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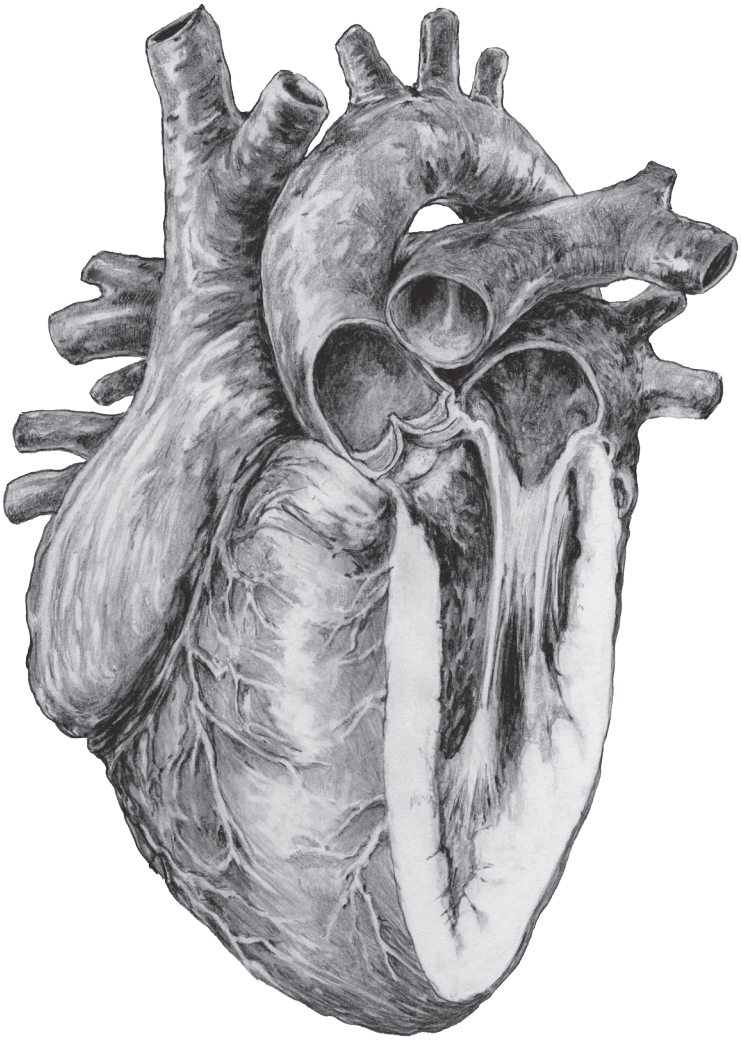

TEMPORAL TRENDS AND OUTCOMES IN AORTIC AND MITRAL VALVE SURGERY IN FINLAND

Monna Myllykangas

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To my family

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ABSTRACT

Aortic valve surgery is the most common type of heart valve surgery in western countries. The main causes for aortic valve surgery are aortic valve stenosis and regurgitation. Mitral valve regurgitation is the most common cause for mitral valve surgery, as mitral stenosis is rare. The proportion of mitral valve repairs has increased during the last decades. It is currently the primary choice for treating mitral valve disease of all etiologies. Cardiac surgery patients have sex-depended differences as to type of surgery and outcome. Women are usually older by the time of surgery, and the comorbidity burden differs between sexes. Results on outcome are conflicting. Thromboembolic prophylaxis is indicated for the first three months after biologic valve replacement. However, often the need for anticoagulation is long-term due to other conditions that increase the risk of thromboembolic complications.

The aim of this study was to elucidate nationwide trends in mitral and aortic valve surgery in Finland. We also studied the sex differences in long-term outcomes after an aortic valve replacement procedure, and the prevalence and type of long-term oral anticoagulation treatment and their association with complications and death in patients who have undergone biological aortic valve replacement.

We found that the proportion of mitral valve repair surgery and the use of bioprosthetic valves have increased. Short- and long-term mortality after mitral valve surgery has decreased. The basic characteristics of aortic valve patients have changed: patients are older, the proportion of women has decreased, and patients have markedly more comorbidities. The use of bioprosthetic aortic valves has increased and short-term mortality has improved while long-term mortality has remained unchanged. Sex is not an independent risk factor for long-term mortality after surgical aortic valve replacement. However, male-sex was associated with higher risk of bleeding, infective endocarditis, and re-surgery. The use of oral anticoagulation after biologic aortic valve replacement appears to be associated with decreased risk of death and increased risk of stroke.

KEYWORDS: mitral valve repair, mitral valve replacement, aortic valve replacement, aortic valve surgery, heart valve surgery, anticoagulation, population trends, nationwide data, gender, long-term survival

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TIIVISTELMÄ

Aorttaläppäkirurgia on tavallisin sydänkirurgian muoto länsimaissa. Tavallisimmat syyt aorttaläppäkirurgialle ovat aorttaläpän ahtauma ja vuoto. Mitraaliläppäkirurgian tavallisin syy on mirtaaliläpän vuoto. Mitraaliläpän ahtauma on nykyään harvinainen. Mitraaliläpän korjausleikkauksien osuus on noussut viimeisien vuosikymmenten aikana. Se on tällä hetkellä ensisijainen mitraaliläpän vajaatoiminnan hoitomuoto riippumatta aiheuttajasta. Sydänkirurgisilla potilailla tiedetään olevan sukupuolesta riippuvaisia eroja. Naiset ovat yleensä vanhempia leikkauksen aikaan, ja perussairauksien aiheuttama taakka eroaa sukupuolten välillä. Tulokset ennusteesta ovat vaihtelevia. Tromboosiprofylaksiaa suositellaan ensimmäisen kolmen kuukauden ajaksi biologisen aorttatekoläppäleikkauksen jälkeen. Kuitenkin antikoagulaation tarve on usein pitkäaikainen muiden tromboembolisia komplikaatioita aiheuttavien sairauksien johdosta.

Tutkimuksemme tavoitteena oli selvittää mitraaliläpän korjaus- ja tekoläppäleikkauksen sekä aorttatekoläppäleikkauksen maanlaajuisia pitkäaikaismuutoksia ja -ennustetta Suomessa. Tavoitteena oli lisäksi tutkia sukupuolieroja pitkäaikaisennusteessa aorttatekoläppäleikkauksen jälkeen. Näiden lisäksi tutkimme pitkäaikaisantikoagulaation esiintyvyyttä ja tyyppiä biologisen aorttatekoläppäleikkauksen jälkeen.

Totesimme, että biologisten läppäproteesien käyttö ja mitraaliläpän korjausleikkausten määrä lisääntyi. Mitraaliläppäkirurgian lyhyt- ja pitkäaikaiskuolleisuus on laskenut. Aorttaläppäpotilaiden taustaominaisuudet muuttuivat seuranta-aikana: potilaat ovat vanhempia, naisten osuus pieneni ja perussairauksien määrä kasvoi. Biologisten aorttaläppäproteesien käyttö lisääntyi, lyhytaikaiskuolleisuus vähentyi ja pitkäaikaisennuste pysyi ennallaan. Sukupuoli ei ole itsenäinen pitkäaikaiskuolleisuuden riskitekijä aorttatekoläppäleikkauksen jälkeen. Miehillä on suurentunut riski vuotokomplikaatioille, infektiiviselle endokardiitille ja uusintaleikkaukselle. Suun kautta otettavien antikoagulanttien pitkäaikaiskäyttö aortan biologisen tekoläppäleikkauksen jälkeen vaikuttaisi liittyvän vähentyneeseen kuolemariskiin ja lisääntyneeseen aivohalvausriskiin.

AVAINSANAT: mitraaliläpän korjausleikkaus, mitraalitekoläppäleikkaus, aorttatekoläppäleikkaus, aorttaläppäkirurgia, antikoagulaatio, potilasvalinta, sukupuoli, pitkäaikaisennuste.

Table of Contents

Abbreviations

(AF)	Atrial fibrillation
(AR)	Aortic regurgitation
(AS)	Aortic stenosis
(AV)	Aortic valve
(BAVR)	Biologic aortic valve replacement
(CABG)	Coronary artery bypass graft
(CI)	Confidence interval
(CRHF)	Care Register for Healthcare in Finland
(HR)	Hazard ratio
(ICD-10)	10th version of International Classification of Diseases
(IE)	Infective endocarditis
(LV)	Left ventricle
(LVEF)	Left ventricular ejection fraction
(TAVR)	Transcatheter aortic valve replacement
(TEE)	Transesophageal echocardiography
(TTE)	Transthoracic echocardiography
(LVESD)	Left ventricular end-systolic dimension
(MI)	Myocardial infarction
(MR)	Mitral regurgitation
(MS)	Mitral stenosis
(MV)	Mitral valve
(NOAC)	Novel oral anticoagulant
(OAC)	Oral anticoagulation
(PVE)	Prosthetic valve endocarditis
(SAVR)	Surgical aortic valve replacement
(SD)	Standard deviation
(TAVR)	Transcatheter aortic valve replacement
(VHD)	Valvular heart disease
(VKA)	Vitamin K antagonist

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. Myllykangas M, Aittokallio J, Pietilä A, Salomaa V, Gunn J, Kiviniemi T, Niiranen T. Population Trends in Mitral Valve Surgery in Finland between 1997 and 2014: the Finnish CVD Register. *Scandinavian Cardiovascular Journal* 2018 Feb;52(1):51–57.

II. Myllykangas M, Gunn J, Pietilä A, Kiviniemi T, Kytö V, Niiranen T, Salomaa V, Aittokallio J. Population trends in aortic valve surgery in Finland between 2001 and 2016. *Scandinavian Cardiovascular Journal*, 2020 Feb;54(1):47–53.

III. Myllykangas M, Aittokallio J, Gunn J, Sipilä J, Rautava P, Kytö V. Gender differences in long-term outcomes after surgical aortic valve replacement: a nationwide propensity matched study. *Journal of Cardiothoracic and Vascular Anesthesia*, 2020 Apr;34(4):932–939.

IV. Myllykangas M, Kiviniemi TO, Gunn JM, Salomaa VV, Pietilä A, Niiranen TJ, Aittokallio J. Anticoagulation Therapy after Biologic Aortic Valve Replacement. *Frontiers in Cardiovascular Medicine*, 2021 Jun;8:698784.

1 Introduction

Surgical aortic valve replacement (SAVR) is the most common type of heart valve surgery in western countries (Vahanian et al. 2021). Aortic valve stenosis (AS), in turn, is the most common valve disease and cause of valve surgery or transcathere intervention (Iung et al. 2003; Nkomo et al. 2006; Vahanianian et al. 2021). SAVR has been the gold standard treatment for AS, but during the last decade, transcatheter aortic valve replacement (TAVR) has emerged as a less-invasive alternative to SAVR, especially in high-risk patients (Makkar et al. 2012; Makkar et al. 2020). Despite extensive studies on morbidity and mortality after SAVR, the results are still controversial (Chiang et al. 2014; Glaser et al. 2016; Goldstone et al. 2017; Chiu et al. 2017). Mitral valve regurgitation (MR) is the most common reason for mitral valve (MV) surgery (Enriquez-Sarano et al. 2009; Otto et al. 2021). The primary treatment for MV insufficiency is MV repair surgery, due to better survival compared to MV replacement (Mohty et al. 2001; Gammie et al. 2009; Vahanian et al. 2021; Otto et al. 2021). The overall mortality after cardiac surgery has decreased even though patients who are referred to cardiac surgery have more underlying diseases (Nashef et al. 2012; Martinsson et al. 2015; Kiviniemi et al. 2016; Otto et al. 2021).

Sex dependent differences in cardiac surgery have long been recognized and widely studied, and differences are also present in valvular heart disease (Cho et al. 2021). Current guidelines use sex-neutral definitions for severe heart valve disease (Vahanian et al. 2021; Otto et al. 2021; Cho et al. 2021). Female sex increases the scores on cardiac surgery risk calculators from EuroSCORE II and The Society of Thoracic Surgery (STS). Calculators are widely used to predict perioperative mortality. Women are less likely to be referred to heart valve surgery than men (Chaker et al. 2017; Kislitsina et al. 2019, Cho et al. 2021). Moreover, women tend to be older and have more advanced valvular heart disease by the time of diagnosis (Fuchs et al. 2010; Elhmidi et al. 2014; Onorati et al. 2014; Chaker et al. 2017; Wong et al. 2018; Kislitsina et al. 2019). It may be due to many coexisting factors; for example, the symptoms of cardiovascular diseases can be atypical in women, which may delay the diagnosis (Chan et al. 2016; Kislitsina et al. 2019).

Lifelong anticoagulation with vitamin K antagonists (VKA) is recommended after insertion of mechanical valve prosthesis (Vahanian et al. 2021; Otto et al. 2021). In turn, after insertion of bioprosthetic valve, the guidelines recommend thromboembolism prophylaxis only for the first three months postoperatively (Vahanian et al. 2021; Otto et al. 2021). However, in some patients, the need for anticoagulation continues lifelong due to other diseases that increase the risk of thromboembolic complications. Atrial fibrillation (AF) is the most common such condition. According to the 2021 update of the European guidelines for the management of valvular heart disease, the novel oral anticoagulants (NOACs) can be considered over VKA after bioprosthetic valve replacement surgery (Vahanian et al. 2021).

There has been paucity of nation-wide population data on MV and aortic valve (AV) surgery. The different procedure types, numbers, and postoperative long-term morbidity and mortality have not been studied so far. By studying nationwide population data, we can improve the care of heart valve surgery patients in the future.

2 Review of the Literature

2.1 Aortic valve surgery

2.1.1 Aortic valve anatomy

Aortic valve (AV) is located between the left ventricle and the aorta (Figure 1 and Figure 2). AV divides one of the highest pressure gradients of the cardiopulmonary system. AV has three cusps (leaflets) that are named right, left, and posterior. The cusps are connected to the aortic root via the aortic annulus and suspended by structures called commissures. Just above AV, there are aortic sinuses (sinuses of Valsalva) that ensure that the openings of coronary arteries are not occluded when AV cusps are open. (De Paulis et al. 2019)

2.1.2 Aortic stenosis

In aortic stenosis (AS), the valve aperture narrows and leads to a reduced AV area (Figure 2). A reduced valve area increases the resistance of blood flow and the transvalvular pressure gradient. These changes place additional burden on the LV and cause hypertrophy. AS is the most common heart valve disease and indication for cardiac surgery in and constitutes a significant health problem among older people (Iung et al. 2003; Nkomo et al. 2006; Vuyisile et al. 2006). AS can be originally congenital, acquired, or both (Fishbein et al. 2019). Rheumatoid heart disease used to be the most common reason for AS, but nowadays, the two main reasons in high income countries are age related degeneration and calcification of aortic cusps and congenitally bicuspid aortic valve (Dare et al. 1993; Fishbein et al. 2019). Bicuspid aortic valve is a rather rare condition, with an incidence of 1–2% (Sabet et al. 1999). However, the bicuspid valve becomes stenotic much more likely than the tricuspid aortic valve, and severe stenosis also tends to present at an earlier age. The prevalence of AS is almost equal between sexes (Lindroos et al. 1993; Aronow et al. 1997; Petrov et al. 2010; Martinsson et al. 2015), and it increases with age (Lindroos et al. 1993; Eveborn et al. 2012). The incidence is estimated to be 0.1–0.2% among younger population aged 44–59 years (Nkomo et al. 2006; Eveborn et al. 2012) and rises from 2.5–2.8% among the 71–79-year-old population (Lindroos et

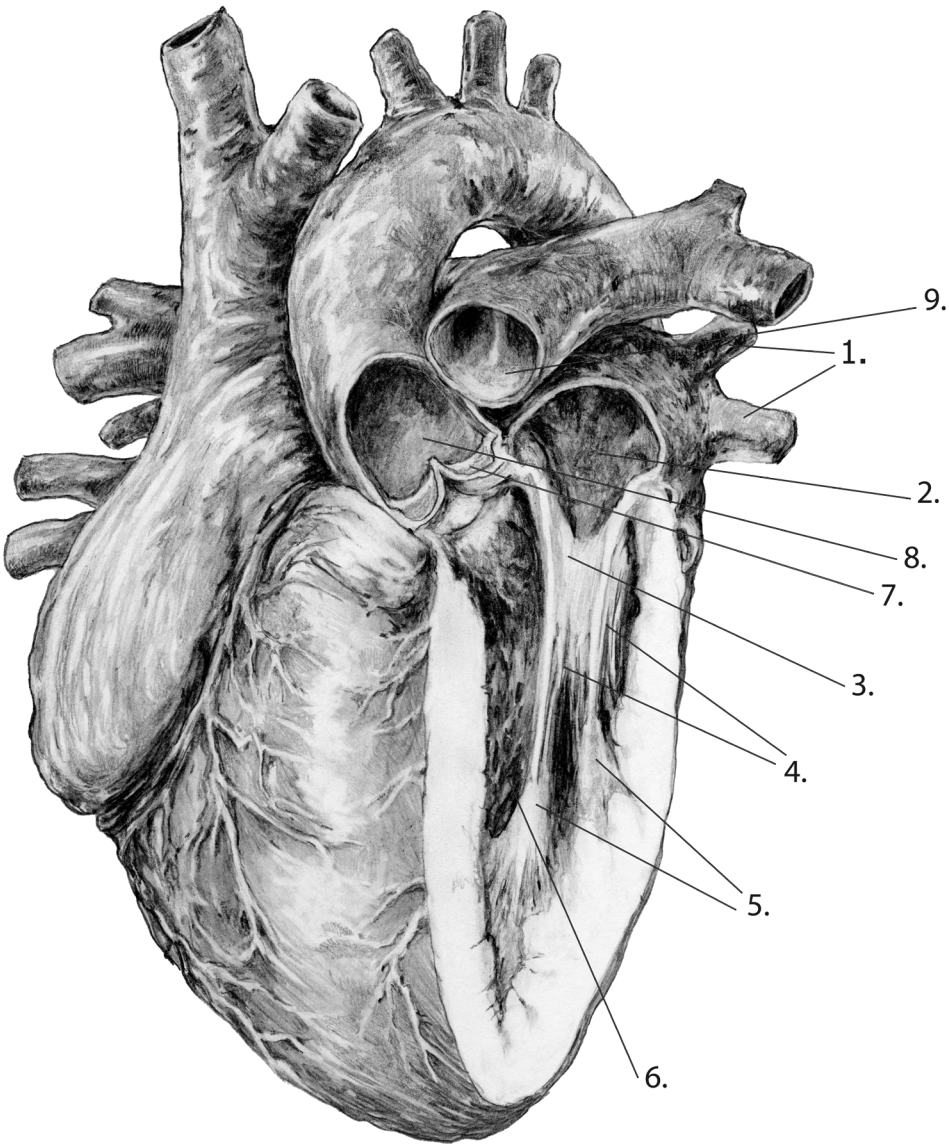

Figure 1. Heart anatomy. 1. Pulmonary veins 2. Left atrium 3. Mitral valve 4. Chordae tendinae 5. Papillary muscles 6. Left ventricle 7. Aortic valve 8. Aorta 9. Pulmonary artery. (Artwork: Inari Raaterova.)

al. 1993; Nkomo et al. 2006) up to 9.8% in the >80-year-old-population (Lindroos et al. 1993; Eveborn et al. 2012). The number of patients with clinically significant AS is constantly increasing because of aging population.

The progression of AS is insidious, with a long latency period until about the age of 60 years, during which increasing obstruction and myocardial overload is generated (Ross et al. 1968). Survival of patients with severe AS are excellent during the latency period, but once the patient becomes symptomatic, the progression of the disease is rapid (Ross et al. 1968; Cheitlin et al. 1979; Kelly et al. 1988), resulting in high rates of death in two years after the first symptoms if not treated properly (Ross et al. 1968; Turina et al. 1987; Kelly et al. 1988; Otto et al. 2021). It is therefore essential to identify the correct time of surgery. The operation should not be performed at a too early stage of stenosis due to the high risks of open-heart surgery, but also should not be delayed until the patient's condition deteriorates excessively, as changes in the myocardium may become irreversible. So, to ensure optimal follow-up of AS progression, physicians should understand the underlying physiology and criteria used to define the severity of the disease.

The diagnosis of AS is based on symptoms, signs, and ultrasound findings (Vahanian et al. 2021). Often patients are experiencing symptoms of heart failure: dyspnoea, angina pectoris, and syncope (Kanwar et al. 2018). However, especially older people may only experience a decline in exercise tolerance. Sometimes the onset of symptoms may be more acute when progress of AS has led to new onset of atrial fibrillation. The classic sign of AS is loud systolic murmur over the second right intercostal space which radiates to the carotid arteries. Transthoracic echocardiography (TTE) is the initial test for patients with suspected AS, and it is indicated when there are symptoms, or a history, of bicuspid aortic valve and when it is needed to determine prognosis and right timing of surgical treatment (Oh et al. 1988; Munt et al. 1999; Vahanian et al. 2021; Otto et al. 2021). The severity of aortic stenosis is determined by measuring maximum transaortic velocity, the Doppler-derived mean pressure gradient, and the aortic valve area (Table 1) (Otto et al. 2021).

Currently there is no effective medical treatment for AS (Fishbein et al. 2019). Antihypertensive drugs, statins, and anticalcific drugs have been studied the most but have not been shown to be of significant benefit in treatment of AS (Marquis-Gravel et al. 2016). The surgical aortic valve replacement (SAVR) is the only effective treatment of AS, and it has been the gold standard for years (Schwarz et al. 1982; Vasques et al. 2012). However, since 2002, transcatheter aortic valve replacement (TAVR) has emerged as a less-invasive alternative to SAVR for appropriately selected patients with symptomatic AS (Makkar et al. 2012; Makkar et al. 2020). Jalava et al. noticed in their recent study that preoperative heart failure is associated with lower survival rates after both SAVR and TAVR (Jalava et al.

2020). They concluded that the need for invasive treatment should be assessed before development of heart failure.

Table 1. Severity classification of Aortic Stenosis according to echocardiographic findings.

Stage	Definition	Transaortic velocity (m/s)	Mean pressure gradient (mmHg)	Aortic valve area (cm^2)	LVEF
A	At risk of AS	<2	<10	3–4	Normal
B	Progressive mild AS	2–2.9	<20	1.5–2.9	Normal
	Progressive moderate AS	3–3.9	20–39	1–1.4	Normal
C1	Asymptomatic severe AS	≥4	≥40	≤1*	Normal
	Asymptomatic very severe AS	≥5	≥60	≤1*	Normal
C2	Asymptomatic severe AS with LV dysfunction	≥4	≥40	≤1*	<50 %
D1	Symptomatic severe high-gradient AS	≥4	≥40	≤1**	Normal
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	<4	<40	≤1	<50 %
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	<4	<40	≤1	≥50 %

*not mandatory to define severe AS. **can be larger when mixed AS/AR. AS, Aortic stenosis; AR aortic regurgitation; LVEF, left ventricular ejection fraction. (Modified from Otto et al. 2021, 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.)

