. This might contribute to the findings of an increased risk of embolisms in IE of the mitral valve. Embolisms are often present before the diagnosis of IE (Arregle et al., 2021; Cabell et al., 2001; Fabri et al., 2006; Hubert et al., 2013), and it can be speculated that if a complete vegetation has already embolized at the time of IE diagnosis, findings of IE in the valves might be little. However, if modern and advanced imaging

technology is applied, even minor signs of IE could be detected. This could contribute to the results of especially older studies.

6.8 Strengths and limitations

One of the main strengths of this thesis is the population-based setting of the first three studies covering the whole of Finland. Thus, the observations of these studies are representative of the entire Finnish population and were not affected by the referral bias limiting a considerable proportion of IE studies conducted in tertiary referral centers. This said, however, the fourth study of this thesis was conducted in a tertiary care hospital, to which IE patients with the severest form of disease and need for surgery are transferred from other hospitals in the area. However, by not restricting patients to only inhabitants of the Turku area, it was possible to include more patients in this study and to examine the interesting factors more precisely. Furthermore, virtually all the IE patients in the area of the Hospital District of Southwest Finland (population approximately 480,000) are treated in Turku University Hospital. An important strength of all four studies of this thesis is also the significant length of the study period.

One of the main limitations of the first three register-based studies was the inevitable incompleteness of the coding. The diagnoses were made by the treating physicians or pathologists, and some errors may have occurred. Certainly, some codes were missing. However, the accuracy of the nationwide, mandatory CRHC used in studies I and III has been found to be precise (Sund, 2012). Furthermore, in the subgroup analysis of this study of IE patients admitted to Turku University Hospital, the specificity of the ICD-10 codes for IE was found to be 96.8%. Accordingly, a previous validation study reported the ICD-10-codes for IE to have 90% sensitivity and 100% specificity (Tan et al., 2016). In the register-based studies, there was no access to detailed clinical data, for example predisposing factors, such as IVDU or the etiology of IE, which limits the results of the first three studies.

In the fourth study, due to the retrospective design, some of the information collected on certain patients was missing because of, for example, a transfer from another hospital. However, the proportion of the cases with missing data within each parameter was relatively small (less than 10%). Moreover, the data were recorded by treating physicians and might have contained errors. Some information of particular interest, for example the vegetation length, which is known to be related to embolic events, was inadequately entered into the patient records and could thus not be applied in the study.

To conclude, this thesis provides novel information on the population-based sex- and age-specific epidemiology and trends of IE. Data on the previously inadequately known long-term mortality of IE patients are also presented. Moreover, this study is

the first one to provide population-level information on fatal IE. Additionally, novel data on the characteristics of the different etiologies and the factors, especially on the microbiological etiology and valve involvement, associated with all embolic events and cerebral embolisms in IE patients are provided. Finally, with the help of the results of this thesis it might be possible to improve the treatment of IE patients in Finland.

7 Conclusions

In this thesis, the sex- and age-specific epidemiology and temporal trends of IE were investigated in a population-based setting. Furthermore, the population-based epidemiology of fatal IE was studied. Moreover, the characteristics of the different microbiological etiologies and the factors associated with embolic events were assessed. The following conclusions can be drawn from this study:

1. The incidence of IE is increasing in young adults but not in the older population in Finland. Men, particularly at middle-age, are at a higher risk of IE than women. Thirty-day mortality of IE has remained unchanged and is similar between sexes.
2. Men are at a two-fold risk of fatal IE compared to women. The incidence of fatal IE increases progressively with age from 50 years onwards, but the proportion of IE-related deaths of all deaths is the highest in the youngest population. The incidence of IE-associated deaths has not changed over the years.
3. Men have longer hospital admissions due to IE than women. Five- and ten-year mortality after IE admission is higher in women. In-hospital and one-year mortality and LOS have remained stable over time.
4. Enterococcal IE is often associated with a previous healthcare procedure or hospital admission and heart failure. *Staphylococcus aureus* etiology and affected multiple valves are related to a higher rate of all embolic events but not cerebral embolisms in IE patients. Detected vegetation is associated with the occurrence of both all embolic events and cerebral embolisms.

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