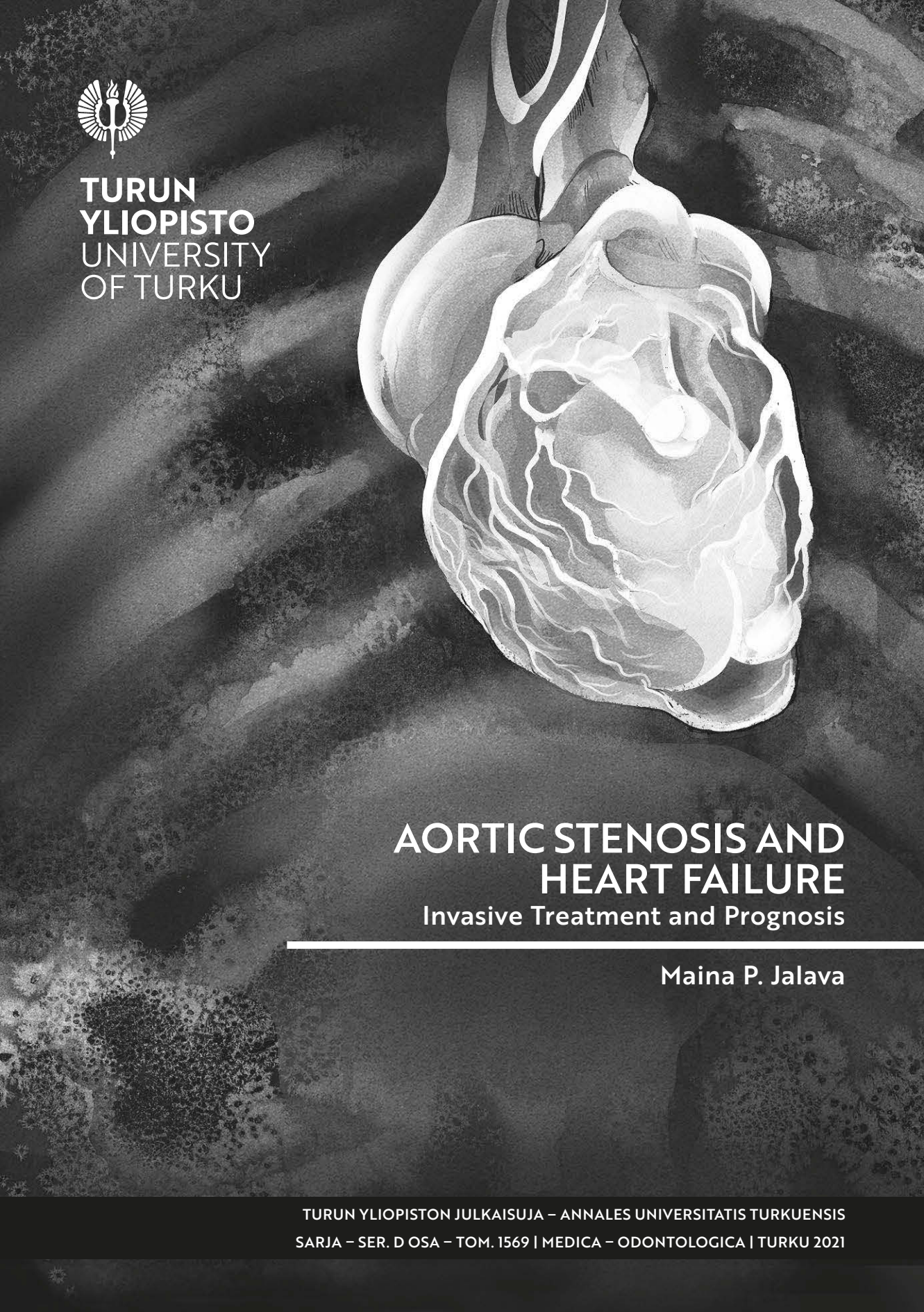

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Invasive Treatment and Prognosis

Maina P. Jalava

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To my family.

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Maina P. Jalava: Aortic Stenosis and Heart Failure – Invasive Treatment and Prognosis
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ABSTRACT

Background: Aortic stenosis (AS) is one the most common heart valve diseases. Symptomatic AS leads to death within a few years if left untreated. For decades, open heart surgery with surgical aortic valve replacement (SAVR) was the only definitive treatment option. Since the first transcatheter aortic valve replacement (TAVR) procedure in 2002, the annual overall procedure numbers have increased over the last decade.

Methods: The nationwide FinnValve registry was created to investigate the outcomes of TAVR and SAVR treatments in Finland from 2008 to 2017, herein with special interest in patients with heart failure.