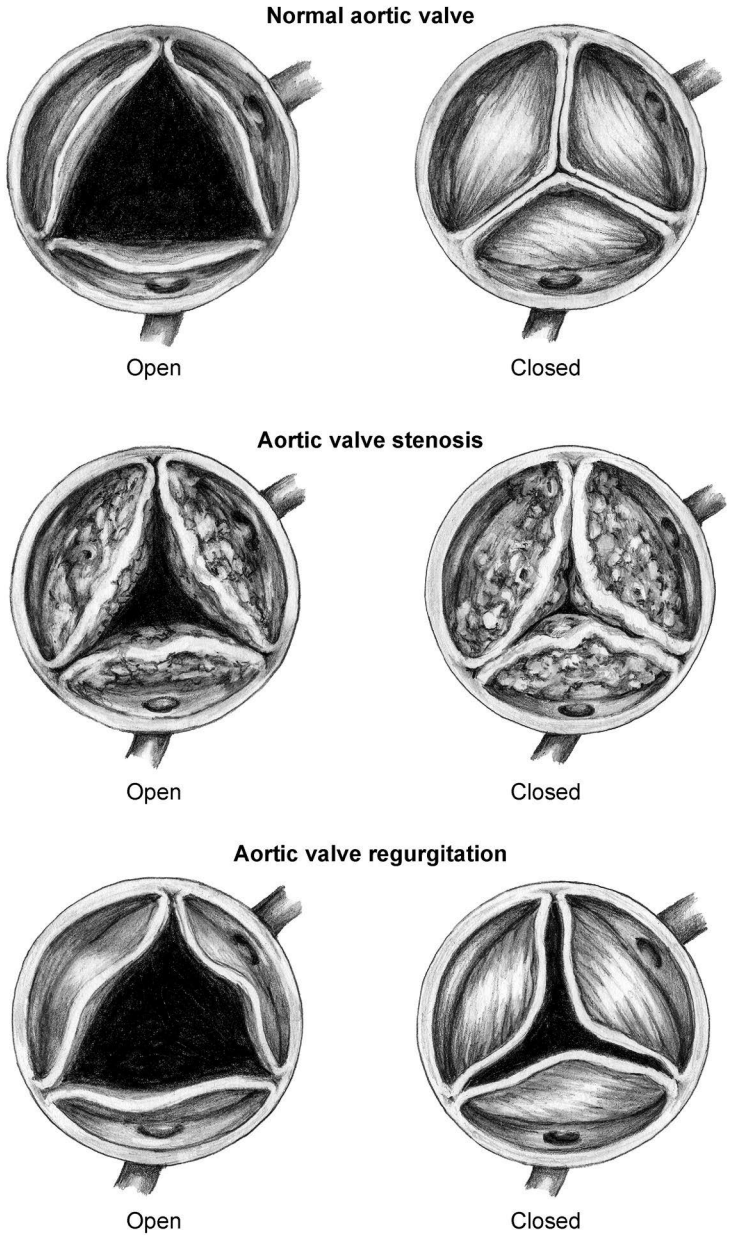

Figure 2. Morphology of normal and pathologic aortic valves. (Artwork: Inari Raaterova.)

2.1.3 Aortic regurgitation

Failure of the aortic valve cusps to coapt during diastole leads to increased backward blood flow, regurgitation, from the aorta into the left ventricle (LV) (Figure 2). This aortic regurgitation (AR) leads to increased LV volume, ventricle wall stress, and eventually LV hypertrophy (Ishii et al. 1996). AR is the most common indication for valve sparing root repair and aortic valve repair. Unlike aortic stenosis (AS), AR can be caused by many different conditions affecting the aortic valve cusps or the aortic root. It can develop acutely or slowly over the years (Fishbein et al. 2019).

The most common causes of AR are atherosclerotic degeneration of the valve and congenital bicuspid AV (Iung et al. 2003, Flint et al. 2019) Atherosclerotic degeneration of the AV is an acquired condition that is usually associated with aging, hypertension, and hyperlipidemia (Flint et al. 2019). Other causes are rheumatoid heart disease, infective endocarditis (IE), aortic root dilatation, aortic dissection, Marfan syndrome, and infectious or inflammatory diseases (Bechet's disease, syphilis) (Iung et al. 2003; Flint et al. 2019; Fishbein et al. 2019). The prevalence of AR increases with age. It is estimated to be 0.1–0.7% in younger population aged 45–64 years (Nkomo et al. 2006) and increases up to 2.0% in population aged ≥75 years (Nkomo et al. 2006).

The clinical picture of AR varies, depending mostly on whether the development is acute or chronic. Acute AR is less common. It often presents as a hemodynamic emergency, developing acute preload increase to which the normal-sized LV cannot adapt rapidly enough. Eventually, it results in pulmonary edema and decline in cardiac output. The patients are at critical state with shortness of breath, tachycardia, and hypotension. In turn, chronic AR develops slowly over time so that the cardiac chambers can adapt to changes in the volume load. Chronic LV volume overload causes compensatory hypertrophy of the cardiac myocytes and leads to chamber dilatation. As AR worsens over time, it causes decline in the systolic function and cardiac output, and eventually heart failure develops. Mild or moderate AR is usually asymptomatic, and even severe AR does not increase morbidity or mortality until LV dilatation has developed (Bonow et al. 1991). Ultimately, when AR advances, the patient experiences angina pectoris and develops exertion dyspnea and orthopnea as symptoms of heart failure (Akinseye et al. 2018).

The diagnosis of AR is based on symptoms, signs, and TTE findings. TTE is the primary method to determine the etiology and severity of AR (Figure 3) (Vahanian et al. 2021; Otto et al. 2021). It is indicated when there are signs or symptoms of AR and also to determine prognosis and right timing of surgical treatment (Bonow et al. 1991; Detaint et al. 2008; Vahanian et al. 2021; Otto et al. 2021). The severity of AR is determined by evaluating anatomy of the valve, valve hemodynamics, severity of the LV dilatation, LV systolic function, and by the symptoms the patient is experiencing (Table 2) (Otto et al. 2021). SAVR is the standard procedure to treat

AR, but also valve repair or valve sparing surgery can be considered based on the patient condition (Vahanian et al. 2021). TAVR is not usually a treatment option in AR (Otto et al. 2021).

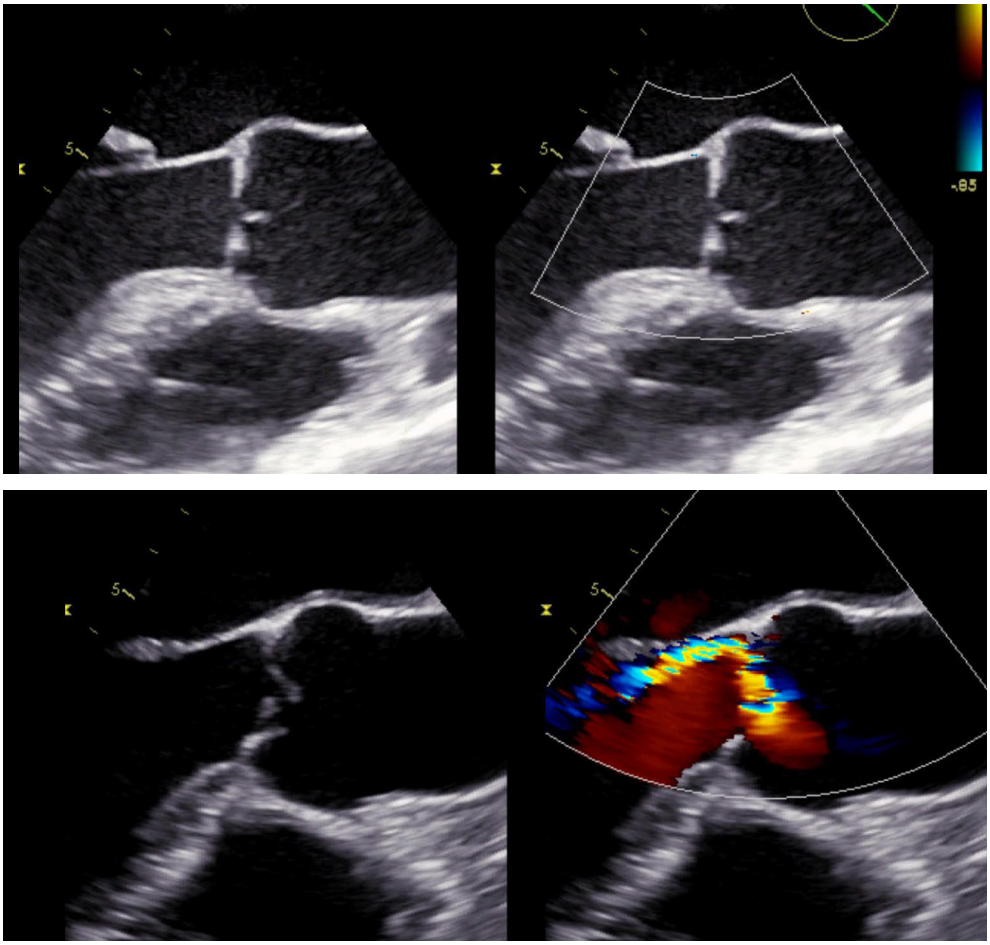

Figure 3. The upper images represent a normal aortic valve: a standard transesophageal echo image on the left and a color doppler ultrasound on the right. The lower images show aortic valve cusp prolapse and regurgitation: a standard transesophageal echo image on the left and a color doppler ultrasound on the right. (Source image: Ville-Veikko Hynninen)

Table 2. Severity classification of Aortic Regurgitation according to echocardiographic findings.

Stage	Definition	JW of LVOT (%)	VC (cm)	Rvol (ml)	RF (%)	ERO (cm^2)	AG	LVEF/LV dilation
A	At risk of AR	>25	>0.3	>30	>30	>0.1	-	Normal/No-mild
B	Progressive mild AR	<25	<0.3	<30	<30	<0.1	1	Normal/No-mild
	Progressive moderate AR	25–64	0.3–0.6	30–59	30–49	0.1–0.29	2	Normal/No-mild
C	Asymptomatic severe AR*	≥65	>0.6	≥60	≥50	≥0.3	3–4	C1: Normal/mild-moderate C2: ≤55%/Severe
D	Symptomatic severe AR*	≥65	>0.6	≥60	≥50	≥0.3	3–4	Normal-<40%/Moderate-severe

*Diagnosis requires evidence of LV dilation. AG, angiographic grade; AR; aortic regurgitation; ERO, effective regurgitant orifice; JW, jet width; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; RF, regurgitant fraction; RVol, regurgitant volume; and VC, vena contracta. (Modified from Otto et al. 2021, 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.)

2.1.4 Invasive treatment of the aortic valve

2.1.4.1 Transcatheter aortic valve replacement

In transcatheter aortic valve replacement (TAVR), the native valve is replaced by a bioprosthetic valve. The procedure can be performed from a transfemoral, transapical, or transaortic approach, transfemoral being the most usual approach. TAVR is known to decrease all-cause and cardiac mortality compared to conservative therapy among surgically inoperable patients with severe symptomatic AS (Makkar et al. 2012). It might be a better treatment option also for patients with intermediate operative-risk due to lower mortality and stroke risk compared to SAVR (Thourani et al. 2016). The lack of studies on the long-term prognosis and valve durability in different severity stages of aortic stenosis (AS) still limits the use of TAVR (Vahanian et al. 2021).

Current European guidelines for the management of valvular heart disease recommend TAVR for patients who are ≥75 years old, or who are unsuitable for operation, or for whom the surgical risk is high, and who are suitable for TAVR (Figure 4) (Vahanian et al. 2021). According to American guidelines for the management of patients with valvular heart disease, TAVR is recommended for

patients with severe AS who are over 80 years and whose life-expectancy is below ten years. TAVR can also be considered an alternative to SAVR for patients aged 65–80 years when no anatomical contraindication for TAVR exist (Otto et al. 2021).

Mäkikallio et al. discovered from the nationwide Finn Valve registry that the number of TAVR operations in patients with severe AS has increased in Finland during the last decade (Mäkikallio et al. 2019). TAVR has become a more common treatment strategy of severe AS than SAVR (Mäkikallio et al. 2019). Patients were on average 81.2 years old, and 55% of the patients were women.

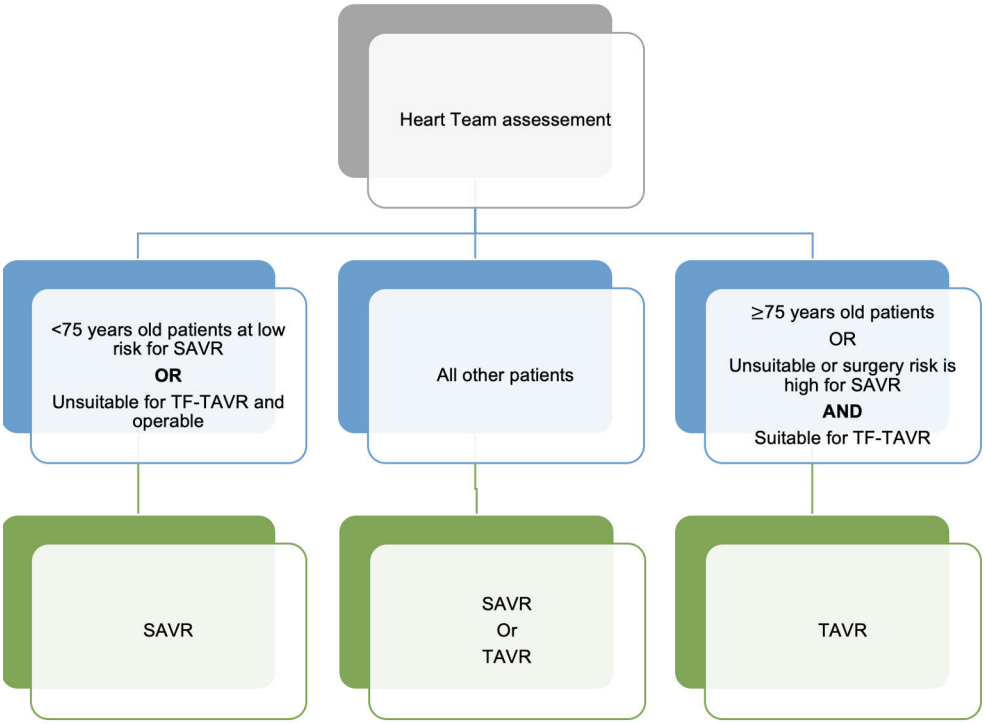

Figure 4. Invasive trearment recommendations for aortic stenosis. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TF-TAVR, transfemoral-transcatheter aortic valve replacement. (Modified from Vahanian A et al. 2021, ESC/EACTS Scientific Document Group; ESC Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2021 Aug 28:ehab395)

2.1.4.2 Surgical aortic valve replacement

Surgical aortic valve replacement (SAVR) is the gold standard for treating aortic stenosis (AS) and the most frequently used treatment for aortic valve disease in non-elderly population. SAVR can be performed either through full sternotomy or mini-invasively through hemisternotomy, full sternotomy being the most usual approach. The native aortic valve is replaced either with a mechanical or a biological valve. The proportions of TAVR and aortic valve (AV) repair have increased during the last decades, while as the proportion of SAVR is decreasing (Mäkikallio et al. 2019). As SAVR can be performed using mechanical or bioprosthetic valve, different factors need to be considered when choosing valves: 1) individual patient characteristics (age, cardiovascular condition, other comorbidities), 2) life expectancy based on individual patient characteristics, 3) risks of lifelong anticoagulation and reoperation, 4) the individual patient's wishes, and 5) joint decision by cardiological team and patient (Rahimtoola 2003).

The application of biological valves has increased during the last decades (Isaacs et al. 2015; Goldstone et al. 2017). Goldstone et al. has reported increased use from 11.5% in 1996 to 51.6% in 2013 (Goldstone et al. 2017). Furthermore, Isaacs et al. reported an increase from 37.7% to 63.6% between time periods 1998–2001 and 2007–2011 (Isaacs et al. 2015). Bioprosthetic valves are recommended only for older patients due to their limited durability and increased risk of reoperation (Glaser et al. 2016; Vahanian et al. 2021; Otto et al. 2021). Furthermore, the guidelines for the age limits of prosthetic valves have changed, and the thresholds for mechanical valves have been lowered. The recent 2020 update of the American College of Cardiology and American Heart Association Joint Committee guidelines for the management of patients with valvular heart disease recommends mechanical valve in aortic position in patients under 50 years of age, individual choice between the valve types in patients of 50–65 years of age, and biologic valve in patients over 65 years of age (Otto et al. 2021). Under certain conditions, the Ross procedure can be considered in patients under 50 years of age who prefer bioprosthetic valve (Otto et al. 2021). In the Ross procedure, the defective AV is replaced using the patient's own pulmonary valve, and the removed pulmonary valve is replaced by a homograft pulmonary valve. The recent 2021 update of European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease recommends mechanical valves in patients aged <60 years, biologic valves in patients aged >65 years, and individual choice in patients aged 60–65 years (Figure 4) (Vahanian et al. 2021).

2.1.4.3 Aortic valve repair

Recently, aortic valve (AV) repair has gained greater popularity as the repair techniques have evolved during the past 20 years. The aim of AV repair is to preserve the native aortic valve and its complex natural functions. It is an attractive alternative to SAVR in patients who meet the criteria for aortic valve replacement surgery due to aortic regurgitation but have little or no calcification of the aortic annulus and cusps (Miyahara et al. 2019; Ram et al. 2020; Otto et al. 2021). With AV repair, it is possible to avoid complications related to prosthetic valves, such as thromboembolism, anticoagulation-related bleedings, prosthetic infective endocarditis (PVE), and structural valve deterioration (Vongpatanasin et al. 1996; Rahimtoola et al. 2003; Brown et al. 2016). AV repair is noticed to have a low reoperation rate, a low rate of complications related to the valve, and a good long-term survival, as well as to indicate better quality of life compared to replacement (de Meester et al. 2014; Arabkhani et al. 2015; Ram et al. 2020). Despite these advantages, the main limiting factor for increased use of this technique is general unsuitability of the native valve for the correction.

The two most widely used principles for valve sparing aortic root surgery are valve reimplantation, or the David procedure, and aortic root remodeling, or the Yacoub procedure (David et al. 1992; Sarsam et al. 1993). In the Yacoub procedure, the aortic root is remodeled with the goal to achieve physiological reconstruction of the aortic root (Sarsam et al. 1993). It is achieved by diminishing aortic root and creating sinuses of Valsalva using a synthetic tube graft (Sarsam et al. 1993). In the David procedure, the aneurysmal portion of ascending aorta and sinuses of Valsalva are removed, and the remaining aortic valve and the coronary arteries are reimplanted within a tubular synthetic graft (David et al. 1992). Concomitantly with the root remodeling, the aortic cusps can be repaired for fenestrations or plicated to optimize cusp coaptation.

2.2 Mitral valve surgery

2.2.1 Mitral valve anatomy

The mitral valve (MV) is a structure that consist of an annulus, two leaflets, three chordae tendinae, and two papillary muscles (Figure 1 and Figure 5). MV annulus is a continuum with the AV through aortic-mitral curtain. The MV has anterior (A) and posterior (P) leaflets that are divided into three scallops. The leaflets meet at two commissures. The chordae tendinae attach leaflets to papillary muscles (Harb et al. 2017).

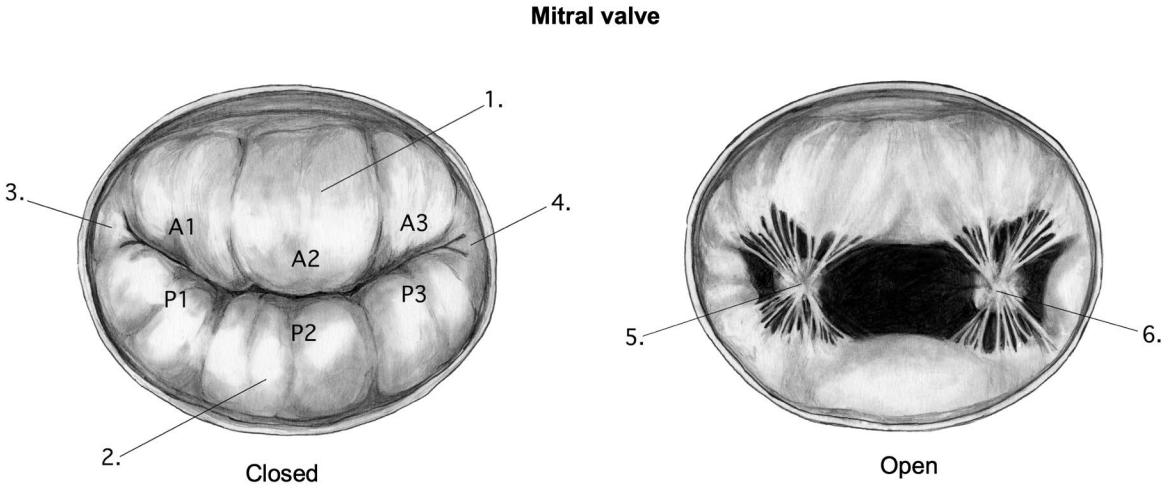

Figure 5. Anatomy of normal mitral valve. 1. Anterior leaflet 2. Posterior leaflet 3. Anterior comissure 4. Posterior comissure 5. Anterolateral papillary muscle 6. Posteromedial papillary muscle. The mitral valve leaflets consists of three discrete segments. These segments are designated A1, A2, and A3 for the anterior leaflet and P1, P2, and P3 for the posterior leaflet. (Artwork: Inari Raaterova.)

2.2.2 Mitral stenosis

Mitral stenosis (MS) means the narrowing of the mitral valve (MV) area to less than 4.0 cm^2, and it becomes symptomatic when MV orifice area narrows to less than 1.5 cm^2 (Helmut et al. 2009; Otto et al. 2020; Vahanian et al. 2021). Narrowing of the MV orifice area leads to increase in left atrium (LA) pressure and decrease in forward flow (Harb et al. 2017). The increase in LA pressure causes enlargement of LA and increase in pulmonary pressure. (Harb et al. 2017). LA enlargement increases the risk of atrial arrhythmias. Increased pulmonary pressures can cause pulmonary edema and hypertension which can lead to right ventricle failure (Harb et al. 2017). The decreased forward slow decreases the cardiac output (Harb et al. 2017).

MS is usually divided into two main groups. The first group is rheumatic MS, which is the leading cause of MS worldwide (Iung et al. 2003; Harb et al. 2017; Al-Taweel et al. 2019; Vahaian et al. 2021). The second group is non-rheumatic MS, which consists of many different pathologies that cause MS. These pathologies are degenerative mitral annular calcification, radiation valvulitis, congenital causes, systemic inflammatory disorders, obstructive lesions, and infective endocarditis (Iung et al. 2003; Harb et al. 2017; Al-Taweel et al. 2019). The incidence of rheumatic MS is decreasing worldwide, while in turn the incidence of degenerative MS is increasing due to more older patient population with many comorbidities (Al-Taweel et al. 2019). The prevalence of MS is 0.1–0.2% regardless of age (Nkomo et al. 2006).

The severity of MS is assessed with doppler echocardiography, and it is based on the determination of the valve area in rheumatic MS and mean gradient in degenerative MS (Baumgartner et al. 2009). Medical therapy includes diuretics, beta-blockers, digoxin, calcium channel blockers and ivabradine and anticoagulation with warfarin in case of atrial fibrillation (AF) (Vahanian et al. 2021). However, all symptomatic patients should be treated primarily invasively (Vahanian et al. 2021). Percutaneous or open mitral commissurotomy should be considered in all patients with favorable characteristics and surgical treatment for the rest of the patients (Vahanian et al. 2021; Otto et al. 2021). The most common surgical procedures are commissurotomy and MV replacement (Vahanian et al. 2021; Otto et al. 2021).

Table 3. Severity classification of Mitral Stenosis according to echocardiographic findings.

Stage	Definition	MVA (cm^2)	Transmitral flow velocity	Diastolic pressure half-time (ms)	LA enlargement	PASP (mmHg)
A	At risk of MS	Mild doming during diastole	Normal	>150	No	Normal
B	Progressive MS	>1.5	Increased	<150	Mild-moderate	Normal
C	Asymptomatic severe MS	≤1.5	Increased	≥150	Severe	>50
D	Asymptomatic severe MS	≤1.5	Increased	≥150	Severe	>50

LA, left atrial; MS, mitral stenosis; MVA, mitral valve area; and PASP, pulmonary artery systolic pressure. (Modified from Otto et al. 2021, 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.)

2.2.3 Mitral regurgitation

Moderate or severe primary mitral regurgitation (MR) is the most common indication for mitral valve (MV) repair or replacement surgery (Enriquez-Sarano et al. 2009; Vahanian 2021; Otto et al. 2021) and the second most common heart valve disease needing surgical correction in Europe (Iung et al. 2003). Pathologies that lead to MR cause alterations in mitral annular size and function, and the valve loses its regurgitation preventive mechanism (Grewal et al. 2010). MR causes increased volume-load to the left atrium (LA) and left ventricle (LV) (Harb et al. 2017). The impact of overload is dependent on the time course of the development of MR, whether it is acute or chronic (Harb et al. 2017). In acute MR, the increase in preload is so sudden that the ventricle does not have time to accommodate for increased volume. It causes increase in LV filling pressure and can lead to pulmonary edema (Harb et al. 2017). Chronic MR may progress insidiously. Hence it is important to identify LV changes at an early stage to recommend operation prior permanent LV damage (Harb et al. 2017).

The prevalence of MR increases with age (Nkomo et al. 2006; Dziadzko et al. 2018). Prevalence is 0.1–0.7% in patients aged 45–64 years and 1.0–2.0% in patients aged ≥65 years. On basis of the etiology, MR is classified as primary or secondary (Enriquez-Sarano et al. 2009; Harb et al. 2017). Primary causes are abnormalities at any level of MV apparatus, while secondary causes are due to alterations in LV geometry that interfere with proper function of MV apparatus (Harb et al. 2017). The most common primary cause of MR is MV prolapse, which is also the most common cause of MR requiring surgery (Enriquez-Sarano et al. 2009; Harb et al. 2017; Gammie et al. 2018) Other reasons for primary MR are infective endocarditis (IE), mitral annular calcification, rheumatic heart disease, connective tissue disorders, congenital malformations, and certain drugs (Harb et al. 2017; Gammie et al. 2018). Secondary causes of MR are further classified as ischemic MR or non-ischemic-MR (Enriquez-Sarano et al. 2009; Harb et al. 2017). In ischemic MR, the decrease in LV function is secondary to coronary artery disease (Harb et al. 2017). Non-ischemic MR can be caused by all types of non-ischemic cardiomyopathies (dilated cardiomyopathy, restrictive cardiomyopathy, and hypertrophic cardiomyopathy), but it can also be secondary to AF and right ventricular pacing (Harb et al. 2017).

After the clinical assessment of signs and symptoms, doppler transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) is the first method to further assess the severity of MR (Figure 6) (Vahanian et al. 2021; Otto et al. 2021). It provides important information about the functional anatomy of the valve, and reparability of the valvular pathology can be assessed (Enriquez-Sarano et al. 1999; Monin et al. 2005). The severity determination should be based on echocardiography measurements of effective orifice area, regurgitant volume, regurgitant fraction using the proximal isovelocity surface area, quantitative Doppler flow measurements, and multiple Doppler parameters (colour jet area, vena

contracta, continuous wave Doppler intensity, and transmitral jet velocity curve) (Table 4) (Otto et al. 2021). Surgery should be considered at early stage of the disease; and surgery is practically inevitable for patients with severe MR, as the risk of cardiac events and death increases each year (Ling et al. 1996). MV repair and surgical MV replacement are the primary ways to treat MR (Vahanian et al. 2021; Otto et al. 2021). However, in severely symptomatic patients, transcatheter mitral valve repair may be considered (Vahanian et al. 2021; Otto et al. 2021).

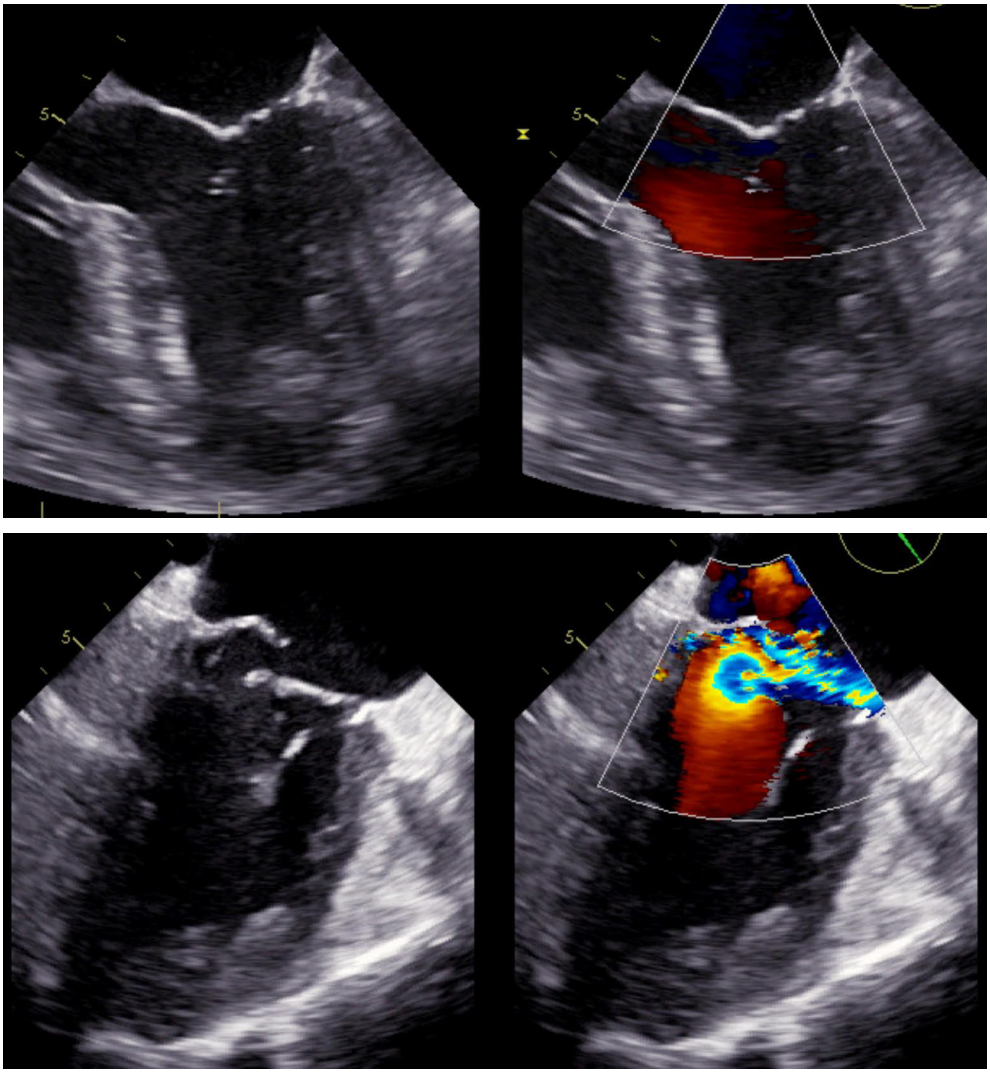

Figure 6. The upper images represent a normal mitral valve: a standard transesophageal echo image on the left and a color doppler ultrasound on the right. The lower images show mitral valve prolapse with severe regurgitation: a transesophageal echo image on the left and a color doppler ultrasound on the right. (Source image: Ville-Veikko Hynninen)

Table 4. Severity classification of chronic primary Mitral Regurgitation according to echocardiographic findings.

Stage	Definition	Central jet MR % LA/eccentric jet MR	VC (cm)	Rvol (ml)	RF (%)	ERO (cm^2)	AG	La/LV enlargement	LVEF/LVESD (%/mm)	PH
A	At risk of MR	<20/None	<0.3	>60	>50	>0.4	-	No/No		Normal
B	Progressive MR	>20–40/late systolic	<0.7	<60	<50	<0.4	1+-2+	Mild/No		Normal
C	Asymptomatic severe MR	>40/holosystolic	≥0.7	≥60	≥50	≥0.4	3+-4+	Moderate-severe/Present	C1: Normal/ mild-moderate C2: ≤55%/ Severe	May be present
D	Symptomatic severe MR	>40/holosystolic	≥0.7	≥60	≥50	≥0.4	3+-4+	Moderate-severe/Present		Present

ERO, effective regurgitant orifice; PH, pulmonary hypertension; LA left atrium/atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; RF, regurgitant fraction; and RVol, regurgitant volume. (Modified from Otto et al. 2021, 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.)

2.2.4 Invasive treatment of mitral valve

Mitral valve (MV) surgery has been evolving over the last decades. During the years 2011 to 2016, the annual overall MV operation rate increased by 24% in North America (Gammie et al. 2018). Moreover, the rate of mitral valve repair surgery has been increasing during the last decades (Gammie et al. 2009; Goldstone et al. 2017). However, a slight decrease in MV repair rate from 67.1% in 2011 to 63.2% in 2016 was seen in the North American population (Gammie et al. 2018). Moreover, in recent years, the use of minimally invasive procedural options has increased in patients with severe symptomatic mitral regurgitation (MR) who are at high surgical risk (Goode et al. 2020). The most common reason for open-heart mitral valve surgery is moderate or severe symptomatic MR (Enriquez-Sarano et al. 2009; Gammie et al. 2018) In the Society of Thoracic Surgeons Adult Cardiac Surgery Database Analysis of isolated MV surgery, only 12.1% of the operated patients had MV stenosis (Gammie et al. 2018). To an increasing extent, the patients who undergo MV surgery are older and have more comorbidities (Gammie et al. 2018). There is a discrepancy between the incidence of MR that meets criteria for surgery and the number of MV surgeries (Dziadzko et al. 2018; Monteagudo et al. 2018). Dziadzko et al. found that only 15% of the population diagnosed with MR was referred for surgery (Dziadzko et al. 2018).

2.2.4.1 Mitral valve repair

Mitral valve (MV) repair is the preferred surgical treatment for MV dysfunction of all other etiologies, except in rheumatic disease, where valve replacement may be a better first line option (Mohty et al. 2001; Suri et al. 2006; Gammie et al. 2009; Gammie et al. 2018; Tsang 2019; Otto et al. 2021). MV repair has many advantages over MV replacement. It preserves left ventricle (LV) function better, carries lower operative mortality and better long-term survival, and helps to avoid anticoagulation (Ren et al. 1996; Suri et al. 2006; Gammie et al. 2009; Gammie et al. 2018; Tsang 2019). The rate of MV repair has increased during the last decades (Savage et al. 2003; Jokinen et al. 2007; Gammie et al. 2009). In the Society of Thoracic Surgeons Adult Cardiac Surgery Database Analysis from year 2011 to year 2016, the overall MV repair rate was 65.6% (Gammie et al. 2018). The life-expectancy after MV repair is reported to be equal with the age- and sex-matched general population, as well as in patients ≥75 years of age (Vassileva et al. 2013).

The aim of MV repair is to restore a sufficient surface of coaptation of posterior and anterior leaflets to ensure competency of the valve. The technique of MV repair varies depending on which part of the valve is affected. The posterior leaflet prolapse is the most common dysfunction seen in degenerative MV disease, followed by bileaflet prolapse and isolated prolapse of the anterior leaflet (Perier et al. 2020). The valve resection used to be the proper way to correct posterior leaflet prolapse, but nowadays, tissue-saving techniques have come alongside (Perier et al. 2020). Surgical techniques to repair anterior leaflet prolapse can be divided into autologous or hybrid techniques (Perier et al. 2020). In the autologous technique, all materials that are used in the surgery are from the patient's own recourses; while in the hybrid technique, the used chordae are artificial (Perier et al. 2020). The anterior leaflet prolapses are more difficult to repair than posterior leaflet prolapses (Tsang 2019). The surgeon must have experience and master at least a few different repair techniques to achieve good valve competence (Tsang 2019; Perier et al. 2020). It is known that the durability of MV repair is very good in patients with degenerative MR, but it has remained controversial in patients with rheumatic heart disease (Chen et al. 2020). According to the recent evidence, the reoperation rate in rheumatic heart disease might be higher after MV repair compared to MV replacement (Chen et al. 2020).

MV surgery is indicated in symptomatic patients with primary MR (Vahanian et al. 2021; Otto et al. 2021). Surgery should be performed while left ventricular ejection fraction (LVEF) is still >60% and left ventricular end-systolic dimension (LVESD) <40 mm (Vahanian et al. 2021; Otto et al. 2021). Watchful waiting has been considered a safe strategy to follow asymptomatic MR patients. However, it is known that early surgery reduces long-term mortality more than watchful waiting. (Goldstone et al. 2015) Transcatheter edge-to edge MV repair may be considered an option to MV surgery, especially in patients with severe symptomatic MR that

cannot be operated due to high surgical risk (Feldman et al. 2011; Feldman et al. 2015; Vahanian et al. 2021; Otto et al. 2021). Urgent MV surgery is indicated in patients with acute severe primary MR (Vahanian et al 2021; Otto et al. 2021). MV replacement surgery is considered a preferable choice especially in case of papillary muscle rupture, but repair surgery can also be considered according to the newest guidelines (Grigioni et al. 2001; Vahanian et al. 2021; Otto et al. 2021).

Indications for surgery of secondary MR are more restrictive due to worse prognosis, and surgery is recommended only if also another indication for surgery exists or if the MR is persisting severe and the patient is symptomatic and appropriate for surgery (Vahanian et al. 2021; Otto et al. 2021).

2.2.4.2 Mitral valve replacement

As stated before, mitral valve (MV) repair is the preferred surgical treatment for MV dysfunction, but when MV repair is not feasible, MV replacement is favored (Vahanian et al 2021; Otto et al. 2021).

MV replacement can be done either with bioprosthetic or mechanical valve. During the last decades, there has been an increase in the use of bioprosthetic valves especially among older patients (Gammie et al. 2009; Vassileva et al. 2013; Goldstone et al. 2017; Gammie et al. 2018). The increase might be due to reports displaying an improvement in outcomes of biological valves (Gammie et al. 2009; Isaacs et al. 2015). At the same time, the characteristics of MV surgery patients have changed: patients are older and have more comorbidities (Nashef et al. 2012). Furthermore, when comparing MV replacement patients to repair, the patients are usually older, more likely to be women, have increased rates of diabetes mellitus, chronic lung disease, and hypertension, and have been admitted to hospital urgently (Nashef et al. 2012; Vassileva et al. 2013; Gammie et al. 2018). The European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease recommend bioprosthetic over mechanical valve in mitral position in patients over 70 years of age, and both valve types are acceptable in patients 65–70 years of age based on individual judgement (Vahanian et al. 2021). The American College of Cardiology and American Heart Association Joint Committee guidelines for the management of patients with valvular heart disease in turn recommend mechanical valve in mitral position in patients under 65 years of age and bioprosthetic valve in patients equal or over 65 years of age who are not suitable for MV repair (Otto et al. 2021). However, in clinical practice, there are many other factors than age affecting the choice of the valve type – for example, contraindications for anticoagulation, life expectancy, risk of reoperation, and the patient's own desire and lifestyle, as mentioned above in the aortic valve replacement paragraph.

2.3 Surgery due to infective endocarditis

2.3.1 Infective endocarditis

2.3.1.1 Native valve endocarditis

Infective endocarditis (IE) in native valves is a severe and devastating state, and it is associated with high mortality and morbidity (Ahtela et al. 2019; Malmberg et al. 2020). In IE, the toxins and enzymes cause valve degeneration and invasion that eventually lead to valve regurgitation, fistulas, paravalvular abscesses, and heart block (Pettersson et al. 2017). Valve regurgitation that has developed rapidly is usually poorly tolerated and may lead to pulmonary edema and cardiogenic shock. The prevalence of IE has increased during the last decades (Pettersson et al. 2017). Incidence of IE is 6.3/100 000 person-years in Finland during time period 2005–2014 (Ahtela et al. 2019) The annual increase in incidence was 7.2–7.6% in population aged 18–30 years, 3.8% in population aged 40–49 years, while no change in incidence rate was seen in population aged ≥50 years. (Ahtela et al. 2019). The increase in incidence of IE in younger population was speculated to be related to increasing drug abuse among young Finnish adults. In general, men are at higher risk of IE (Heiro et al. 2007; Ahtela et al. 2019). Managing IE includes antimicrobial therapy and properly timed highly demanding surgical intervention (Pettersson et al. 2017). The prognosis is mainly determined by the pathogen, valve position (aortic, mitral), and type of diseased valve (native or prosthesis) (Pettersson et al. 2017). The most common and most destructive pathogens are staphylococci and streptococci bacteria (Pettersson et al. 2017).

2.3.1.2 Prosthetic valve endocarditis

Prosthetic valve endocarditis (PVE) is a potentially life-threatening complication of heart valve surgery. Prosthetic valves can be affected by infection early or late after the surgery. The early PVE is defined as infection during the first year after operation (Ivanovic et al. 2019). PVE accounts for about 10–30% of all IE cases, and the risk is 0.3–1.2% per patient yearly (Habib et al. 2008; Slipczuk et al. 2013; Habib et al. 2015). The prevalence of PVE at 5 years is 5.7% and is equal between mechanical and bioprosthetic valves (Oxenham et al. 2003; Ivanovic et al. 2019). There is a relation between the causative pathogen and the time to PVE. In early PVE, the most common pathogens are Staphylococcus aureus (36%), coagulase negative staphylococci (17%), and fungi (Ivanovic et al. 2019). In late PVE, the proportion of Staphylococcus aureus and coagulase negative staphylococci decreases to 18–20%, while the proportion of enterococci and Streptococcus viridans increases to 10–13%

(Ivanovic et al. 2019). Age, staphylococcal infection, early PVE, congestive heart failure, stroke, and intracardiac abscess are associated with decreased survival in PVE (Habib et al. 2008).

2.3.2 Invasive treatment of infective endocarditis

Indications for surgical intervention in managing infective endocarditis (IE) are heart failure, severe valve dysfunction, persistent infection, prosthetic valve endocarditis, paravalvular abscess, cardiac fistula, large vegetations, and prevention of embolic complications, especially in the brain (Pettersson et al. 2017). The indications for surgery are identical in PVE (Ivanovic et al. 2019). Endocarditis surgery is challenging and technically complex. The hospital length of stay after both aortic and mitral valve replacement surgery is significantly longer in patients operated for IE than for other reasons (Malmberg et al. 2020; Anttila et al. 2021).

Two recent studies investigated the long-term outcomes of adult native-valve IE patients treated with first-time surgical aortic valve replacement (SAVR) (Malmberg et al. 2020) or mitral valve (MV) replacement (Anttila et al. 2021) in Finland from 2004 to 2008, using propensity score-matching. Of all included SAVR and MV replacement patients, 1.9% and 13.8%, respectively, were operated for IE (Malmberg et al. 2020; Anttila et al. 2021). In patients with IE, a history of drug abuse was seen in 9.3% of the SAVR population and in 11.8% of the MV replacement population (Malmberg et al. 2020; Anttila et al. 2021). SAVR patients operated for IE were younger and were more often men than patients without IE (Malmberg et al. 2020). MV replacement patients operated due to IE were also younger and had coagulopathy, cerebrovascular disease, and systemic rheumatic disease more often than patients without IE (Anttila et al. 2021). In non-matched IE patients, mechanical aortic valve prosthesis was more commonly used (53.7%) compared to the control group (29.9%) (Malmberg et al. 2020). In addition, mechanical mitral valve was more commonly used in non-matched IE patients (54.7%) compared to the control group (40.5%) (Anttila et al. 2021).

2.4 Outcomes after valve surgery

Bioprosthetic and mechanical valves are both associated with valve-related complications like thromboembolic- and bleeding-complications, structural failure, and infective endocarditis (Zellner et al. 1999; Kvidal et al. 2000; Oxenham et al. 2003; Akins et al. 2008; David et al. 2016). Previous thromboembolic or bleeding events significantly increase the risk for such complications after valve surgery (Kvidal et al. 2000).

2.4.1 Survival

The data on survival after surgical aortic valve replacement (SAVR) is inconsistent. Some studies have concluded that in non-elderly patients, survival is better when using mechanical valves (Glaser et al. 2016; Goldstone et al. 2017), while others have concluded that no difference between mechanical and biological valves exists (Chiang et al. 2014). Two recent population-based, propensity score-matched studies compared long-term outcomes between mechanical and bioprosthetic aortic valves in patients of two different age groups undergoing SAVR in Finland. In the first study, the patients were over 70 years old (Kytö et al. 2019) and in the latter 50–70 years old (Kytö et al. 2020). The 10-year survival in non-elderly patients was significantly better with mechanical valve prosthesis (81.4%) compared to biological valve (72.4%). On the contrary, the survival was better in elderly patients with biological valve prosthesis (57.8%) compared to mechanical valve (46.1%). These findings are in line with current guidelines recommending mechanical valve prosthesis for non-elderly and biological valve prosthesis for elderly patients (Vahanian et al. 2021; Otto et al. 2021). Even though the durability of the mechanical valve is good in non-elderly patients after SAVR, life expectancy is lower compared to the general population (Korteland et al. 2017).

The operative and long-term mortality is higher after mitral valve (MV) replacement compared to MV repair (Vassileva et al. 2013; Gammie et al. 2018). Vassileva et al. examined the long-term survival after MV repair and replacement in patients ≥65 years of age. They noticed that the 1-, 5-, and 10-year Kaplan-Meier survival estimates for MV repair were 90.9%, 77.1%, and 53.6%, respectively, and for MV replacement, the estimates were 82.6%, 64.7%, and 37.2% (Vassileva et al. 2013). Oxeham et al. noticed no difference in long-term survival between mechanical and bioprosthetic valves in mitral position (Oxenham et al. 2003). However, Goldstone et al. noticed differences when dividing patients to subgroups by age: the long-term mortality was higher in patients with bioprosthetic valves compared to mechanical valves in age groups of 40–49 and 50–69 years, but not in the age group of over 70 years old (Goldstone et al. 2017).

There was no difference in 30-day and 1-year mortality between MV replacement or SAVR patients operated for infective endocarditis (IE) compared to matched non-IE control groups (Malmberg et al. 2020; Anttila et al. 2021). However, 10-year mortality was significantly higher in both MV replacement and SAVR groups operated for native valve IE compared to non-IE control groups (Malmberg et al. 2020; Anttila et al. 2021).

2.4.2 Bleeding events

The risk of bleeding complications is higher in patients with mechanical valves due to the long-term anticoagulation therapy (Oxenham et al. 2003; Goldstone et al. 2017; Kytö et al. 2019). For mechanical valves in aortic position, the rate of bleeding is 16% after 10-year follow-up and 61% after 20-year follow-up. For bioprosthetic valves, the rates were 6% and 42% (Oxenham et al. 2003). For mechanical valves in mitral position, the rate of bleeding is reported to be 14% after 10-year follow-up, and 53% after 20-year follow-up, while the rates were 11% and 37%, respectively, for bioprosthetic valves (Oxenham et al. 2003).

The risk of bleeding complications in patients with native IE of the aortic valve is significantly higher during the first year after SAVR compared to non-IE controls (Malmberg et al. 2020). The risk decreases during the 10-year follow-up (Malmberg et al. 2020). On the contrary, the risk of bleeding complications in patients with native IE of the mitral valve is significantly higher during the cumulative 10-year follow-up after MV replacement compared to non-IE controls (Anttila et al. 2021).

2.4.3 Stroke and other cardiovascular events

In their recent study, Kytö et al. compared the long-term outcomes between mechanical and bioprosthetic aortic valve (AV) in Finland (Kytö et al. 2019). They noticed no significant difference in ischemic stroke events between the mechanical and bioprosthetic AV groups. However, Goldstone et al. noticed that the ischemic stroke risk was significantly lower with bioprosthetic valve compared to mechanical valve in patients aged 45–54 years (Goldstone et al. 2017).

There is no significant difference in the risk of thromboembolic complications between mechanical and biological valves (Oxenham et al. 2003). In patients with mechanical valves in aortic position, the rate of thromboembolic complications is reported to be 10% after 10-year follow-up, and 24% after 20-year follow-up. In patients with bioprosthetic valves, the rates were 23% and 39%, respectively. With mechanical valves in mitral position, the rate of thromboembolic complications is reported to be 30% after 10-year follow-up, and 53% after 20-year follow-up. With bioprosthetic valves, the rates were 29% and 31%, respectively (Oxenham et al. 2003).

The short and long-term risk for ischemic stroke is equal after MV replacement when comparing patients with native IE of the mitral valve to matched non-IE controls (Anttila et al. 2021). However, the short- and long-term risks of ischemic stroke were significantly higher after SAVR in patients with IE of the aortic valve than in non-IE patients (Malmberg et al. 2020).

2.4.4 Reoperations

Mechanical valves have good long-term durability. The risk of reoperation is higher in patients with bioprosthetic valves (Oxenham et al. 2003; Goldstone et al. 2017; Korteland et al. 2017). Korteland et al. conducted a meta-analysis of mechanical surgical aortic valve replacement (SAVR) in non-elderly (≥18 ≤55 years) patients (Korteland et al. 2017). They noticed that the lifetime risk for reoperation after SAVR is 8–15%, and the most common reasons for reoperation were endocarditis and non-structural valve dysfunction.

Reoperations after mechanical aortic valve (AV) were also uncommon in both non-elderly and elderly patients in the Finnish population (Kytö et al. 2019; Kytö et al. 2020). In non-elderly patients with mechanical valves, the 10-year cumulative reoperation rate was 1.4% (Kytö et al. 2020), and in elderly patients, it was 0.8% (Kytö et al. 2019). However, in non-elderly patients with bioprosthetic valves, there was an increasing trend in the cumulative risk of reoperation during long-term follow-up (1-year rate, 1.3%; 5-year rate, 4.1%; 10-year rate, 8.5%). (Kytö et al. 2020) In elderly patients with bioprosthetic valves, the reoperation risk was not increased (Kytö et al. 2019). Moreover, Goldstrone et al. noticed in the American population that the risk of reoperation was higher after bioprosthetic aortic valve replacement than mechanical (Goldstone et al. 2017).

The reoperation rate after mitral valve (MV) repair is 2.1%; after MV replacement, it is 4.1%. (Gammie et al. 2018) The risk of reoperation after MV replacement was lower in patients who received a bioprosthetic valve compared to those who received a mechanical valve (Goldstone et al. 2017).

The 10-year cumulative risk for AV reoperation was equal after SAVR in the IE group compared to the non-IE control group (Malmberg et al. 2020). The risk was 4.3% in the IE group and 8.4% in the non-IE controls. In a larger population of AV IE patients, the risk of reoperation after SAVR was as high as 20.6% during a median follow-up time of 6.8 years (Toyoda et al. 2018).

2.5 Risk-Modifying factors in valve surgery

2.5.1 Sex and outcome

Sex differences in cardiovascular diseases and cardiac surgery are recognized and have received wide attention in recent years (Cho et al. 2021). It has been suggested that the effect of sex differences on the outcome may be due to many coexistent factors. For example, sex hormones, genes, environmental influences, lifestyle, and differences in treatment may explain differences in outcome (Regitz-Zagrosek et al. 2017). Estrogen is thought to have a protective effect on vascular diseases and may

cause the delay in onset of aortic stenosis (AS) in women, partly explaining the higher age at the time of diagnosis (Nordstrom et al. 2003). Women preserve better ejection fraction and myocardial contractility in AS than men (Regitz-Zagrosek et al. 2017). Despite the fact that women have a smaller body surface and corresponding aortic valve annulus, the current guidelines use sex-neutral thresholds to define severe AS (Vahanian et al. 2021; Otto et al. 2021; Cho et al. 2021).

Female sex has been related to worse overall outcome after cardiac surgery (Onorati et al. 2014). It might be because women are older and have more serious comorbidities by the time of surgery than men (Duncan et al. 2006; Doenst et al. 2006; Avierinos et al. 2008; Kulik et al. 2009; Hamed et al. 2009; Fuchs et al. 2010; Hartzell et al. 2011; Onorati et al. 2014; Elhmidi et al. 2014; Wong et al. 2018; Kislitsina et al. 2019, Johnston et al. 2019). Women undergoing coronary artery bypass graft (CABG), mitral, aortic, tricuspid valve, or combined surgery are known to have more heart valve disease, atrial fibrillation, hypertension, cerebrovascular and peripheral arterial disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypothyroidism, and anaemia (Johnston et al. 2019). In contrast, men were more likely to have myocardial infarction (MI) and previous percutaneous coronary intervention, to undergo isolated CABG, to be morbidly obese, or to abuse alcohol (Johnston et al. 2019). Moreover, the symptoms of cardiovascular diseases differ between men and women. The symptoms in women can be atypical and therefore delay diagnosis and the decision of surgery (Chan et al. 2016; Kislitsina et al. 2019) These sex differences might explain the overall observation of decreased long-term survival in women after cardiac surgery and female sex being an independent risk factor for long-term mortality (Johnston et al. 2019).

Women are less likely to undergo mitral valve (MV) repair than replacement (Avierinos et al. 2008; Vassileva et al. 2013; Kislitsina et al. 2019), even though it is known that the outcome is better after repair surgery. (Suri et al. 2006; Gammie et al. 2009; Gammie et al. 2018; Tsang 2019). Klitsina et al. noticed in their study on sex differences in MV surgery that women have more severe disease by the time of surgery and because of that, women often need more complex surgery than men (Kislitsina et al. 2019). In a propensity-matched study of men and women with similar stages of MV valve disease at the time of the surgery, the differences between sexes disappeared (Kislitsina et al. 2019). It was proposed that the differences in surgical approaches between men and women in unmatched population depend mostly on the severity of the disease rather than sex. The lower rate of MV repair surgery might also be partly due to the higher incidence of anterior and bileaflet prolapse in women (Avierinos et al. 2008).

Similar differences between sexes have also been seen in aortic valve (AV) surgery patients. Women are less often referred to AV replacement surgery due to aortic stenosis (AS) than men (Chaker et al. 2017; Cho et al. 2019). This may be

explained by the higher age and risk profile of women at the time of diagnosis (Onorati et al. 2014; Chaker et al. 2017). There is also evidence of sex-dependent differences in pathogenesis and progression of AV calcification. These factors might partly explain the differences in the mechanics of AS between men and women (Chaker et al. 2017). The in-hospital mortality after heart valve surgery seems to be higher in women compared to men (Chaker et al. 2017; Wong et al. 2018; Johnston et al. 2019; Cho et al. 2021). There is evidence that the long-term survival is equal between men and women (Doenst et al. 2006; Fuchs et al. 2010; Elhmidi et al. 2014) but also that the long-term survival is higher in women (Kulik et al. 2009).

2.5.2 Long-term oral anticoagulation and outcome

The aim of antithrombotic therapy after prosthetic heart valve surgery is to prevent valve thrombosis and to decrease the risk of other thromboembolic complications. However, when considering antithrombotic therapy, the risk of bleeding should be considered. The recommendations for anticoagulation after heart valve prosthesis surgery are presented in Figure 7.

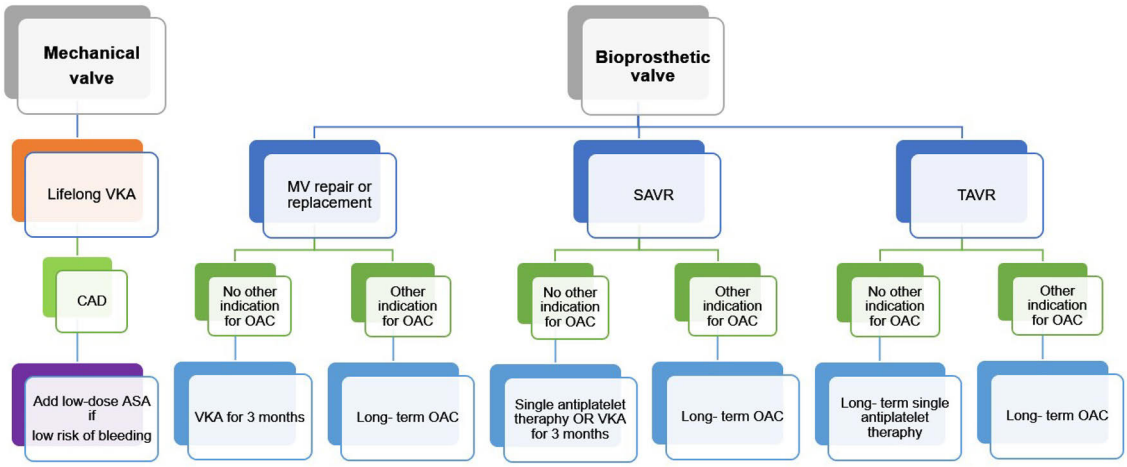

Figure 7. Recommendations for antithrombotic therapy after heart valve prosthesis surgery. ASA, acetylsalicylic acid; CAD, coronary artery disease; MV, mitral valve; SAVR, surgical aortic valve replacement; OAC, oral anticoagulant; TAVR, transcatheter aortic valve replacement; VKA, vitamin K anticoagulant. (Modified from Vahanian A et al. 2021, ESC/EACTS Scientific Document Group; ESC Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2021 Aug 28:ehab395)

2.5.2.1 Mechanical valve

Lifelong vitamin K antagonists (VKA) are recommended for patients with mechanical valve, and novel oral anticoagulants (NOACs) are not officially approved for these patients (Vahanian et al. 2021; Otto et al. 2021). Combining low-dose aspirin (75–100 mg/day) to VKA in patients with mechanical valves should be considered after a thromboembolic complication, in addition to good monitoring of VKA treatment, and also if patient has concomitant atherosclerotic disease (Vahanian et al. 2021). In patients with coronary stents or high ischemic risk, triple therapy with aspirin (75–100 mg/day) and clopidogrel (75 mg/day) should be considered for at least one month (Vahanian et al. 2021).

2.5.2.2 Bioprosthetic valve

The evidence and practices of anticoagulation after bioprosthetic valve implementation are incoherent. After bioprosthetic surgical aortic valve replacement (SAVR) or mitral valve (MV) replacement, the American Guidelines for the management of patients with valvular heart disease recommend vitamin K antagonist (VKA) for at least 3 months and for as long as 6 months postoperatively for patients who are at low risk of bleeding (Otto et al. 2021). The European Guidelines for the management of valvular heart disease recommend VKA or single antiplatelet therapy for the first 3 months after biological valve surgery (Vahanian et al. 2021). After biological MV replacement or repair, it is recommended to initiate VKA for the first three months (Vahanian et al. 2021). However, after surgical aortic valve replacement (SAVR), a choice can be made between VKA and single antiplatelet therapy (Vahanian et al. 2021). Lifelong anticoagulation is recommended for all patients with bioprosthetic valves who have other indications for anticoagulation, and novel oral anticoagulants (NOACs) can be considered over VKA in patients with atrial fibrillation (AF) (Vahanian et al. 2021). After transcatheter aortic valve replacement (TAVR), single antiplatelet therapy is indicated lifelong for patients who have no other reason for oral anticoagulation (OAC) (Vahanian et al. 2021).

3 Aims

The aim of this thesis was to investigate the long-term trends and outcomes in mitral and aortic valve surgery in Finland.

The thesis consisted of four studies, and their aims were:

1. To examine nationwide trends in open-heart surgical mitral valve replacement and repair procedures between 1997 and 2014 in Finland.
2. To examine nationwide trends in surgical aortic valve replacement procedures between 2001 and 2016 in Finland.
3. To examine the sex differences in long-term outcomes after surgical aortic valve replacement procedures between 2004 and 2014 in Finland.
4. To examine the prevalence and type of oral anticoagulation treatment and their association with complications and death after the mandatory 3-month warfarin treatment period in patients who have undergone biological aortic valve replacement procedure between 2010 and 2016 in Finland.

4 Patients and Methods

The summary of the four studies of this thesis is presented in Table 5.

Table 5. Summary of studies I to IV.

	DESING	AIMS	PATIENTS	FOLLOW-UP TIME	OUTCOME
STUDY I	Retrospective	To examine nationwide trends in surgical MV replacement and repair procedures	3 684 adult patients who underwent primary MV repair or replacement procedure ± CABG for MR	1997–2014	1. 28-day all-cause postoperative mortality 2. 6-year all-cause postoperative mortality 3. 6-year incidence of cardiovascular events
STUDY II	Retrospective	To examine nationwide trends in SAVR procedures	12 139 adult patients who underwent primary SAVR ± CABG	2001–2016	1. 28-day all-cause postoperative mortality 2. 4-year all-cause postoperative mortality 3. 4-year incidence of cardiovascular events 4. 4-year risk of intracranial bleeding
STUDY III	Retrospective	To examine the sex differences in long-term outcomes after SAVR procedures	7 616 patients aged ≥18 years who had primary SAVR ± CABG	2004–2014	1. 10-year survival Secondary: 1. 10-year occurrence of major bleeding, 2. Ischemic stroke, 3. IE, 4. AV reoperation
STUDY IV	Retrospective	To examine the prevalence and type of OAC and association with complications and death after 3-month warfarin treatment period	3 880 patients who had primary BAVR ± CABG and were alive 3 months after surgery	2010–2016	1. Death 2. Stroke 3. Major bleeding

AV, aortic valve; BAVR, biological aortic valve replacement; CABG, cardiopulmonary bypass graft; IE, infective endocarditis; MR, mitral regurgitation; MV, mitral valve; OAC, oral anticoagulation; SAVR, surgical aortic valve replacement

4.1 Nationwide studies on the demographics of mitral valve and aortic valve surgery (Study I and II)

4.1.1 Data sources

In the first and second study of this thesis, we investigated the trends on open-heart mitral and aortic valve surgery in Finland by using nationwide register data. We used the data from the Finnish Cardiovascular Disease Register (Sydän- ja verisuonitautirekisteri). We formed it by combining cardiovascular-related patient data from three nationwide electronic health care registers with compulsory reporting. The registers were the Care Register for Healthcare in Finland registry (CRHF) (National Hospital Discharge Register, Hoitoilmoitusjärjestelmä, Hilmo), the national Drug Reimbursement Register (Kelan lääkekorvausrekisteri), and the Causes of Death Register (Kuolinsyyrekisteri). The institutional ethics review board of the National Public Health Institute approved the research use of the Finnish Cardiovascular Disease Register.

We collected the data on diagnoses and procedures from the National Hospital Discharge Register. This register also includes a separate detailed section on cardiac surgery patients. We collected the data on causes of death from the National Causes of Death Register. The CRHF register contains diagnoses for each secondary and tertiary care outpatient and inpatient visit, and the Causes of Death Register contains diagnoses of underlying, contributing, or immediate causes of death. The recording of the diagnoses is done by the treating physicians. Recording is mandatory and done using the codes from the Finnish version of the 10th version of International Classification of Diseases (ICD-10).

In the first study of mitral valve (MV) surgery, we used data from 1997 to 2014; and in the second study of aortic valve (AV) surgery, we used data from 2001 to 2016.

4.1.2 Study population

In the first study, 3 684 patients underwent primary open-heart MV surgery during the study period 1997–2014; and in the second study, 12 146 patients underwent primary SAVR between 2001 and 2016. The procedures were performed in Finland and with or without concomitant coronary artery bypass graft (CABG).

Patient groups in Study I:

1. All mitral valve procedures
2. Mitral valve repair
3. Bioprosthetic or mechanical mitral valve replacement

Patient groups in Study II:

1. All surgical aortic valve replacement procedures
2. Mechanical valve
3. Bioprosthetic valve

4.1.3 Covariates

We considered a patient to have diabetes, hypertension, or chronic lung disease (i.e., asthma or chronic obstructive pulmonary disease) if specific medication for the disease in question was found in the Drug Reimbursement Register, or if ICD-10 codes found in the CRHF register matched with these diseases prior mitral or aortic valve surgery.

In the records, information on urgency of the procedure was not available before the year 2003, because all procedures in which the patient had arrived in the hospital through the emergency room were defined as urgent. After 2003, procedures were defined as urgent if they were necessary to perform within one week of arrival to the hospital.

In Study II, we included all infective endocarditis (IE) patients in the population.

4.1.4 Follow-up and outcomes

The follow-ups of adverse events ended on December 31, 2014, and December 31, 2016, in the first and second study, respectively. We identified the outcome events from the National Hospital Discharge and Causes of Death Registers. These nationwide registers cover nearly 100% of the cases, with the only exception being patients who permanently moved abroad during the follow-up period. The percentage of the Finnish population moving abroad annually is 0.1–0.2% but is likely lower among elderly cardiac patients.

Outcomes in Study I:

1. 28-day all-cause postoperative mortality
2. 6-year all-cause postoperative mortality
3. 6-year incidence of cardiovascular events

Outcomes in in Study II:

1. 28-day all-cause postoperative mortality
2. 4-year all-cause postoperative mortality
3. 4-year incidence of cardiovascular events
4. 4-year risk of intracranial bleeding

In both studies, we defined cardiovascular mortality as mortality related to disease of the circulatory system (ICD-10 codes I20-25, I46, R96, R98, I61, I63, and I64) as the underlying, contributing, or immediate cause of death. We defined myocardial infarction by ICD-10 codes I21 and I22 as the hospital discharge diagnosis or as the underlying, contributing, or immediate cause of death. We defined stroke, excluding subarachnoid hemorrhage, by ICD-10 codes I61 and I63 (not I63.6) as the hospital discharge diagnosis or as the underlying, contributing, or immediate cause of death. In the second study, we defined intracranial bleeding as cerebral bleeding or non-traumatic intracranial bleeding (I61 and I62), excluding subarachnoidal hemorrhage.

4.1.5 Statistical methods

To assess the longitudinal changes in procedure types, patient characteristics, and post-procedural outcomes, we divided the study period in the first study into three six-year categories by the year of the mitral valve (MV) operation: 1997–2002, 2003–2008, and 2009–2014; and in the second study into four four-year categories by the year of the surgical aortic valve (SAVR) operation: 2001–2004, 2005–2008, 2009–2012, and 2013–2016. In the first study, we calculated the annual incidence rates for MV procedures during three study periods by using population information from Statistics Finland (Tilastokeskus).

In both studies, we compared trends in the patient characteristics across the time strata using the Cochran-Armitage trend test for categorical variables and regression analysis for continuous variables. We used Cox proportional hazards regression models in both studies to estimate the hazard ratios for post-procedural mortality and cardiovascular events in different time periods. We divided the total follow-up period into six-year periods in the first study and four-year periods in the second study. In addition, we used Cox proportional hazards regression to assess the 28-day post-procedural hazard of all-cause mortality in the different time periods. We used the first study periods in both studies as reference categories in all models. In Study I, we evaluated the hazard ratios for mortality and cardiovascular events per 1-year increase in calendar year of procedures between 1997 and 2014. In Study II, we evaluated proportional hazard assumptions graphically through plotting the Schoenfeld residuals, and we obtained no strong evidence against proportionality. In both studies, we adjusted the models for sex, age, urgency of the surgery, diabetes (yes/no), hypertension (yes/no), chronic lung disease (yes/no), previous myocardial infarction (MI) (yes/no), and previous ischemic stroke (yes/no). We also adjusted the model for concomitant coronary artery bypass graft (CABG) (yes/no) in study I.

4.2 Sex differences after surgical aortic valve replacement (Study III)

4.2.1 Study design and outcomes

In the third study of this thesis, we investigated the sex differences and long-term outcome after primary surgical aortic valve replacement (SAVR) (±CABG) in a nationwide population-based, propensity score-matched study in Finland.

Primary outcome:

1. 10-year survival after surgical aortic valve replacement

Secondary outcomes:

1. 10-year occurrence of major bleeding
2. Ischemic stroke
3. Infective endocarditis
4. Aortic valve reoperation

We performed interim analyses at the 1-year and 5-year follow-ups. We excluded perioperative events that occurred during the admission of primary SAVR surgery from the analyses of secondary outcomes. We included all patients ≥18 years of age who underwent SAVR surgery between 2004 and 2014 in Finland. We used propensity score matching in the identification of comparable groups of men and women.

4.2.2 Study population

During the study period from January 1, 2004, to December 31, 2014, a total of 8 193 patients aged ≥18 years underwent primary surgical aortic valve replacement (SAVR) operation either with mechanical or bioprosthetic valve. We identified the patients retrospectively from the CRHF registry. This nationwide mandatory registry is held by The National Institute for Health and Welfare of Finland (Terveyden ja hyvinvoinnin laitos). It collects data of all hospital admissions in Finland (Gunn et al. 2018). During the study period, SAVR operations were performed in 6 public hospitals (5 university hospitals and 1 central hospital) and 2 private hospitals. The final study population was composed of 7 616 patients after unsuitable patients had been excluded.

Exclusion criteria:

1. Concomitant surgery of the aorta (n = 192)
2. Concomitant surgery of other heart valves (mitral valve n = 222, tricuspid valve n = 64)
3. Concomitant surgery of other cardiac or pulmonary vasculature defects (n = 95)
4. Concomitant surgery of infective endocarditis (n = 203)
5. Previous valve replacement (n = 38)

We collected the mortality data from the Causes of Death Register. This nationwide mandatory registry is also held by The National Institute for Health and Welfare of Finland. The follow-up of survival ended 10 years after the primary SAVR operation or on December 31, 2016, whichever came first. The study was approved by the National Institute for Health and Welfare of Finland (permissions no.: THL/143/5.05.00/2015 and THL/1569/5.05.00/2016) and Statistics Finland (TK53-1410-15).

4.2.3 Propensity score matching

We used standardized difference scores to assess effect sizes in baseline characteristics between groups. We assessed the comorbidity burden by using the Charlson comorbidity index. We created a propensity score based on patient baseline characteristics using logistic regression. We used the obtained score for 1:1 caliber matching with a 0.10 caliber width of the logit of the standard deviation without a replacement to balance for baseline differences between men and women (Coca-Perraillon 2007).

4.2.4 Statistical methods

We studied the group differences using the chi-square test or *t* test as appropriate. A follow-up was calculated for survivors. We studied outcomes using the Kaplan-Meier method and Cox regression, with female sex as the reference. We did the confirmations of proportionality hazard assumptions by using a visual examination of Schoenfeld residuals. We used interaction analyses to evaluate an effect modification by prosthetic valve type. We used the cause-specific hazard models to account for competing risks of mortality in analyses of other outcomes. Results are presented as the mean, median, percentage, or hazard ratio (HR) with 95% confidence interval (CI) or standard deviation (SD). We considered a p-value <0.05 statistically significant and a standardized difference >0.20 to mean an imbalance in

baseline characteristics. We performed analyses by using the SAS version 9.4 (SAS Institute Inc., Cary, NC).

4.3 Anticoagulation after aortic valve surgery (Study IV)

4.3.1 Data sources

In the fourth publication in this thesis, we investigated the prevalence and prognosis of oral anticoagulation treatment after biologic aortic valve replacement (BAVR). We collected the data for study IV from the Finnish Cardiovascular Diseases Register, which is described in detail above (section 4.1.1).

We collected the data on drug purchases for reimbursed medications from the Drug Reimbursement Register.

Surveyed drugs:

1. Warfarin
2. Novel oral anticoagulants
    a. Rivaroxaban
    b. Edoxaban
    c. Dabigatran
    d. Apixaban

We collected the data after postoperative three-month warfarin treatment. The grouping of the patients was based on the medication use. We analyzed the drug purchases in three-month periods.

4.3.2 Follow-up and outcomes

We used data from January 1, 2010, to January 31, 2016. The median follow-up time was 3.0 years.

Outcomes:

1. Death
2. Stroke
3. Major bleeding (gastro-intestinal bleeding or intracranial non-traumatic bleeding, excluding subarachnoid hemorrhage)

We defined intracranial bleeding using the ICD-10 codes I61 and I62. We defined the gastrointestinal bleedings using the ICD-10 codes I85, K22.6, K25-29, K62.5, K66.1, and K92. We defined stroke using the ICD-10 codes I63 (ischemic stroke) and I64 (stroke, not specified).

4.3.3 Statistical methods

We performed risk estimation of adverse outcomes using Cox proportional hazards regression models which were adjusted for age, sex, procedure urgency, previous myocardial infarction, previous stroke, concomitant coronary artery bypass, diabetes, hypertension, chronic lung disease, and previous atrial fibrillation.

Anticoagulation status was divided in three states:

1. No oral anticoagulation therapy (no-OAC)
2. Warfarin
3. Non-vitamin K antagonist oral anticoagulants (NOAC)

Anticoagulation status with three possible states (no-OAC, warfarin, or NOAC) was included in the model as the state that was current at the time of the outcome event. Drugs are distributed from the pharmacy every 3 months in Finland. If discontinuation or change in medication was detected, the patient was moved to another group after 3 months from the latest drug purchase. Therefore, an individual patient can be included both in the warfarin and NOAC groups if both medications were purchased during the 3 months before the end of follow-up. Three months after operation was determined as the baseline for the Cox models. Statistical analyses were done using the R statistical software version 3.6.0 (R Core Team, 2019).

5 Results

5.1 Mitral valve surgery

5.1.1 Mitral valve surgery rates and types

During the study period from 1997 to 2014, a total of 3 684 mitral valve (MV) operations were performed in Finland (Table 6). During the follow-up time of 18 years, the annual incidence of MV operations was 3.9/100 000. When divided into three time periods – 1997–2002, 2003–2008, and 2009–2013 – incidence rates were 3.3/100 000, 4.5/100 000, and 3.8/100 000, respectively. The proportions of MV repair and replacement procedures were 62.4% and 37.6%, respectively (Table 6). During the follow-up time, MV repair surgery became more common than replacement surgery (Figure 8). An increasing trend in the use of bioprosthetic valves was seen. Moreover, the use of bioprosthetic valves became more common (Figure 8). MV surgery was classified as urgent in 20.4% of all patients. The proportion of urgent procedures increased markedly from 1997–2002 (6.0%) to 2009–2014 (29.0%) (Table 6; $p<0.001$ for trend for all). During the same time periods, the amount of concomitant CABG surgery decreased (Table 6; $p<0.001$ for trend). This trend was not seen in MV replacement surgery (Table 6; $p=0.825$ for trend), so the decrease was driven by MV repair surgery ($p<0.001$ for trend) with concomitant coronary artery bypass graft (CABG).

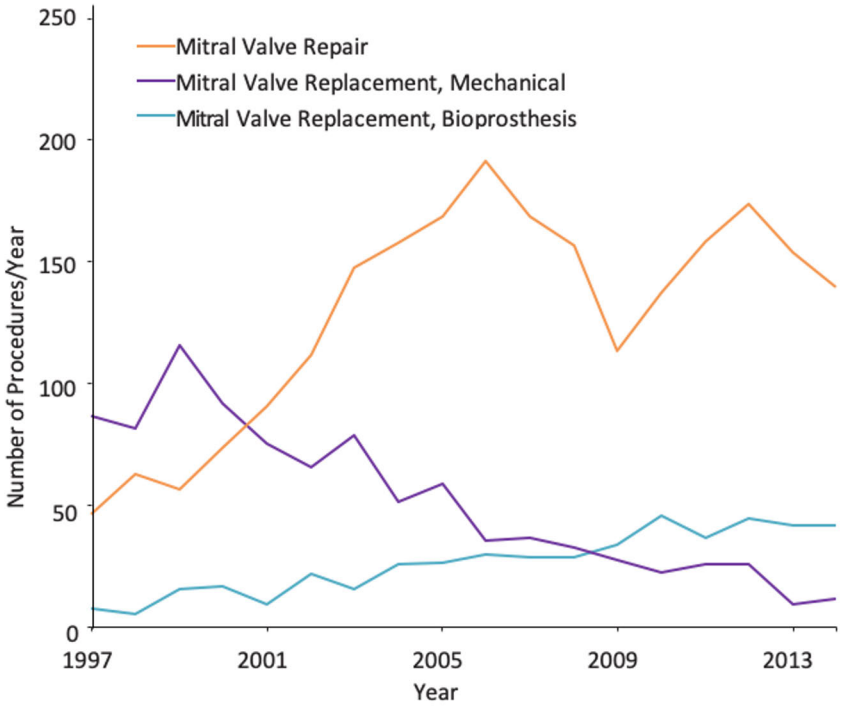

Figure 8. Trends in the numbers of the open surgical mitral valve procedures in Finland from 1997 to 2014.

5.1.2 Patient selection

The characteristics of mitral valve (MV) surgery patients are presented in Table 6. MV surgery patients were on average 66.0 years old, and 33.4% of the patients were women. During the study period, there was a significant increase in the age of the patients ($p<0.01$) and decrease in the total number and proportion of women ($p<0.001$). These changes were seen in both MV replacements and repairs (Table 6). In addition, the proportion of patients with hypertension ($p=0.023$ for trend) and diabetes ($p=0.026$ for trend) increased in the MV surgery group (Table 6)

Table 6. The characteristics of mitral valve surgery patients in Finland from 1997 to 2014.

Characteristic	Overall	1997–2002	2003–2008	2009–2014	P(trend)
ALL PROCEDURES, *N*	3684	1024	1428	1232	
Age, (year)	66.0 (10.7)	65.0 (10.2)	65.6 (10.6)	67.2 (11.0)	<0.001
Women	1231 (33.4)	401 (39.2)	464 (32.5)	366 (29.7)	<0.001
Urgent	750 (20.4)	61 (6.0)	332 (23.2)	357 (29.0)	<0.001
Previous MI	584 (15.6)	166 (16.2)	229 (16.0)	189 (15.3)	0.56
Previous stroke	272 (7.4)	71 (6.9)	103 (7.2)	98 (8.0)	0.35
Concomitant CABG	355 (9.6)	106 (10.4)	171 (12.0)	78 (6.3)	<0.001
Diabetes	451 (12.2)	115 (11.2)	161 (11.3)	175 (14.2)	0.03
Hypertension	1240 (33.7)	316 (30.9)	487 (34.1)	437 (35.5)	0.02
Chronic lung disease	366 (9.9)	92 (9.0)	139 (9.7)	135 (11.0)	0.12
MV REPLACEMENT, *N*	1386	586	441	359	
Age, (year)	67.0 (10.9)	66.0 (10.2)	67.0 (11.5)	68.7 (11.0)	<0.001
Women	590 (42.6)	269 (45.9)	179 (40.6)	142 (39.6)	0.04
Urgent	320 (23.1)	43 (7.3)	137 (31.1)	140 (39)	<0.001
Previous MI	267 (19.3)	102 (17.4)	90 (20.4)	75 (20.9)	0.16
Previous stroke	109 (7.9)	44 (7.5)	30 (6.8)	35 (9.7)	0.28
Concomitant CABG	158 (11.4)	55 (9.4)	76 (17.2)	27 (7.5)	0.83
Diabetes	214 (15.4)	72 (12.3)	67 (15.2)	75 (20.9)	<0.001
Hypertension	484 (34.9)	187 (31.9)	163 (37)	134 (37.3)	0.07
Chronic lung disease	158 (11.4)	60 (10.2)	52 (11.8)	46 (12.8)	0.22
MV REPAIR, *N*	2298	438	987	873	
Age (year)	65.3 (10.5)	63.8 (10.2)	65.0 (10.1)	66.6 (10.9)	<0.001
Women	641 (27.9)	132 (30.1)	285 (28.9)	224 (25.7)	0.06
Urgent	430 (18.7)	18 (4.1)	195 (19.8)	217 (24.9)	<0.001
Previous MI	317 (13.8)	64 (14.6)	139 (14.1)	114 (13.1)	0.41
Previous stroke	163 (7.1)	27 (6.2)	73 (7.4)	63 (7.2)	0.57
Concomitant CABG	197 (8.6)	51 (11.6)	95 (9.6)	51 (5.8)	<0.001
Diabetes	237 (10.3)	43 (9.8)	94 (9.5)	100 (11.5)	0.26
Hypertension	756 (32.9)	129 (29.5)	324 (32.8)	303 (34.7)	0.06
Chronic lung disease	208 (9.1)	32 (7.3)	87 (8.8)	89 (10.2)	0.08

Numbers are mean±SD for age and n (%) for other variables. MI, myocardial infarction; MV, mitral valve; CABG, coronary artery bypass grafting.

5.1.3 Short-term mortality after mitral valve procedures

The hazard ratios for all-cause mortality within 28 days after mitral valve (MV) surgery are presented in Table 7. During the follow-up periods of 1997–2002 and 2009–2014, the multivariable-adjusted risk of early post-operative mortality decreased by 45% (HR, 0.55; 95% CI, 0.37–0.83). The same change was seen in both MV repair (HR, 0.59; 95% CI, 0.28–1.25) and replacement procedures (HR, 0.77; 95% CI, 0.46–1.27). However, the decrease remained non-significant because the numbers of procedures and events were low. (Table 7) A decrease was seen in the adjusted mortality per 1-year procedure year increase in the MV repair group (HR, 0.93; 95% CI, 0.89–0.98).

5.1.4 Long-term outcome after mitral valve procedures

HRs for 6-year incidence of cardiovascular events and all-cause mortality after primary surgical mitral valve (MV) procedure during time periods 1997–2002 and 2003–2008 are presented in Table 8. The HRs for mortality and cardiovascular events per 1-year increase in procedure year between 1997 and 2014 are also presented in Table 8. There were no significant changes seen in the risk of cardiovascular events from follow-up period 1997–2002 to 2003–2008 (Table 8). During the same time periods, there was a significant decrease in multivariable-adjusted 6-year postoperative mortality after all MV surgery operations (HR, 0.80; 95% CI, 0.67–0.97). When MV repairs and replacements were analyzed separately, this decrease was no longer significant. The year of surgery was added to the model as a continuous exposure variable, but no statistically significant changes were seen in the risk of cardiovascular events (Table 8). However, every 1-year increase in procedure year was associated with a lower risk of death after all procedures (HR, 0.97; 95% CI, 0.95–0.99) and MV repairs (HR, 0.96; 95% CI, 0.92–0.99). During the entire study period, the proportion of cardiovascular deaths remained almost unchanged (25% in 1997–2002 versus 26% in 2003–2008; P>0.05).

Table 7. Hazard ratios for 28-day postoperative mortality after first surgical mitral valve procedure in Finland in 1997–2014.

Procedure	Time period			Per 1-year increase in procedure year
	1997–2002	2003–2008	2009–2014	
ALL PROCEDURES				
N of deaths	57	85	50	192
Incidence per 1000 person-days	2.1	2.2	1.5	1.9
Crude	1.00 (ref)	1.07 (0.76–1.50)	0.73 (0.50–1.07)	0.98 (0.95–1.00)
Adjusted	1.00 (ref)	0.89 (0.62–1.26)	0.55 (0.37–0.83)**	0.95 (0.92–0.98)**
MV REPLACEMENT				
N of deaths	45	39	29	113
Incidence per 1000 person-days	2.9	3.4	3.1	3.1
Crude	1.00 (ref)	1.16 (0.75–1.78)	1.07 (0.67–1.71)	1.01 (0.98–1.05)
Adjusted	1.00 (ref)	0.83 (0.52–1.31)	0.77 (0.46–1.27)	0.98 (0.94–1.03)
MV REPAIR				
N of deaths	12	46	21	79
Incidence per 1000 person-days	1.0	1.7	0.9	1.3
Crude	1.00 (ref)	1.72 (0.91–3.25)	0.88 (0.43–1.79)	0.97 (0.92–1.02)
Adjusted	1.00 (ref)	1.36 (0.70–2.63)	0.59 (0.28–1.25)	0.93 (0.89–0.98)*

*p<0.05; **p<0.01. Numbers are hazard ratios (95% confidence intervals). Adjusted models include age, sex, type of procedure (urgent vs. non-urgent), diabetes, hypertension, chronic lung disease, concomitant CABG, and prevalent myocardial infarction and stroke as covariates. Ref, reference; MV, mitral valve.

Table 8. Hazard ratios for 6-year postoperative cardiovascular events and mortality after primary surgical mitral valve procedure in Finland in 1997–2008 and hazard ratios per 1-year increase in procedure year between 1997 and 2014.

Procedure	Cardiovascular events			Postoperative mortality		
	Time period		HR per 1-year increase in procedure year (1997–2014)	Time period		HR per 1-year increase in procedure year (1997–2014)
	1997–2002	2003–2008		1997–2002	2003–2008	
ALL PROCEDURES				3463	3346	
N of deaths	202	271	223	70.5 (11.7)	69.5 (11.6)	339
Incidence per 1000 person-days	42	40	71	1418 (40.9)	1208 (36.1)	106
Crude	1.00 (ref)	0.95 (0.79–1.14)	1.00 (0.97–1.02)	626 (18.1)	555 (16.6)	1.00 (0.98–1.02)
Adjusted	1.00 (ref)	0.86 (0.71–1.24)	0.98 (0.95–1.01)	398 (11.5)	337 (10.1)	0.97 (0.95–0.99)*
MV REPLACEMENT				250 (7.2)	240 (7.2)	
N of deaths	144	101	113	445 (12.9)	317 (9.5)	197
Incidence per 1000 person-days	56	53	36	758 (21.9)	551 (16.5)	61
Crude	1.00 (ref)	0.95 (0.74–1.23)	1.02 (0.98–1.06)	1810 (52.3)	1569 (46.9)	1.04 (1.01–1.07)
Adjusted	1.00 (ref)	0.80 (0.61–1.05)	0.98 (0.94–1.02)	362 (10.5)	247 (7.4)	1.00 (0.97–1.03)
MV REPAIR				2682 (77.4)	2320 (69.3)	
N of deaths	58	170	110	985	820	142
Incidence per 1000 person-days	26	34	35	58.4 (11.5)	56.8 (11.5)	44
Crude	1.00 (ref)	1.34 (0.99–1.80)	1.01 (0.97–1.05)	263 (26.7)	187 (22.8)	0.99 (0.96–1.03)
Adjusted	1.00 (ref)	1.22 (0.90–1.61)	1.00 (0.96–1.05)	179 (18.2)	151 (18.4)	0.96 (0.92–0.99)*

*p<0.05. Numbers are hazard ratios (95% confidence intervals). Adjusted models include age, sex, type of procedure (urgent vs. non-urgent), diabetes, hypertension, chronic lung disease, concomitant CABG and prevalent myocardial infarction and stroke as covariates. CABG, coronary artery bypass grafting; Ref, reference; MV, mitral valve.

5.2 Aortic valve surgery

5.2.1 Surgical aortic valve replacement rates and types

During years 2001 to 2016, a total of 12 139 patients underwent surgical aortic valve replacement (SAVR), and the incidence of SAVRs was 14 per 100 000 person-days. The use bioprosthetic valves ($p<0.001$) increased during these years ($p<0.001$). (Table 9) The use of bioprosthetic valves increased from 42.9% to 75.5% from period 2001–2004 to period 2013–2016, respectively ($p<0.001$) (Table 9). During the same time, the use of mechanical valves decreased significantly ($p<0.001$) (Table 9). A total of 16% of the procedures were classified as urgent, and their proportion increased markedly during the 16 years ($p<0.001$) (Table 9). However, the significant increase in urgent procedures was seen only in the mechanical valve group ($p<0.001$), when analyzing the two different valve groups separately. During the first and last period, the proportion of concomitant CABG procedures decreased markedly from 22% to 9.5% ($p<0.001$) (Table 9). A parallel change was also seen in the mechanical and bioprosthetic valve groups from 16% to 4.4% ($p<0.001$) and 30% to 11.1% ($P<0.001$), respectively (Table 9).

5.2.2 Patient selection

Trends in patient characteristics are presented in Table 9. From 2001 to 2016, the mean age of surgical aortic valve replacement (SAVR) patients was constantly 69.1 years. The mean age of mechanical and bioprosthetic valve groups was also constant: 59.5 (11.8) years and 74.7 (7.3) years, respectively. Of all patients during the entire study period, 39.1% were women. The proportion of women decreased during the years ($p=0.001$), and the decrease was greatest during the last period (Figure 9). The same change was seen in both mechanical and bioprosthetic valve groups ($p<0.001$ for both) (Table 9). Women received bioprosthetic valves more often than men, and the proportion of women in mechanical and bioprosthetic valve groups were 27.7% and 45.7%, respectively. The indication for surgery was aortic stenosis (AS) in 72.8% of the patients, and the proportion stayed constant during the study period (Table 9).

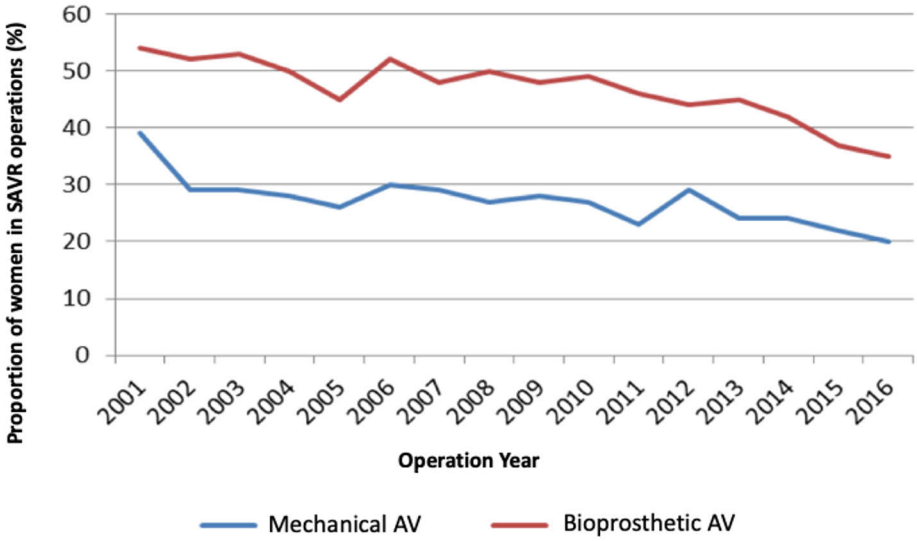

Figure 9. Decreasing proportion of women in the surgical aortic valve operations with mechanical and bioprosthetic valves from 2001 to 2016. AV, aortic valve; SAVR, surgical aortic valve replacement

During 2001–2016, the number of comorbidities of SAVR patients increased. More patients had hypertension ($p<0.001$), diabetes ($p=0.01$), and previous stroke ($p=0.01$) (Table 9). During 2001–2016, a decrease was however seen in the incidence of myocardial infarction ($p=0.05$), especially in the mechanical valve group ($p<0.001$). When the mechanical and bioprosthetic valve groups were analyzed separately, the increase in comorbidities was not seen in the mechanical valve group, while in the bioprosthetic valve group there was an increase in patients with hypertension ($p=0.01$) (Table 9).

Table 9. The characteristics of aortic valve surgery patients in Finland from 2001 to 2016.

Characteristic	Overall	2001–2004	2005–2008	2009–2012	2013–2016	P(trend)
ALL PROCEDURES, *n*	12139	2335	2995	3463	3346	<.001
Age (year)	69.1 (11.8)	67.0 (12.1)	68.8 (11.6)	70.5 (11.7)	69.5 (11.6)	0.42
Women	4745 (39.1)	934 (40.0)	1185 (39.6)	1418 (40.9)	1208 (36.1)	0.01
Urgent	2001 (16.5)	243 (10.4)	577 (19.3)	626 (18.1)	555 (16.6)	<.001
Previous MI	1371 (11.3)	264 (11.3)	372 (12.4)	398 (11.5)	337 (10.1)	0.05
Previous stroke	818 (6.7)	122 (5.2)	206 (6.9)	250 (7.2)	240 (7.2)	0.01
Concomitant CABG	1908 (15.7)	513 (22.0)	633 (21.1)	445 (12.9)	317 (9.5)	<.001
Diabetes	2205 (18.2)	327 (14.0)	569 (19.0)	758 (21.9)	551 (16.5)	0.01
Hypertension	5655 (46.6)	875 (37.5)	1401 (46.8)	1810 (52.3)	1569 (46.9)	<.001
Chronic lung disease	1076 (8.9)	182 (7.8)	285 (9.5)	362 (10.5)	247 (7.4)	0.57
AS	8834 (72.8)	1620 (69.4)	2212 (73.9)	2682 (77.4)	2320 (69.3)	0.83
MECHANICAL VALVE, *N*	4468	1334	1329	985	820	<.001
Age, (year)	59.5 (11.8)	60.9 (12.1)	60.6 (11.6)	58.4 (11.5)	56.8 (11.5)	0.54
Women	1238 (27.7)	414 (31.0)	374 (28.1)	263 (26.7)	187 (22.8)	<.001
Urgent	717 (16.0)	124 (9.3)	263 (19.8)	179 (18.2)	151 (18.4)	<.001
Previous MI	350 (7.8)	119 (8.9)	124 (9.3)	70 (7.1)	37 (4.5)	<0.01
Previous stroke	222 (5.0)	65 (4.9)	73 (5.5)	48 (4.9)	36 (4.4)	0.56
Concomitant CABG	533 (11.9)	213 (16.0)	201 (15.1)	83 (8.4)	36 (4.4)	<.001
Diabetes	624 (14.0)	168 (12.6)	212 (16.0)	151 (15.3)	93 (11.3)	0.65
Hypertension	1640 (36.7)	436 (32.7)	528 (39.7)	376 (38.2)	300 (36.6)	0.06
Chronic lung disease	298 (6.7)	90 (6.7)	99 (7.4)	68 (6.9)	41 (5.0)	0.15
BIOLOGIC VALVE, *N*	7671	1001	1666	2478	2526	<.001
Age (year)	74.7 (7.3)	75.1 (5.7)	75.4 (6.2)	75.3 (7.6)	73.6 (8.2)	0.99
Women	3507 (45.7)	520 (51.9)	811 (48.7)	1155 (46.6)	1021 (40.4)	<.001
Urgent	1284 (16.7)	119 (11.9)	314 (18.8)	447 (18.0)	404 (16.0)	0.20
Previous MI	1021 (13.3)	145 (14.5)	248 (14.9)	328 (13.2)	300 (11.9)	0.01
Previous stroke	596 (7.8)	57 (5.7)	133 (8.0)	202 (8.2)	204 (8.1)	0.06
Concomitant CABG	1375 (17.9)	300 (30.0)	432 (25.9)	362 (14.6)	281 (11.1)	<.001
Diabetes	1581 (20.6)	159 (15.9)	357 (21.4)	607 (24.5)	458 (18.1)	0.61
Hypertension	4015 (52.3)	439 (43.9)	873 (52.4)	1434 (57.9)	1269 (50.2)	0.01
Chronic lung disease	778 (10.1)	92 (9.2)	186 (11.2)	294 (11.9)	206 (8.2)	0.08

Numbers are mean±SD for age and n (%) for other variables. AS, aortic stenosis; MI, myocardial infarction; CABG, coronary artery bypass grafting.

5.2.3 Short-term mortality after surgical aortic valve replacement

Hazard ratio (HR) for 28-day all-cause mortality is seen in Table 10. From 2001 to 2016, the all-cause mortality within 28 days after surgical aortic valve replacement (SAVR) was 3.5%. There was a decrease in the short-term mortality from 2001–2004 to 2009–2012; 153/100 000 to 127/100 000, respectively (HR, 0.61; 95% CI, 0.46–0.80) and from 2001–2004 to 2013–2016; 153/100 000 to 89/100 000, respectively (HR, 0.47; 95% CI, 0.35-0.63). In the bioprosthetic valve group, there was also a steady decrease in all four-year time periods from 2001–2004 to 2005–2008 (HR, 0.66; 95% CI 0.47–9.92), 2009–2012 (HR, 0.54; 95% CI, 0.39–0.75), and 2013–2016 (HR, 0.41; 95% CI, 0.29–0.58). However, the short-term mortality remained unchanged in the mechanical valve group (Table 10).

Table 10. Hazard ratios for 28-day postoperative mortality after first surgical aortic valve replacement in Finland in 2001–2016.

Procedure	Time period			
	2001–2004	**2005–2008**	**2009–2012**	**2013–2016**
ALL PROCEDURES				
N of deaths	97	129	120	81
Incidence per 1000 person-days	153	159	127	89
Crude	1.00	1.04 (0.80–1.35)	0.83 (0.64–1.08)	0.58 (0.44–0.78) ***
Adjusted	1.00	0.80 (0.61–1.05)	0.61 (0.46–0.80) **	0.47 (0.35–0.63) ***
MECHANICAL VALVE				
N of deaths	34	48	21	14
Incidence per 1000 person-days	93	132	77	62
Crude	1.00	1.43 (0.92–2.21)	0.83 (0.48–1.44)	0.68 (0.36–1.26)
Adjusted	1.00	1.08 (0.68–1.70)	0.79 (0.45–1.37)	0.75 (0.40–1.41)
BIOLOGICAL VALVE				
N of deaths	63	81	99	67
Incidence per 1000 person-days	235	180	147	98

5.2.4 Long-term outcome after surgical aortic valve replacement

Table 11 shows hazard ratios (HR) for 4-year risk of cardiovascular events, all-cause mortality, and intracranial bleedings. A decrease was seen in multivariable-adjusted risk of cardiovascular events when analyzing mechanical and bioprosthetic valve groups together. The decrease was 17% from 2001–2004 to 2005–2008 (HR, 0.83; 95% CI, 0.70–0.99) and 26% from 2001–2004 to 2009–2012 (HR, 0.76; 95% CI, 0.64–0.91). When the two groups were analyzed separately, the decrease was seen only in patients who underwent bioprosthetic valve procedure (HR 0.79; 95% CI, 0.63–0.98) (Table 11). Overall, crude 4-year postoperative mortality increased from 2001–2004 to 2009–2012 (HR, 1.23; 95% CI, 1.07–1.42) but stayed unchanged in the multivariable-adjusted models (HR, 0.92; 95% CI, 0.80–1.05) (Table 11). The risk of intracranial bleeding stayed unchanged from 2001 to 2016 in both valve groups (Table 11)

Table 11. Hazard ratios for 4-year incidence of cardiovascular events, postoperative mortality and intracranial bleedings (I61+I62) after first surgical aortic valve replacement in Finland in 2001–2016.

Procedure	Cardiovascular events			Mortality			Intracranial bleeding		
	Time period			**Time period**			**Time period**		
	2001–2004	**2005–2008**	**2009–2012**	**2001–2004**	**2005–2008**	**2009–2012**	**2001–2004**	**2005–2008**	**2009–2012**
ALL PROCEDURES									
N of events	225	289	333	313	472	568	27	31	27
Incidence per 1000 person-days	26	25	25	37	44	46	319	287	217
Crude	1.00	1.00 (0.84–1.19)	1.00 (0.84–1.18)	1.00	1.18 (1.02–1.36)*	1.23 (1.07–1.42)**	1.00	0.90 (0.54–1.51)	0.68 (0.40–1.16)
Adjusted	1.00	0.83 (0.70–0.99)*	0.76 (0.64–0.91)**	1.00	0.96 (0.83–1.11)	0.92 (0.80–1.05)	1.00	0.81 (0.48–1.36)	0.60 (0.35–1.04)
MECHANICAL VALVE									
N of events	110	109	63	128	156	92	14	16	6
Incidence per 1000 person-days	22	21	17	26	32	25	281	326	162
Crude	1.00	0.99 (0.76–1.29)	0.77 (0.56–1.05)	1.00	1.24 (0.98–1.56)	0.97 (0.74–1.26)	1.00	1.16 (0.57–2.38)	0.58 (0.22–1.50)
Adjusted	1.00	0.91 (0.69–1.19)	0.78 (0.57–1.06)	1.00	1.10 (0.86–1.39)	1.01 (0.77–1.33)	1.00	1.11 (0.53–2.30)	0.60 (0.23–1.57)
BIOPROSTHETIC VALVE									
N of events	115	180	270	185	316	476	13	15	21
Incidence per 1000 person-days	31	29	29	53	54	54	374	255	241
Crude	1.00	0.93 (0.74–1.18)	0.94 (0.76–1.17)	1.00	1.01 (0.85–1.22)	1.03 (0.87–1.22)	1.00	0.68 (0.32–1.43)	0.64 (0.32–1.28)
Adjusted	1.00	0.82 (0.64–1.03)	0.79 (0.63–0.98)*	1.00	0.89 (0.74–1.06)	0.89 (0.75–1.06)	1.00	0.59 (0.29–1.20)	0.59 (0.29–1.20)

*p<0.05; **p<0.01. Numbers are hazard ratios (95% confidence intervals). Adjusted models include age, sex, type of procedure (urgent vs. non-urgent), diabetes, hypertension, chronic lung disease and prevalent myocardial infarction as covariates.

5.2.5 Sex differences in surgical aortic valve replacement patients

Altogether 7 616 adult patients underwent primary surgical aortic valve replacement (SAVR) from 2004 to 2014. Of these, 4 508 (59.2%) were men and 3 108 (40.8%) were women. Female patients were older than male patients, 73 years and 67 years, respectively ($p<0.0001$) (Table 12). Female patients had aortic stenosis (AS) more often; men, however, had more comorbidities and concomitant coronary artery bypass graft (CABG) (Table 12). Women received a bioprosthetic valve more often (77.6%) than men (59.4%) ($p<0.0001$) (Table 12).

The final study population used to analyze sex differences in SAVR patients after propensity score matching included 2 814 men and 2 814 women. The groups were comparable in terms of their characteristics (Table 13).

The survival after SAVR was 94.4% and 92.9% at 1-year follow-up, 81.2% and 83.6% at 5 years, and 66.8% and 67.5% at 10 years in men and women, respectively. There were no differences in long-term mortality within 10 years after SAVR between men and women (HR 1.09; CI 0.98–1.22; $p = 0.107$) (Figure 10). No sex difference was seen in 5-year (HR 1.14; CI 1.00–1.30; $p=0.053$) or in 1-year mortality (HR 0.93; CI 0.76–1.14; $p = 0.476$).

The cumulative incidence of major bleeding after SAVR was 3.0% and 1.4% at 1 year, 10.2% and 7.3% at 5 years, and 21.5% and 19.7% at 10 years in men and women, respectively. The 10-year bleeding hazard after SAVR was significantly higher among men than women (HR 1.36; CI 1.13–1.63; $p = 0.0009$). A significant difference was seen in the incidence of major bleeding between sexes at the 1-year (HR 2.07; CI 1.40–3.06; $p = 0.0003$) and 5-year (HR 1.52; CI 1.22–1.88; $p = 0.0001$) follow-up. There was no sex difference in bleeding sites ($p=0.239$). Gastrointestinal (38.5%) and intracranial (27.6%) bleedings were the most common sites of bleeding at 10-year follow-up.

During the 10-year period, no sex difference was seen in the incidence of stroke after SAVR (HR 1.06; CI 0.85–1.31; $p = 0.614$). In addition, the hazard ratio was similar between sexes within the 1-year (HR 1.11; CI 0.76–1.62 $p = 0.595$) and 5-year follow-ups (HR 1.21; CI 0.95–1.54; $p = 0.123$).

IE after SAVR occurred in 2.1% and 1.0% within 1 year, in 3.4% and 2.1% within 5 years, and in 4.7% and 2.6% within 10 years in men and women, respectively. Significantly higher 10-year hazard of IE was seen in men (HR 1.77; CI 1.25–2.51; $p = 0.001$). The type of valve modified the risk (interaction $p = 0.020$). The risk was equal between sexes in patients with mechanical valves (HR 0.94; CI 0.50–1.75; $p = 0.899$), whereas in patients with bioprosthetic valves, the risk was higher in men than women (HR 2.23; CI 1.50 3.58; $p = 0.0001$). The difference between sexes in the incidence of infective endocarditis after SAVR was already

present at the 1-year (HR 2.06; CI 1.30–3.26; p = 0.002) and 5-year (HR 1.78; CI 1.24–2.57; p = 0.002) follow-ups.

Men had a higher risk of early re-operations than women. The difference between men and women at the first-year follow-up was 0.8% vs. 0.1% (HR 2.98; CI 1.27–7.00; p = 0.013), and at the 5-year follow-up, 1.9% vs. 0.9% (HR 2.23; CI 1.28–3.89; p = 0.005). However, no difference was seen between men and women during the whole 10-year follow-up (2.4% vs. 3.8%; HR 1.35; CI 0.86–2.13; p = 0.189). These differences were the same irrespective of valve type.

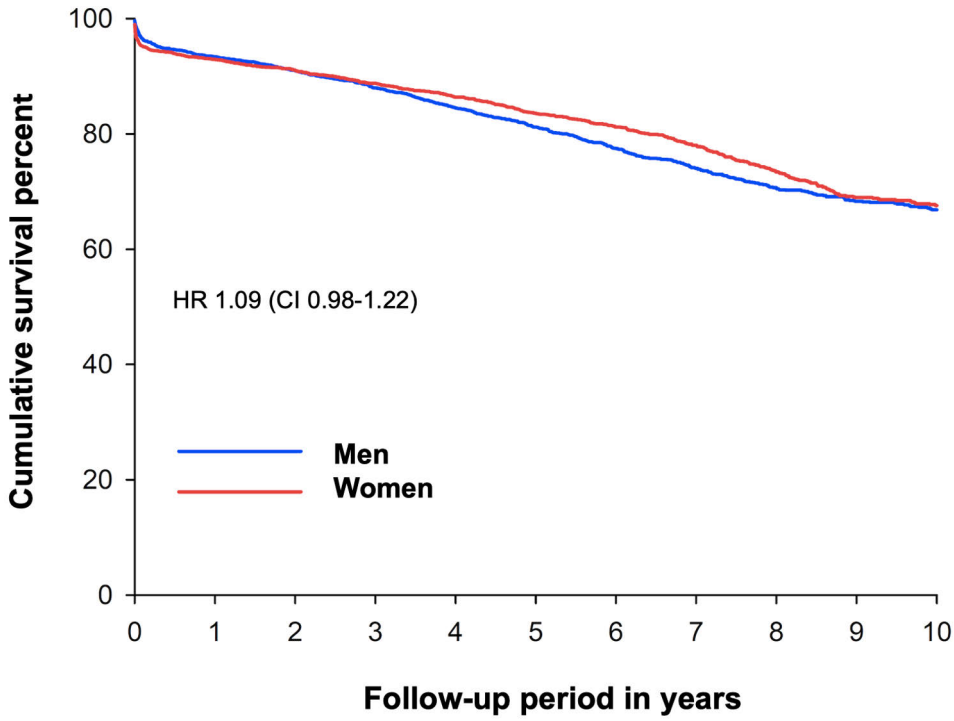

Figure 10. Sex-stratified survival after first-time surgical aortic valve replacement (±coronary artery bypass surgery) among propensity-matched patients from 2004 to 2014. HR, hazard ratio; CI, confidence interval.

Table 12. Characteristics of all patients aged ≥18 years with primary surgical aortic valve replacement (±CABG) with mechanical or biological valve prosthesis in Finland during 2004–2014 (original cohort) by sex. (n=7616)

Variable	Original Cohort			
	Men n=4508	**Women n=3108**	**Standardized difference**	**P-value**
Age, (years)	67.1 (11.9)	73.0 (9.3)	0.55	<0.0001
Valvular stenosis	3671 (81.4%)	2902 (93.4%)	0.37	<0.0001
Charlson comorbidity index score			0.09	0.0019
0	2656 (58.9%)	1947 (62.6%)		
1	1122 (26.1%)	745 (24.0%)		
2	470 (24.9%)	276 (8.9%)		
≥3	260 (5.8%)	140 (4.5%)		
Atrial fibrillation	714 (15.8%)	443 (14.3%)	0.04	0.058
Concomitant CABG	1525 (33.8%)	899 (28.9%)	0.11	<0.0001
Mechanical valve prosthesis	1832 (40.6%)	696 (22.4%)	0.40	<0.0001
Urgent or emergency surgery	252 (5.6%)	150 (4.8%)	0.03	0.143
Operation year			0.09	0.134
2004	383 (8.5%)	244 (7.9%)		
2005	423 (9.4%)	232 (7.5%)		
2006	371 (8.2%)	271 (8.7%)		
2007	430 (9.5%)	278 (8.9%)		
2008	368 (8.2%)	282 (9.1%)		
2009	389 (8.6%)	282 (9.1%)		
2010	388 (8.6%)	285 (9.2%)		
2011	453 (10.1%)	302 (9.7%)		
2012	437 (9.7%)	331 (10.7%)		
2013	473 (10.5%)	335 (10.8%)		
2014	393 (8.7%)	266 (8.6%)		

Numbers are mean±SD for age.
CABG, coronary artery bypass surgery; SD, standard deviation.

Table 13. Characteristics of propensity-matched patients aged ≥18 years with primary surgical aortic valve replacement (±CABG) with mechanical or biological valve prosthesis in Finland during 2004–2014 by sex.

Variable	Propensity-Mached Cohort			
	Men n=2814	Women n=2814	Standardized difference	P-value
Age, (years)	71.8 (9.1)	72.2 (9.4)	0.05	0.078
Valvular stenosis	2596 (92.3%)	2608 (92.7%)	0.02	0.545
Charlson comorbidity index score			0.02	0.952
0	1710 (60.8%)	1721 (61.2%)		
1	684 (24.3%)	688 (24.5%)		
2	279 (9.9%)	267 (9.5%)		
≥3	141 (5.0%)	138 (4.9%)		
Atrial fibrillation	413 (14.7%)	425 (15.1%)	0.01	0.653
Concomitant CABG	905 (32.2%)	884 (31.4%)	0.02	0.548
Mechanical valve prosthesis	699 (24.8%)	686 (24.4%)	0.01	0.688
Urgent or emergency surgery	134 (4.8%)	145 (5.2%)	0.02	0.499
Operation year			0.03	0.134
2004	216 (7.7%)	222 (7.9%)		
2005	228 (8.1%)	220 (7.8%)		
2006	245 (8.7%)	247 (8.8%)		
2007	253 (9.0%)	259 (9.2%)		
2008	245 (8.7%)	246 (8.7%)		
2009	252 (9.0%)	256 (9.1%)		
2010	258 (9.2%)	257 (9.1%)		
2011	291 (10.3%)	274 (9.7%)		
2012	288 (10.2%)	296 (10.5%)		
2013	298 (10.6%)	296 (10.5%)		
2014	240 (8.5%)	241 (8.6%)		

Numbers are mean±SD for age.
CABG, coronary artery bypass surgery; SD, standard deviation.

5.2.6 Long-term anticoagulation after biologic aortic valve replacement

From 2010 to 2016, altogether 4 079 patients underwent primary open-heart biologic aortic valve replacement (BAVR). During the first 3 months after surgery, 4.9% of the patients died, 0.7% had non-traumatic intracranial or gastrointestinal bleeding, and 2.6% had ischemic stroke (Table 14).

Table 14. Complications during the first 3 months after the operation (n=4079).

Complication	N (%)
Any complication	335 (8.2)
Intracranial nontraumatic bleeding or gastrointestinal bleeding	28 (0.7)
Ischemic stroke	108 (2.6)
Death	199 (4.9)
No complications	3744 (91.8)

The baseline characteristics of the final study population of 3 880 patients are presented in Table 15. After the first three months after the operation, 95.1% of the patients were alive and 57.9% of the patients had oral anticoagulation (OAC). During the follow-up, warfarin was the most common OAC used, while only 7.5% used NOAC. There was no difference in the proportion of women in different groups (42.6–44.6%). However, patients with OAC were older and had more comorbidities such as diabetes, hypertension, chronic obstructive lung disease, and previous AF. Furthermore, patients with warfarin had a history of MI or ischemic stroke more often, and the BAVR were urgent more often (Table 15).

Complications were grouped by medication use for the 3-month period after BAVR till the end of the study period. The complication rates are presented in Table 16. The rates of bleeding complications were similar in the OAC and no-OAC groups. However, more ischemic strokes were seen in patients with OAC, 17.3/1000 person-years and 19.7/1000 person-years in patients with warfarin and NOAC, respectively. The incidence of death was significantly lower in the novel oral anticoagulant (NOAC) group compared to no-OAC group (p=0.0002). Despite the increased risk of ischemic stroke, the risk of death was markedly lower in the OAC group (Table 17).

Table 15. Preoperative characteristics of biologic aortic valve replacement patients between 2010–2016.

Characteristic	Any OAC	p-value	Warfarin	p-value	NOAC	p-value	no-OAC
All procedures, *n*	2245		2158		168		1635
Age (year)	75.4 (7.1)	**<0.001**	75.5 (7.1)	**<0.001**	74.9 (5.9)	**<0.001**	72.6 (8.8)
Women	958 (42.7)	0.511	920 (42.6)	0.499	75 (44.6)	0.821	715 (43.7)
Urgent	378 (16.8)	**0.009**	370 (17.1)	**0.005**	23 (13.7)	0.98	225 (13.8)
Previous MI	271 (12.1)	**0.047**	264 (12.2)	**0.034**	19 (11.3)	0.601	164 (10.0)
Previous stroke	215 (9.6)	**<0.001**	209 (9.7)	**<0.001**	12 (7.1)	0.576	99 (6.1)
Concomitant CABG	246 (11.0)	0.116	236 (10.9)	0.114	19 (11.3)	0.63	206 (12.6)
Diabetes	707 (31.5)	**<0.001**	679 (31.5)	**<0.001**	60 (35.7)	**0.01**	432 (26.4)
Hypertension	1370 (61.0)	**<0.001**	1311 (60.8)	**<0.001**	103 (61.3)	**0.006**	821 (50.2)
Chronic lung disease	353 (15.7)	**0.001**	340 (15.8)	**0.001**	32 (19.0)	**0.009**	197 (12.0)
Previous AF	748 (33.3)	**<0.001**	728 (33.7)	**<0.001**	45 (26.8)	**<0.001**	76 (4.6)

Patients were grouped according to the medication use. If the medication was discontinued or changed, the patient was moved to another group after 3 months from the latest drug purchase, so one patient can be in both Warfarin and NOAC group. Warfarin and NOAC medications were surveyed 3 months after the operation until the end of the follow-up, any drug purchase during the period was considered. Numbers are mean±SD for age and n (%) for other variables. p-values any OAC vs. no-OAC, Warfarin vs. no-OAC & NOAC vs. no-OAC. AF, atrial fibrillation; MI, myocardial infarction; BAVR, biologic aortic valve replacement; CABG, coronary artery bypass grafting; OAC, oral anticoagulation; NOAC, non-vitamin K antagonist oral anticoagulant.

Table 16. Bleeding complications and mortality from 3 months after operation until end of follow-up. (n=3880).

Incidence 3 months after operation	Warfarin n=2158	p-value	NOAC n=168	p-value	no-OAC n=1635
Median follow-up, years	3.2		3.1		2.9
Bleeding complication, n (n/1000 person years)	48 (6.8)	0.559	4 (7.2)	0.744	29 (5.9)
Ischemic stroke, n (n/1000 person years)	122 (17.3)	<0.0001	11 (19.7)	0.039	35 (7.2)
Death, n (n/1000 person years)	342 (48.5)	0.089	10 (17.9)	0.0002	204 (41.9)

Patients are grouped according to the antithrombotic medication. If the medication was discontinued or changed, the patient was moved to another group after 3 months from the latest drug purchase. Bleeding complication = Intracranial nontraumatic bleeding or gastrointestinal bleeding. p-values Warfarin vs. no-OAC & NOAC vs. no-OAC. OAC, oral anticoagulation; NOAC, non-vitamin K antagonist oral anticoagulant.

Table 17. Risk of complications in oral anticoaculation theraphy users vs. patients not using oral anticoagulation theraphy.

	HR (95% CI)	
Complication	**Warfarin vs. no-OAC**	**Any OAC vs. no-OAC**
Any complication	1.03 (0.87–1.23), p=0.700	1.01 (0.85–1.20), p=0.913
Bleeding complication	1.00 (0.61–1.65), p=0.996	1.00 (0.61–1.65), p=0.995
Ischemic stroke	2.45 (1.66–3.21), p<0.001	2.39 (1.62–3.53), p<0.001
Death	0.82 (0.67–0.99), p=0.039	0.79 (0.65–0.96), p=0.016

Patients are grouped according to the medication use (warfarin only and all the OACs including warfarin = any OAC). If the medication was discontinued or changed, the patient was moved to another group after 3 months from the latest drug purchase. Hazard ratios are warfarin vs. no-OAC and any OAC vs. no-OAC. The models are adjusted for age, sex, procedure urgency, previous myocardial infarction, previous stroke, concomitant CABG, diabetes, hypertension, chronic lung disease and previous atrial fibrillation. CI, Confidence interval; HR, Hazard ratio; OAC, oral anticoagulation; CABG, coronary artery bypass grafting.

6 Discussion

6.1 Methodological considerations

In three studies of this thesis (I, II, IV), the data from 1997 to 2016 was collected from the large nationwide Finnish Cardiovascular Disease register. The register was formed by combining cardiovascular data from the National Hospital Discharge Register (CRHF), the National Drug Reimbursement Register, and the Causes of Death Register. In Study III, the data was collected separately from the CRHF Register, the National Drug Reimbursement Register, and the Causes of Death Register from year 2004 to 2014. These three administrative registers are nationwide electronic health care registers to which reporting is mandatory. Due to their mandatory nature, these registers include data on almost all patients who have had mitral or aortic valve surgery in Finland for the last nearly 20 years.

Over the last four decades, there has been a major increase in the number of national cardiac registries, and the use of registries has been associated with improvements in patient outcomes and mortality (Dawson et al. 2021). Despite its many advantages, the true value of a registry is determined by how complete and accurate its data is. The validity of coronary, stroke, and heart failure diagnoses in the Finnish registers has been described in detail previously (Pajunen et al. 2005; Tolonen et al. 2007; Mähönen et al. 2013). The coverage of the Finnish Cardiovascular Diseases Register data is known to be high, for example over 90% for revascularization procedures (Mähönen et al. 2013). In Finland, administrative registers have been widely used for epidemiological studies because they have good coverage and are cost-effective, and because by using combined data from different registers, we can improve sensitivity (Mähönen et al. 2013). A recent review about the characteristics and quality of national cardiac registries stated that registries that could be linked to existing population-based registries, like ours in Finland, were associated with a higher quality score (Dawson et al. 2021). Moreover, cardiac surgery registries had the highest quality scores of all registries. In the quality assessment, the Finnish Cardiovascular Diseases Register received a score of 17 of the maximum 24. The average score for the included cardiac registers (n=16) was 16.6 (Dawson et al. 2021).

The strengths of our studies include the use of large nationwide administrative registers with good coverage. Due to the mandatory reporting, these registers contain data on virtually all patients who have undergone cardiac surgery in Finland over a period of 19 years. Furthermore, for the same reason, all our studies are virtually free of selection bias.

6.2 Mitral valve surgery

Our first study of this thesis demonstrated how mitral valve (MV) surgery has evolved during the 17-year study period from 1997 to 2014 in Finland. We found that the proportion of MV repair procedures increased, whereas the proportion of MV replacements decreased. The use of bioprosthetic valves exceeded the number of mechanical valves. Moreover, we noticed that during the study period, short- and long-term mortality decreased although patients were older and had more underlying diseases, and the proportion of urgent procedures increased.

Our findings of the increased use of bioprosthetic valves and MV repairs are in line with results of other studies (Gammie et al. 2009; Vassileva et al. 2013). The rapid increase in MV repairs in years 2000–2016 stabilized during 2007–2014, during which time a decrease in mortality was also observed. These changes may be due to improvement in patient selection. In the late 1990s and early 2000s, it was thought that the reduction of the mitral annulus could improve survival in ischemic mitral regurgitation (MR) (Bax et al. 2004). However, later guidelines recommended a more conservative approach to ischemic MV regurgitation (Vahanian et al. 2012). Later, Smith et al. demonstrated that performing MV repair during the same operation with coronary artery bypass graft (CABG) in ischemic MR did not improve outcome in patients with ischemic mitral regurgitation (Smith et al. 2014).

We noticed a significant change in the characteristic of MV surgery patients during the study period. Our findings showed that patients are older by the time of surgery and have more diabetes and hypertension. The changes in the characteristic are similar to what was seen in a Finnish study of coronary artery bypass graft patients (Kiviniemi et al. 2016).

In 2012, the European guidelines for the management of heart valve diseases recommended a more aggressive approach to urgent mitral repair (Vahanian et al. 2012). These recommendations likely led to an increase in the proportion of urgent procedures from 6% to 29% from 1997–2002 to 2009–2014, respectively. During this period, the survival after mitral valve surgery improved. In addition to altered treatment of urgent MV regurgitation, improved outcome may also be due to advances in perioperative and intensive care (Morrow et al. 2012) and advanced and wide-spread use of perioperative echocardiography (Lancellotti et al. 2013). In our study, we noticed some sex differences. We have demonstrated a decrease in the

proportion of women having MV surgery during the study period 1997–2014. The change was seen in both repair and replacement surgery. Avernos et al. earlier showed that women have anterior and bileaflet prolapse more often than men, which could partly explain the lower rates of MV surgery in women (Avierinos et al. 2008). Moreover, women tend to be older and the disease tends to be more severe at the time of operation, which might partly explain the worse outcome in women after cardiac surgery (Avierinos et al. 2008; Mokhles et al. 2016).

6.3 Aortic valve surgery

In three studies of this thesis (II, III, IV), we elucidated the trends and outcomes of aortic valve (AV) surgery in Finland during years 2001–2016. We demonstrated how AV surgery and characteristics of the patients have evolved over the years. We also studied sex differences in surgical aortic valve replacement (SAVR) patients and anticoagulation after biologic aortic valve replacement (BAVR). We noticed that the use of bioprosthetic valves has increased. However, we also noticed that the mean age of the patients increased, which favors the use of bioprosthetic valves. Despite the patients having more comorbidities, we saw an improvement in short-term mortality, and long-term mortality remained unchanged. Moreover, we noticed that sex is not an independent risk factor for long-term mortality. However, when biologic valve was used, men were at higher risk for bleeding complications and re-operation after SAVR and infective endocarditis (IE). Permanent postoperative oral anticoagulation (OAC) use seems to reduce mortality after BAVR.

6.3.1 Patient selection and outcome

In Study II, the mean age in both groups stayed constant from 2001 to 2016, being significantly higher in the biologic aortic valve replacement (BAVR) group. The mean ages were 59.5 years in mechanical valve patients and 74.7 in bioprosthetic valve patients. Our findings suggest that age-dependent guidelines in valve selection are well implemented in the practice in Finland (Vahanian et al. 2012; Nishimura et al. 2014). The overall higher mean age of the patients might partly explain the decrease in the use of mechanical valves. Similar findings were made in a Swedish nationwide study, where an increase in the mean age of aortic stenosis (AS) patients by the time of the diagnosis was noticed (Martinsson et al. 2015). The decrease in the use of mechanical valves could be explained by the higher age of the patients at the time of the surgery.

In line with our findings, the use of bioprosthetic valves has generally increased (Glaser et al. 2016; Goldstone et al. 2017). There are varying results about the optimal age recommendations for biological and mechanical valves. Some studies

support the use of bioprosthetic valves also in middle-aged patients after finding no difference in mortality (Chiang et al. 2014; McClure et al. 2014; Chikwe et al. 2015), whereas several studies, in line with recommendations, show lower long-term mortality with mechanical valve prosthesis in patients aged 50–69 years (Brown et al. 2008; Glaser et al. 2016; Goldstone et al. 2017). As early as 2009, an increase in the use of bioprosthetic valves also in younger patient populations could be seen (Barnett and Ad 2009). Increasing use of bioprosthetic valves in younger patients might be due to a newer generation of bioprosthetic valves, which have shown good long-term integrity (Une et al. 2014; Bourguignon et al. 2015). New American and European guidelines for the management of the heart valve disease have been released after the end of our study period (2016), and the age-recommendation for bioprosthetic valves has been lowered by 5 years in both guidelines (Vahanian et al. 2012; Nishimura et al. 2014). The recent 2021 update of European guideline for the management of valvular heart disease recommends mechanical valves in patients aged <60 years, biologic valves in patients aged >65 years, and individual choice in patients aged 60–65 years (Vahanian et al. 2021). The American guideline for the management of patients with valvular heart disease in turn recommend mechanical aortic valve in patients aged <50 years, individual choice between mechanical and bioprosthetic valve in patients aged 50–65 years, and bioprosthetic valve in patients aged >65 years (Otto et al. 2021).

The comorbidity burden increased during our study period. Patients had more diabetes, previous stroke, and hypertension. However, we saw a decrease in the proportion of patients with previous myocardial infarction (MI). This probably reflects the changing global burden of diseases: the incidence of coronary heart disease and stroke in Western countries has decreased, while rates of hypertension and diabetes are on the rise (Kiviniemi et al. 2016; Salomaa et al. 2016).

Statistically, there was some increase in the urgency of the procedures over the study period. However, the change is only seen in time periods 2001–2004 and 2005–2008; after 2005, the proportion of urgent procedures remained constant. Before 2003, information on urgency was not available in the registers, so we defined all procedures in which the patient had arrived at the hospital through the emergency room as urgent. Based on these facts, we can assume that at least part of the increase in the proportion of urgent procedures is due to change we made in the definition of urgent surgery rather than actual change in the clinical practice.

6.3.2 Sex differences in surgical aortic valve replacement patients

Sex difference in cardiovascular diseases has received attention in recent years. It has been suggested that sex differences in outcome may be due to many different

coexistent causes. For example, sex hormones, genes, environmental influences, lifestyle, and differences in treatment are proposed (Regitz-Zagrosek et al. 2017). Estrogen is thought to have a protective effect on vascular diseases and might cause the delay in onset of aortic stenosis (AS) in women, partly explaining the higher age at the time of diagnosis (Nordstrom et al. 2003). It is also known that in AS patients, women preserve better ejection fraction and myocardial contractility than men (Regitz-Zagrosek et al. 2017).

In Study III, we noticed, in line with results from other studies, that women are older by the time of surgical aortic valve replacement (SAVR), and the burden of underlying diseases differs between men and women (Duncan et al. 2006; Doenst et al. 2006; Kulik et al. 2009; Fuchs et al. 2010; Hartzell et al. 2011; Chaker et al. 2017; Regitz-Zagrosek et al. 2017; Wong et al. 2018). We noticed that AS was more common in women, whereas men had overall more underlying diseases, i.e., atherosclerotic comorbidities. Our findings support the finding from other studies that men assigned to SAVR have more atherosclerotic comorbidities and more concomitant coronary artery bypass graft (CABG) than women (Hartzell et al. 2011; Regitz-Zagrosek et al. 2017; Chaker et al. 2017). However, there are also studies where the women studied have had more underlying diseases than men, contrary to our findings (Onorati et al. 2014; Chaker et al. 2017).

Female sex is one of the risk factors affecting mortality in the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) (Nashef et al. 2012) and the Society of Thoracic Surgeons score (O'Brien et al. 2018; Shahian et al. 2018). Previous results on sex differences in outcome after SAVR are controversial (Doenst et al. 2006; Kulik et al. 2009; Fuchs et al. 2010; Chaker et al. 2017). Women have higher unadjusted and adjusted in-hospital mortality following SAVR compared to men (Chaker et al. 2017; Wong et al. 2018). However, there are also studies that report no difference between sex in survival (Duncan et al. 2006; Onorati et al. 2014; ter Woorst et al. 2019). Female sex is related to lower long-term mortality (Fuchs et al. 2010). Conflicting study results of survival may be related to many factors – for example, different study populations, varying research settings, national differences, different study eras, and co-variables.

In Study II, we noticed a consistently declining proportion of women undergoing SAVR during the study period of 2001 to 2016. The study by Martinsson et al. showed that the incidence of AS does not differ significantly between men and women (Martinsson et al. 2015). Hence, our markedly smaller proportion of women undergoing SAVR is a noteworthy finding. As stated before, survival of women after open-heart surgery is worse compared to men, but survival after transcatheter aortic valve replacement (TAVR) seems to be better in women compared to men (Yousif et al. 2018). Moreover, women are usually older by the time of surgery. Due to all these reasons, physicians might be more willing to refer women to conservative

treatment or TAVR over surgery. We did not have data on the sex distribution of TAVR patients in Finland during our study period. However, Mäkikallio et al. has used the FinnValve registry to investigate TAVR surgeries in Finland (Mäkikallio et al. 2019). The nationwide FinnValve registry includes data from all TAVR operations from 2008 to 2017. Mäkikallio et al. observed that the proportion of TAVR operations has increased from 2008 to 2017, patients were on average 81.2 years old, and 55% of the patients were women. (Mäkikallio et al. 2019) Therefore, it is likely that the decrease in the proportion of women in the study period from 2013 to 2016 is related to the increase in the use of TAVR. Moreover, it is likely that the number of SAVR procedures will decrease even more due to TAVR operations in the coming years. TAVR surgery does not explain all sex differences seen in Study II. TAVR surgeries began in Finland in 2008, so they explain only the changes in the latest period of our study. The proportion of women was already smaller from the beginning of the study period, especially in the mechanical SAVR group.

In Study II, we noticed some differences between men and women in mid- and long-term morbidity. The risk for bleeding complications within 10 years after SAVR was markedly higher among men. However, we saw no difference in bleeding site between sexes. Similarly, in line with our findings, men who use OAC for AF have been shown to have a higher risk for bleeding complications (Pancholy et al. 2014). All pathophysiological mechanisms causing differences in bleeding characteristics are not identified, but they may be due to differences in lifestyle, platelet function, and coagulation mechanisms (Renda et al. 2019). We found no difference in incidence of ischemic stroke between sexes, although previous studies have reported the ischemic stroke risk to be higher among women (Doenst et al. 2006; Kulik et al. 2009).

Prosthetic valve surgery increases the risk of infective endocarditis (IE) substantially (Thornhill et al. 2018), and about 10–30% of all IE is prosthesis-related (Slipczuk et al. 2013; Habib et al. 2015). It is well known that men have a higher risk of endocarditis in the general population (Slipczuk et al. 2013; Ostergaard et al. 2018; Thornhill et al. 2018; Ahtela et al. 2019). In Study IV, we discovered that men are at higher risk for IE. However, the sex difference was significant only with bioposthetic valves. Our findings are in line with other studies (Thornhill et al. 2018; Ostergaard et al. 2018; Grubitzsch et al. 2018). Ostergaard et al studied the incidence of IE and risk factors for IE in a nationwide cohort of Danish patients after left-sided heart valve replacement (Ostergaard et al. 2018). They discovered that male sex and bioprosthetic valves increased the risk of IE after both SAVR and MV replacement. However, Kytö et al. discovered in a Finnish nationwide study that the risk of IE was comparable between mechanical and bioprosthetic valves after SAVR in patients aged over 70 years (Kytö et al. 2019). It is thought that the degeneration and calcification of biological valves might increase the bacterial adhesion to the valve

and thereby increase the risk of IE (Pressman et al. 2017). However, it is not known how sex affects this process. IE might also explain our finding in Study III that re-operation rates are higher among men at 1- and 5-year follow-ups. This could be explained by an increased risk of prosthesis infection after valve prosthesis surgery because surgery is the primary treatment. (Habib et al. 2015) In Study II, we observed the re-operation rates to be higher among men in mid-term follow-up. Furthermore, we noticed in Study III that reoperation rates were higher in mid-term follow-up. This could be explained by findings from a previous study, where median time to hospitalization after SAVR due to IE was about 1.7 years (Butt et al. 2019).

6.3.3 Long-term anticoagulation after biologic aortic valve replacement

In Study IV, our aim was to study the oral anticoagulation (OAC) use after the first three months postoperatively. The data consisted of 4 079 patients who underwent their first biologic aortic valve replacement (BAVR) in Finland. Mortality was 4.9% during the first 3 months postoperatively, so the final population was 3 871 patients.

We discovered the ischemic stroke risk to be increased among patients using OAC compared to non-users. It could be explained by the fact that users of OAC have an underlying higher risk of ischemic stroke, bigger comorbidity burden, and increased incidence of atrial fibrillation (AF). AF alone increases the risk of stroke by 20–25% compared sinus rhythm and additional risk factors further increase the risk (Chugh et al. 2001). Despite the higher risk of ischemic stroke, it seems that using OAC could be advantageous compared to no-OAC, since the risk of death is lower. There is also evidence that patients with AF and valvular heart disease (VHD) have a higher incidence of bleeding complications (Pan et al. 2017). We noticed that the incidence of bleeding complications was equal in OAC and no-OAC groups, contrary to previous findings. Lopez-Lopez et al. concluded in their study that novel oral anticoagulants (NOACs) were associated with a lower risk of bleeding complications compared to warfarin in patients with AF without valvular heart disease (VHD) (Lopez-Lopez et al. 2017), and similar findings have also been made with AF and VHD (Pan et al. 2017; Malik et al. 2019). Discrepancy in our results compared to others may be explained by frequent and regular follow-up of cardiac surgery patients in Finland and the consequent lower risk of overdose of warfarin compared to other AF patients.

A recent meta-analysis compared the efficacy and safety of novel oral anticoagulants (NOACs) with warfarin in patients with AF and VHD or bioprosthetic valve. They concluded that NOACs are more effective than warfarin in preventing stroke, myocardial infarction, and intracranial bleeding complications in patients

with AF and VHD; furthermore, outcomes were similar for NOACs and warfarin among patients with AF and bioprosthetic valve. (Malik et al. 2019)

In our study population, the risk of death was markedly higher among no-OAC group than among patients using OACs. This finding may be due to discontinuation of medications from patients with poor prognosis or a situation where patients are in long-term inpatient care without purchasing medicines from a pharmacy and consequently without entry in the Drug Reimbursement Register. However, if there is no other reason for the anticoagulation in addition to the bioprosthetic valve, it is not justified to initiate use of the drug because of the increased risk of bleeding complications. (Vahanian et al. 2021)

6.4 Limitations of the study

The four retrospective studies of this thesis are based on administrative register databases and therefore have typical limitations of observational retrospective register studies. We had no access to more detailed information on the data, and we had no information about the grade of valvular heart disease (VHD), nor the severity of the symptoms and EuroSCORE. However, we included several components from EuroSCORE (age, sex, lung disease, urgency, and history of MI) to cover this deficiency. Furthermore, in the case of drugs, we knew for certain only that the drugs were purchased from the pharmacy, not whether they were actually taken or why they were stopped or initiated. We also lacked the information about specific valve types or surgical techniques – we knew only whether the valve was biologic or mechanical. Moreover, in Study IV, the small number of patients using novel oral anticoagulants (NOACs) prevented us from analyzing NOAC and warfarin separately in the multivariable models, so they were analyzed as one group: any oral anticoagulant (OAC).

Due the retrospective observational nature of our four studies, it is possible that unidentified confounding factors may also have influenced the results.

6.5 Clinical aspects/Future considerations

In all four studies of this thesis, we studied the nationwide characteristics and prognosis of mitral and aortic valve surgery patients in Finland. Through our studies, we have gained new valuable information about these cardiac surgery patients in Finland. With this real-world evidence, we can improve the care of our patients by identifying factors related to risk of complications and prognosis and by improving techniques. Furthermore, this knowledge is essential for the interpretation of past and future studies.

In the future, we need to ascertain that we continue to monitor heart valve diseases and the results of current treatment, so that we can evaluate the treatment methods and further improve the care of our patients.

7 Summary and Conclusions

These studies provide valuable information about heart valve surgery in Finland. This knowledge can help us to improve the management of heart valve surgery patients in the future.

The conclusions based on our results are:

1. The number of mitral valve repairs has increased, and the number of mitral valve replacements has decreased. The use of bioprosthetic mitral valves has increased. Short- and long-term mortality has decreased despite the increased comorbidity burden and the larger proportion of operations that were urgent.
2. The use of bioprosthetic aortic valves has increased. The characteristics of surgical aortic valve patients have changed: patients are older, the proportion of women has decreased, and the proportion of patients with comorbidities has increased. The short-term mortality has improved, and the long-term mortality has remained unchanged.
3. Sex is not an independent risk factor for long-term mortality after surgical aortic valve replacement. Male sex was associated with higher risk of bleeding, infective endocarditis (when using biological prostheses), and re-operation.
4. The oral anticoagulation use after biologic aortic valve replacement appears to be associated with a decreased risk of death and an increased risk of ischemic stroke. The incidence of bleeding complications was equal between patients who use oral anticoagulants and those who do not.

Kiitokset

Suurimmat kiitokset kuuluvat ohjaajilleni, dosentti *Jenni Aittokalliolle* ja professori *Jarmo Gunnille*, heidän tuestaan ja avustaan väitöskirjaprosessin kaikissa vaiheissa. Jenniä on kiittäminen siitä, että päätin spontaanisti ryhtyä projektiin leikkaus-osastolla käydyn kahvipöytäkeskustelun päätteeksi. Hän on ollut vahvasti mukana väitöskirjatyöskentelyssä ja tiivis yhteydenpito on ollut erityisen korvaamatonta. Iltamyöhään käydyt ”tieteellisesti tasokkaat” Whatsapp-keskustelut ovat olleet tärkeitä niinä hetkinä, joina asioiden ymmärtäminen ja väitöskirjatyöskentely on tuntunut ylitsepääsemättömältä. Jarmo on niin ikään ollut erinomainen ohjaaja. Mahdollisuus tukeutua hänen sydänkirurgiseen asiantuntemukseensa oli erittäin keskeistä etenkin työskentelyn loppusuoralla.

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Turussa joulukuussa 2021
Monna Myllykangas

References

Ahtela E, Oksi J, Porela P, Ekstrom T, Rautava P, Kyto V. Trends in occurrence and 30-day mortality of infective endocarditis in adults: population-based registry study in Finland. *BMJ Open.* 2019; 9(4): e026811–026811.

Akins CW, Miller DC, Turina MI, et al. Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions. *The Annals of thoracic surgery.* 2008; 85(4): 1490–5.

Akinseye OA, Pathak A, Ibebuogu UN. Aortic Valve Regurgitation: A Comprehensive Review. *Curr Probl Cardiol.* 2018; 43(8): 315–34.

Al-Taweel A, Almahmoud MF, Khairandish Y, Ahmad M. Degenerative mitral valve stenosis: Diagnosis and management. *Echocardiography (Mount Kisco, N.Y.)* 2019; 36(10): 1901–9.

Anttila V, Malmberg M, Gunn J, Rautava P, Kytö V. Infective endocarditis and outcomes of mitral valve replacement. *Eur J Clin Invest.* 2021; Sep;51(9):e13577

Arabkhani B, Mookhoek A, Di Centa I, et al. Reported Outcome After Valve-Sparing Aortic Root Replacement for Aortic Root Aneurysm: A Systematic Review and Meta-Analysis. *The Annals of thoracic surgery.* 2015; 100(3): 1126–31.

Aronow WS, Ahn C, Kronzon I. Prevalence of echocardiographic findings in 554 men and in 1,243 women aged > 60 years in a long-term health care facility. *Am J Cardiol.* 1997; 79(3): 379–80.

Avierinos JF, Inamo J, Grigioni F, Gersh B, Shub C, Enriquez-Sarano M. Sex differences in morphology and outcomes of mitral valve prolapse. *Ann Intern Med.* 2008; 149(11): 787–95.

Barnett SD, Ad N. Surgery for aortic and mitral valve disease in the United States: A trend of change in surgical practice between 1998 and 2005. *The Journal of Thoracic and Cardiovascular Surgery.* 2009; 137(6): 1422–9.

Baumgartner H, MD, Hung J, MD, Bermejo, Javier, MD, PhD, et al. Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice. *Journal of the American Society of Echocardiography.* 2009; 22(1): 1–23.

Bax JJ, Braun J, Somer ST, et al. Restrictive Annuloplasty and Coronary Revascularization in Ischemic Mitral Regurgitation Results in Reverse Left Ventricular Remodeling. *Circulation.* 2004; 110(11 suppl 1): II-103–103.

Bonow RO, Lakatos E, Maron BJ, Epstein SE. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation.* 1991; 84(4): 1625–35.

Bourguignon T, Bouquiaux-Stablo AL, Candolfi P, Mirza A, Loardi C, May MA, El-Khoury R, Marchand M, Aupart M. Very Long-Term Outcomes of the Carpentier-Edwards Perimount Valve in Aortic Position. *Annals of Thoracic Surgery.* 2015; 99(3): 831–7.

Brown JW, Patel PM, Ivy Lin JH, Habib AS, Rodefeld MD, Turrentine MW. Ross Versus Non-Ross Aortic Valve Replacement in Children: A 22-Year Single Institution Comparison of Outcomes. *The Annals of thoracic surgery.* 2016; 101(5): 1804–10.

Brown ML, Schaff HV, Lahr BD, et al. Aortic valve replacement in patients aged 50 to 70 years: Improved outcome with mechanical versus biologic prostheses. *The Journal of Thoracic and Cardiovascular Surgery.* 2008; 135(4): 878–84.

Butt JH, Ihlemann N, De Backer O, et al. Long-Term Risk of Infective Endocarditis After Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol.* 2019; 73(13): 1646–55.

Chaker Z, Badhwar V, Alqahtani F, et al. Sex Differences in the Utilization and Outcomes of Surgical Aortic Valve Replacement for Severe Aortic Stenosis. *J Am Heart Assoc.* 2017; 6(9): 10.1161/JAHA.117.006370.

Chan V, Chen L, Elmistekawy E, Ruel M, Mesana TG. Determinants of late outcomes in women undergoing mitral repair of myxomatous degeneration. *Interactive cardiovascular and thoracic surgery.* 2016; 23(5): 779–83.

Cheitlin MD, Gertz EW, Brundage BH, Carlson CJ, Quash JA, Bode RS. Rate of progression of severity of valvular aortic stenosis in the adult. *Am Heart J.* 1979; 98(6): 689–700.

Chen S, Chen C, Chien-Chia Wu V, Chou A, Cheng Y, Chang S, Chu P. Mitral valve repair versus replacement in patients with rheumatic heart disease. *The Journal of thoracic and cardiovascular surgery.* 2020; 29:S0022-5223(20)32459-4 .

Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and Long-term Outcomes Following Bioprosthetic vs Mechanical Aortic Valve Replacement in Patients Aged 50 to 69 Years. *JAMA.* 2014; 312(13): 1323–9.

Chikwe J, Chiang YP, Egorova NN, Itagaki S, Adams DH. Survival and Outcomes Following Bioprosthetic vs Mechanical Mitral Valve Replacement in Patients Aged 50 to 69 Years. *JAMA.* 2015; 313(14): 1435–42.

Cho L, Kibbe MR, Bakaeen F, Aggarwal NR, Davis MB, Karmalou T, Lawton JS, Ouzounian M, Preventza O, Russo AM, Shroyer AW, Zwischenberger BA, Lindley KJ. Cardiac Surgery in Women in the Current Era: What Are the Gaps in Care? *Circulation.* 2021; 5;144(14):1172–1185.

Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol.* 2001; 37(2): 371–8.

Coca-Perraillon M. Local and Global Optimal Propensity Score Matching. *SAS Global Forum; Paper* 185–2007.

Dare AJ, Veinot JP, Edwards WD, Tazelaar HD, Schaff HV. New observations on the etiology of aortic valve disease: a surgical pathologic study of 236 cases from 1990. *Hum Pathol.* 1993; 24(12): 1330–8.

David TE, Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. *J Thorac Cardiovasc Surg.* 1992; 103(4): 617,21; discussion 622.

David TE, David CM, Feindel CM, Manlhiot C. Reimplantation of the aortic valve at 20 years. *The Journal of thoracic and cardiovascular surgery.* 2016; 153(2): 232–8.

Dawson LP, Biswas S, Lefkovits J, Stub D, Burchill L, Evans SM, Reid C, Eccleston D. Characteristics and Quality of National Cardiac Registries: A Systematic Review. *Circ Cardiovasc Qual Outcomes.* 2021; 14(9):e007963.

De Meester C, Pasquet, Agnès, Gerber, Bernhard L., Vancraeynest, David, Noirhomme P, El Khoury G, Vanoverschelde, Jean-Louis J. Valve repair improves the outcome of surgery for chronic severe aortic regurgitation: A propensity score analysis. *The Journal of thoracic and cardiovascular surgery.* 2014; 148(5): 1913–20.

Denti P, Maisano F, Alfieri O. Devices for mitral valve repair. *J Cardiovasc Transl Res.* 2014; 7(3): 266–81.

De Paulis R, Salica A. Surgical anatomy of the aortic valve and root-implications for valve repair. Ann *Cardiothorac Surg.* 2019; 8(3):313–321.

Detaint D, Messika-Zeitoun D, Maalouf J, Tribouilloy C, Mahoney DW, Tajik AJ, Enriquez-Sarano M. Quantitative Echocardiographic Determinants of Clinical Outcome in Asymptomatic Patients With Aortic Regurgitation: A Prospective Study. *Journal of the American College of Cardiology: Cardiovascular Imaging.* 2008; 1(1): 1–11.

Dillon J, Yakub MA, Kong PK, Ramli MF, Jaffar N, Gaffar IF. Comparative long-term results of mitral valve repair in adults with chronic rheumatic disease and degenerative disease: Is repair for "burnt-

out" rheumatic disease still inferior to repair for degenerative disease in the current era? *The Journal of thoracic and cardiovascular surgery.* 2015; 149(3): 771–9.

Doenst T, Ivanov J, Borger MA, David TE, Brister SJ. Sex-specific long-term outcomes after combined valve and coronary artery surgery. *Ann Thorac Surg.* 2006; 81(5): 1632–6.

Duncan AI, Lin J, Koch CG, Gillinov AM, Xu M, Starr NJ. The impact of gender on in-hospital mortality and morbidity after isolated aortic valve replacement. *Anesth Analg.* 2006; 103(4): 800–8.

Dziadzko V, Clavel MA, Dziadzko M, et al. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet.* 2018; 391(10124): 960–9.

Elhmidi Y, Piazza N, Mazzitelli D, Wottke M, Lange R, Bleiziffer S. Sex-related differences in 2197 patients undergoing isolated surgical aortic valve replacement. *J Card Surg.* 2014; 29(6): 772–8.

Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. *Lancet.* 2009; 373(9672): 1382–94.

Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. The Tromsø Study. *Heart.* 2012; Mar;99(6):396–400.

Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med.* 2011; 364(15): 1395–406.

Feldman T, Kar S, Elmariah S, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. *J Am Coll Cardiol.* 2015; 66(25): 2844–54.

Fishbein G, Fishbein M. Pathology of the Aortic Valve: Aortic Valve Stenosis/Aortic Regurgitation. *Curr Cardiol Rep.* 2019; 21(8): 1–9.

Flint N, Wunderlich NC, Shmueli H, Ben-Zekry S, Siegel RJ, Beigel R. Aortic Regurgitation. *Curr Cardiol Rep*. 2019 Jun 3;21(7):65.

Fuchs C, Mascherbauer J, Rosenhek R, et al. Gender differences in clinical presentation and surgical outcome of aortic stenosis. *Heart.* 2010; 96(7): 539–45.

Gammie JS, Chikwe J, Badhwar V, et al. Isolated Mitral Valve Surgery: The Society of Thoracic Surgeons Adult Cardiac Surgery Database Analysis. *The Annals of thoracic surgery.* 2018; 106(3): 716–27.

Gammie JS, Sheng S, Griffith BP, Peterson ED, Rankin JS, O'Brien SM, Brown JM. Trends in Mitral Valve Surgery in the United States: Results From The Society of Thoracic Surgeons Adult Cardiac Database. *The Annals of thoracic surgery.* 2009; 87(5): 1431–9.

Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50–69 years. *European heart journal.* 2016; 37(34): 2658–67.

Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, Woo YJ. Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. *The New England journal of medicine.* 2017; 377(19): 1847–57.

Goode D, Dhaliwal R, Mohammadi H. Transcatheter Mitral Valve Replacement: State of the Art. *Cardiovasc Eng Technol.* 2020; 11(3):229–253.

Grewal J, Suri R, Mankad S, et al. Mitral annular dynamics in myxomatous valve disease: new insights with real-time 3-dimensional echocardiography. *Circulation.* 2010; 121(12): 1423–31.

Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation.* 2001; 103(13): 1759–64.

Grubitzsch H, Tarar W, Claus B, Gabbieri D, Falk V, Christ T. Risks and Challenges of Surgery for Aortic Prosthetic Valve Endocarditis. *Heart Lung Circ.* 2018; 27(3): 333–43.

Gunn J, Valo J, Sipila J, Rautava P, Sihvo E, Kyto V. Trends and results of lung cancer surgery in Finland between 2004 and 2014. *Eur J Cardiothorac Surg.* 2018; 54(1): 127–33.

Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery

(EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J.* 2015; 36(44): 3075–128.

Habib G, Thuny F, Avierinos J. Prosthetic Valve Endocarditis: Current Approach and Therapeutic Options. *Progress in cardiovascular diseases.* 2008; 50(4): 274–81.

Hamed O, Persson PJ, Engel AM, McDonough S, Smith JM. Gender differences in outcomes following aortic valve replacement surgery. *Int J Surg.* 2009; 7(3): 214–7.

Harb SC, Griffin BP. Mitral Valve Disease: a Comprehensive Review. *Curr Cardiol Rep.* 2017; 19(8):73.

Hartzell M, Malhotra R, Yared K, Rosenfield HR, Walker JD, Wood MJ. Effect of gender on treatment and outcomes in severe aortic stenosis. *Am J Cardiol.* 2011; 107(11): 1681–6.

Heiro M, Helenius H, Hurme S, Savunen T, Engblom E, Nikoskelainen J, Kotilainen P. Short-term and one-year outcome of infective endocarditis in adult patients treated in a Finnish teaching hospital during 1980-2004. *BMC infectious diseases.* 2007; 7(1): 78.

Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. *J Thorac Cardiovasc Surg.* 2015; 149(5): 1262,9.e3.

Ishii K, Hirota Y, Suwa M, Kita Y, Onaka H, Kawamura K. Natural history and left ventricular response in chronic aortic regurgitation. *Am J Cardiol.* 1996; 78(3): 357–61.

Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J.* 2003; 24(13): 1231–43.

Ivanovic B, Trifunovic D, Matic S, Petrovic J, Sacic D, Tadic M. Prosthetic valve endocarditis – A trouble or a challenge? *Journal of cardiology.* 2019; 73(2): 126–33.

Jalava MP, Laakso T, Virtanen M, et al. Transcatheter and Surgical Aortic Valve Replacement in Patients With Recent Acute Heart Failure. *Ann Thorac Surg.* 2020; 109(1): 110–7.

Johnston A, Mesana TG, Lee DS, Eddeen AB, Sun LY. Sex Differences in Long-Term Survival After Major Cardiac Surgery: A Population-Based Cohort Study. *J Am Heart Assoc.* 2019; 3;8(17):e013260.

Jokinen JJ, Hippelainen MJ, Pitkanen OA, Hartikainen JE. Mitral valve replacement versus repair: propensity-adjusted survival and quality-of-life analysis. *Ann Thorac Surg.* 2007; 84(2): 451–8.

Kanwar A, Thaden JJ, Nkomo VT. Management of Patients With Aortic Valve Stenosis. *Mayo Clinic proceedings.* 2018; 93(4): 488–508.

Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. *Am J Cardiol.* 1988; 61(1): 123–30.

Kislitsina ON, Zareba KM, Bonow RO, et al. Is mitral valve disease treated differently in men and women? *European journal of preventive cardiology.* 2019; 26(13): 1433–43.

Kiviniemi TO, Pietila A, Gunn JM, Aittokallio JM, Mahonen MS, Salomaa VV, Niiranen TJ. Trends in rates, patient selection and prognosis of coronary revascularisations in Finland between 1994 and 2013: the CVDR. *EuroIntervention.* 2016; 12(9): 1117–25.

Korteland NM, Etnel JRG, Arabkhani B, et al. Mechanical aortic valve replacement in non-elderly adults: meta-analysis and microsimulation. *European heart journal.* 2017; 38(45): 3370–7.

Kulik A, Lam BK, Rubens FD, et al. Gender differences in the long-term outcomes after valve replacement surgery. *Heart.* 2009; 95(4): 318–26.

Kvidal P, Bergström R, Malm T, Ståhle E. Long-term follow-up of morbidity and mortality after aortic valve replacement with a mechanical valve prosthesis. *European heart journal.* 2000; 21(13): 1099–111.

Kyto V, Myllykangas M, Sipilä J, Niiranen T, Rautava P, Gunn J. Ten-year outcomes with mechanical vs. biological aortic valve prosthesis in patients >70 years. *The Annals of Thoracic Surgery.* 2019 Nov;108(5):1354–1360.

Kytö V, Sipilä J, Ahtela E, Rautava P, Gunn J. Mechanical Versus Biologic Prostheses for Surgical Aortic Valve Replacement in Patients Aged 50 to 70. *The Annals of thoracic surgery.* 2020; 110(1): 102–10.

Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *European heart journal cardiovascular imaging.* 2013; 14(7): 611–44.

Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol.* 1993; 21(5): 1220–5.

Ling LH, Enriquez-Sarano M, Seward JB, Tajik AJ, Schaff HV, Bailey KR, Frye RL. Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med.* 1996; 335(19): 1417–23.

Lopez-Lopez JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ.* 2017 Nov 28;359:j5058. Erratum in: *BMJ.* 2017 Dec 4;359:j5631. Erratum in: *BMJ.* 2018 May 23;361:k2295.

Mahonen M, Jula A, Harald K, et al. The validity of heart failure diagnoses obtained from administrative registers. *Eur J Prev Cardiol.* 2013; 20(2): 254–9.

Makikallio T, Jalava MP, Husso A, et al. Ten-year experience with transcatheter and surgical aortic valve replacement in Finland. *Ann Med.* 2019; 51(3–4): 270–9.

Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter Aortic-Valve Replacement for Inoperable Severe Aortic Stenosis. *The New England journal of medicine.* 2012; 366(18): 1696–704.

Makkar RR, Thourani VH, Mack MJ, et al. Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. *The New England journal of medicine.* 2020; 382(9): 799–809.

Malik AH, Yandrapalli S, Aronow WS, Panza JA, Cooper HA. Oral anticoagulants in atrial fibrillation with valvular heart disease and bioprosthetic heart valves. *Heart.* 2019; 105(18): 1432–6.

Malmberg M, Ahtela E, Sipilä JOT, Gunn J, Rautava P, Kytö V. Surgical aortic valve replacement and infective endocarditis. *Eur J Clin Invest.* 2021 Jun;51(6):e13476.

Marquis-Gravel G, Redfors B, Leon M, Généreux P. Medical Treatment of Aortic Stenosis. *Circulation.* 2016; 134(22): 1766–84.

Martinsson A, Li X, Andersson C, Nilsson J, Smith J, Sundquist K. Temporal Trends in the Incidence and Prognosis of Aortic Stenosis: A Nationwide Study of the Swedish Population. *Circulation.* 2015; 131(11): 988–94.

Maurer G. Aortic regurgitation. *Heart.* 2006; 92(7): 994–1000.

McClure RS, McGurk S, Cevasco M, Maloney A, Gosev I, Wiegerinck EM, Salvio G, Tokmaji G, Borstlap W, Nauta F, Cohn LH. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: A propensity-matched analysis. *Journal of Thoracic and Cardiovascular Surgery.* 2014; 148(5): 1931–9.

Miyahara S, Schneider U, Morgenthaler L, Schäfers H. (Almost) All Nonstenotic Bicuspid Aortic Valves Should Be Preserved or Repaired. *Seminars in thoracic and cardiovascular surgery.* 2019; 31(4): 656–60.

Mohty D, Orszulak TA, Schaff HV, Avierinos JF, Tajik JA, Enriquez-Sarano M. Very long-term survival and durability of mitral valve repair for mitral valve prolapse. *Circulation.* 2001; 104(12 Suppl 1): I1–7.

Mokhles MM, Siregar S, Versteegh MI, et al. Male-female differences and survival in patients undergoing isolated mitral valve surgery: a nationwide cohort study in the Netherlands. *European journal of cardio-thoracic surgery.* 2016; 50(3): 482–7.

Monteagudo Ruiz JM, Galderisi M, Buonauro A, Badano L, Aruta P, Swaans MJ, Sanchis L, Saraste A, Monaghan M, Theodoropoulos KC, Papitsas M, Liel-Cohen N, Kobal S, Bervar M, Berlot B, Filippatos G, Ikonomidis I, Katsanos S, Tanner FC, Cassani D, Faletra FF, Leo LA, Martinez A, Matabuena J, Grande-Trillo A, Alonso-Rodriguez D, Mesa D, Gonzalez-Alujas T, Sitges M,

Carrasco-Chinchilla F, Li CH, Fernandez-Golfin C, Zamorano JL. Overview of mitral regurgitation in Europe: results from the European Registry of mitral regurgitation (EuMiClip). *Eur Heart J Cardiovasc Imaging.* 2018 May 1;19(5):503–507.

Morrow DA, Fang JC, Lee Page R, et al. Evolution of Critical Care Cardiology: Transformation of the Cardiovascular Intensive Care Unit and the Emerging Need for New Medical Staffing and Training Models: A Scientific Statement From the American Heart Association. *Circulation.* 2012; 126(11): 1408–28.

Munt B, Legget ME, Kraft CD, Miyake-Hull CY, Fujioka M, Otto CM. Physical examination in valvular aortic stenosis: correlation with stenosis severity and prediction of clinical outcome. *Am Heart J.* 1999; 137(2): 298–306.

Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardiothorac Surg.* 2012; 41(4): 734–5.

Nishimura, Rick A., Otto, Catherine M., Bonow, Robert O., et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. *Journal of the American College of Cardiology.* 2014; 63(22): e57–e185.

Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet.* 2006; 368(9540): 1005–11.

Nordstrom P, Glader CA, Dahlen G, Birgander LS, Lorentzon R, Waldenstrom A, Lorentzon M. Oestrogen receptor alpha gene polymorphism is related to aortic valve sclerosis in postmenopausal women. *J Intern Med.* 2003; 254(2): 140–6.

O'Brien SM, Feng L, He X, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 2-Statistical Methods and Results. *Ann Thorac Surg.* 2018; 105(5): 1419–28.

Oh JK, Taliercio CP, Holmes DR, Reeder GS, Bailey KR, Seward JB, Tajik AJ. Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: prospective Doppler-catheterization correlation in 100 patients. *J Am Coll Cardiol.* 1988; 11(6): 1227–34.

Onorati, Francesco, D'Errigo P, Barbanti M, et al. Different impact of sex on baseline characteristics and major periprocedural outcomes of transcatheter and surgical aortic valve interventions: Results of the multicenter Italian OBSERVANT Registry. *The Journal of thoracic and cardiovascular surgery.* 2014; 147(5): 1529–39.

Ostergaard L, Valeur N, Ihlemann N, et al. Incidence and factors associated with infective endocarditis in patients undergoing left-sided heart valve replacement. *Eur Heart J.* 2018; 39(28): 2668–75.

Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021; 143(5): e35–71.

Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *Heart.* 2003; 89: 715.

Pajunen P, Koukkunen H, Ketonen M, et al. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. *Eur J Cardiovasc Prev Rehabil.* 2005; 12(2): 132–7.

Pan KL, Singer DE, Ovbiagele B, Wu YL, Ahmed MA, Lee M. Effects of Non-Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2017; 6(7):10.1161/JAHA.117.005835.

Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. *Am J Cardiol.* 2014; 113(3): 485–90.

Perier P, Hohenberger W, Batz G, Lakew F, Diegeler A. Mitral valve repair for degenerative mitral valve regurgitation. *Indian J Thorac Cardiovasc Surg.* 2020; 36(Suppl 1): 12–7.

Petrov G, Regitz-Zagrosek V, Lehmkuhl E, et al. Regression of myocardial hypertrophy after aortic valve replacement: faster in women? *Circulation.* 2010; 122(11 Suppl): 23.

Pettersson GB, Coselli JS, Pettersson GB, et al. 2016 The American Association for Thoracic Surgery (AATS) consensus guidelines: Surgical treatment of infective endocarditis: Executive summary. *The Journal of thoracic and cardiovascular surgery.* 2017; 153(6): 1241,1258.e29.

Pressman GS, Rodriguez-Ziccardi M, Gartman CH, Obasare E, Melendres E, Arguello V, Bhalla V. Mitral Annular Calcification as a Possible Nidus for Endocarditis: A Descriptive Series with Bacteriological Differences Noted. *J Am Soc Echocardiogr.* 2017; 30(6): 572–8.

Rahimtoola SH. Choice of prosthetic heart valve for adult patients. *Journal of the American College of Cardiology.* 2003; Mar 19;41(6):893–904.

Ram D, Bouhout I, Karliova I, Schneider U, El-Hamamsy I, Schäfers H. Concepts of Bicuspid Aortic Valve Repair: A Review. *The Annals of thoracic surgery.* 2020; 109(4): 999–1006.

Regitz-Zagrosek V, Kararigas G. Mechanistic Pathways of Sex Differences in Cardiovascular Disease. *Physiol Rev* 2017; Jan;97(1):1–37.

Ren JF, Aksut S, Lighty GW Jr, Vigilante GJ, Sink JD, Segal BL, Hargrove WC 3rd. Mitral valve repair is superior to valve replacement for the early preservation of cardiac function: relation of ventricular geometry to function. *Am Heart J.* 1996 May;131(5):974–81.

Renda G, Patti G, Lang IM, et al. Thrombotic and hemorrhagic burden in women: Gender-related issues in the response to antithrombotic therapies. *Int J Cardiol.* 2019; 286: 198–207.

Ross J, Braunwald E. Aortic stenosis. *Circulation.* 1968; 38(1 Suppl): 61–7.

Sabet HY, Edwards WD, Tazelaar HD, Daly RC. Congenitally Bicuspid Aortic Valves: A Surgical Pathology Study of 542 Cases (1991 Through 1996) and a Literature Review of 2,715 Additional Cases. *Mayo Clinic proceedings.* 1999; 74(1): 14–26.

Salomaa V, Pietilä A, Peltonen M, Kuulasmaa K. Changes in CVD Incidence and Mortality Rates, and Life Expectancy: North Karelia and National. *Global heart.* 2016; 11(2): 201.

Sarsam MAI, Yacoub M. Remodeling of the aortic valve anulus. *The Journal of thoracic and cardiovascular surgery.* 1993; 105(3): 435–8.

Savage EB, Ferguson TB, DiSesa VJ. Use of mitral valve repair: analysis of contemporary United States experience reported to the Society of Thoracic Surgeons National Cardiac Database. *Ann Thorac Surg.* 2003; 75(3): 820–5.

Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. *Circulation.* 1982; 66(5): 1105–10.

Shahian DM, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1-Background, Design Considerations, and Model Development. *Ann Thorac Surg.* 2018; 105(5): 1411–8.

Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS, Figueredo VM. Infective endocarditis epidemiology over five decades: a systematic review. *PLoS One* 2013; 8(12): e82665.

Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011 Jun 9;364(23):2187–98.

Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. *Scand J Public Health.* 2012; 40(6): 505–15.

Suri RM, Schaff HV, Dearani JA, et al. Survival Advantage and Improved Durability of Mitral Repair for Leaflet Prolapse Subsets in the Current Era. *The Annals of thoracic surgery.* 2006; 82(3): 819–26.

ter Woorst JF, Hoff AHT, van Straten AHM, Houterman S, Soliman-Hamad MA. Impact of Sex on the Outcome of Isolated Aortic Valve Replacement and the Role of Different Preoperative Profiles. *Journal of cardiothoracic and vascular anesthesia.* 2019; 33(5): 1237–43.

Thornhill MH, Jones S, Prendergast B, Baddour LM, Chambers JB, Lockhart PB, Dayer MJ. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. *Eur Heart J.* 2018; 39(7): 586–95.

Thornhill MH, Jones S, Prendergast B, Baddour LM, Chambers JB, Lockhart PB, Dayer MJ. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. *European heart journal.* 2018; 39(7): 586–95.

Thourani, Vinod H, Dr Prof, Kodali S, MD, Makkar RR, MD, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *The Lancet* 2016; 387(10034): 2218–25.

Tolonen H, Salomaa V, Torppa J, Sivenius J, Immonen-Raiha P, Lehtonen A, FINSTROKE register. The validation of the Finnish Hospital Discharge Register and Causes of Death Register data on stroke diagnoses. *Eur J Cardiovasc Prev Rehabil.* 2007; 14(3): 380–5.

Toyoda N, Itagaki S, Tannous H, Egorova NN, Chikwe J. Bioprosthetic Versus Mechanical Valve Replacement for Infective Endocarditis: Focus on Recurrence Rates. *The Annals of thoracic surgery.* 2018; 106(1): 99–106.

Tsang W. Recent advances in understanding and managing mitral valve disease. *F1000 research.* 2019; 8: 1686.

Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. *Eur Heart J.* 1987; 8(5): 471–83.

Une D, Ruel M, David TE. Twenty-year durability of the aortic Hancock II bioprosthesis in young patients: is it durable enough? *European Journal of Cardio-Thoracic Surgery.* 2014; 46(5): 825–30.

Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). *European heart journal.* 2012; 33(19): 2451–96.

Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W; ESC/EACTS Scientific Document Group; ESC Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2021; 28:ehab395.

Vasques F, Messori A, Lucenteforte E, Biancari F. Immediate and late outcome of patients aged 80 years and older undergoing isolated aortic valve replacement: a systematic review and meta-analysis of 48 studies. *Am Heart J.* 2012; 163(3): 477–85.

Vassileva CM, Mishkel G, McNeely C, Boley T, Markwell S, Scaife S, Hazelrigg S. Long-term survival of patients undergoing mitral valve repair and replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. *Circulation.* 2013; 127(18): 1870–6.

Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med.* 1996; 335(6): 407–16.

Wong SC, Yeo I, Bergman G, Feldman DN, Singh H, Minutello R, Kim LK. The Influence of Gender on In-Hospital Clinical Outcome Following Isolated Mitral or Aortic Heart Valve Surgery. *Cardiovasc Revasc Med.* 2019 Jun;20(6):468–474.

Yousif N, Obeid S, Binder R, Denegri A, Shahin M, Templin C, Luscher TF. Impact of gender on outcomes after transcatheter aortic valve implantation. *J Geriatr Cardio.l* 2018; 15(6): 394–400.

Zellner JL, Kratz JM, Crumbley AJ, Stroud MR, Bradley SM, Sade RM, Crawford FA. Long-term experience with the St. Jude Medical valve prosthesis. *Ann Thorac Surg.* 1999; 68(4): 1210–8.

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