Results: The FinnValve registry includes data from 6463 patients who underwent primary TAVR (2130 patients) or SAVR with bioprosthesis (4333 patients) for severe AS. Annual SAVR and TAVR numbers were 367 and 21 in 2008, 565 and 181 in 2013 and 335 and 622 in 2017 ($p<0.0001$). Since 2008, two-year survival improved from 71.4% to 83.9% for TAVR ($p<0.001$), and from 87.2% to 91.6% for SAVR ($p=0.006$). The prevalence of recent acute heart failure and left ventricular systolic dysfunction were 11.4% and 20.8% in the SAVR cohort and 11.3% and 27.7% in the TAVR cohort, respectively. Both acute heart failure and systolic dysfunction were associated with increased morbidity and mortality after TAVR and SAVR when compared to no heart failure. After acute heart failure, 3-year survival in the TAVR cohort were 66.6% and in the SAVR cohort 68.6%, respectively ($p=0.166$). In patients with left ventricular dysfunction 4-year survival after TAVR was 65.9% and 69.6% after SAVR (RMST ratio, 1.002, 95%CI 0.929–1.080, $p=0.964$).

Conclusions: TAVR has led to a more widespread use of invasive treatment for severe AS. Both acute heart failure and left ventricular dysfunction are associated with increased morbidity and mortality. TAVR is a valid alternative to SAVR in these patients. Intermediate survival is similar in heart failure patients

KEYWORDS: Aortic stenosis, heart failure, surgical aortic valve replacement, SAVR, transcatheter aortic valve replacement, TAVR.

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TIIVISTELMÄ

Tausta: Aorttaläppäahtauma on yleinen sydämen läppävika. Oireinen tauti johtaa hoitamattomana kuolemaan muutamassa vuodessa. Avosydänkirurginen keinoläppäleikkaus (surgical aortic valve replacement, SAVR) oli pitkään ainoa parantava hoitovaihtoehto. Vuodesta 2002 alkaen sen rinnalla vaihtoehtona on ollut katetriläppätoimenpide (transcatheter aortic valve replacement, TAVR). Tämän seurauksena aorttaläppätoimenpiteet ovat sittemmin lisääntynet nopeasti.

Metodit: Kansalliseen FinnValve-rekisteriin on kerätty TAVR- ja SAVR-potilaiden tiedot Suomessa vuosilta 2008–2017. Selvitimme hoidon ja ennusteen kehittymistä tänä aikana. Erityinen mielenkiinto kohdistui potilaisiin, joilla on sydämen vajaatoiminta.

Tulokset: FinnValve-rekisteri käsittää 6 463 potilasta, joille on tehty vaikean aorttaläppäahtauman vuoksi joko primaarinen TAVR (2 130 potilasta) tai SAVR biologisella keinoläpällä (4 333 potilasta). Vuosina 2008, 2013 ja 2017 kirurginen läppätoimenpide tehtiin 367, 565 ja 335 potilaalle ja katetriläppätoimenpide 21, 181 ja 622 potilaalle ($p < 0.0001$). Tutkimusajanjakson aikana kahden vuoden elossaolo parani 71,4–83,9 % TAVR:n jälkeen ($p < 0,001$), ja 87,2–91,6 % SAVR:n jälkeen ($p = 0,006$). Akuutin sydämen vajaatoiminnan ja vasemman kammion systolisen vajaatoiminnan esiintyvyydet olivat 11,4 % ja 20,8 % SAVR-kohortissa ja 11,3 % sekä 27,7 % TAVR-kohortissa. Sekä akuutti että systolinen vajaatoiminta lisäävät sairastavuutta ja kuolleisuutta verrattuna normaaliin sydämen toimintaan. Akuuttiin vajaatoimintaan sairastuneiden potilaiden elossaolo 3 vuoden kohdalla oli 66,6 % TAVR:n ja 68,6 % SAVR:n jälkeen, $p = 0,166$. Vasemman kammion systolista vajaatoimintaa sairastavien potilaiden 4 vuoden elossaolo oli TAVR:n jälkeen 65,9 % ja 69,6 % SAVR:n jälkeen (RMST ratio, 1,002, 95 % CI 0,929–1,080, $p = 0,964$).

Päätelmät: TAVR:n käyttö on lisääntynyt nopeasti aorttaläppäahtauman hoitona. Sekä akuutti sydämen vajaatoiminta että vasemman kammion systolinen vajaatoiminta lisäävät aorttaläppäahtaumapotilaiden sairastavuutta ja kuolleisuutta. TAVR vaikuttaa olevan hyvä vaihtoehto SAVR:n rinnalla vajaatoimintapotilaille. Keskipitkän seuranta-ajan kuolleisuus on yhtä hyvä kummankin toimenpiteen jälkeen näillä potilailla.

AVAINSANAT: Aorttaläppäahtauma, sydämen vajaatoiminta, SAVR, TAVR.

Table of Contents

Abbreviations

ACC/AHA	American College of Cardiology / American Heart Association
ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AHF	Acute heart failure
AKI	Acute kidney injury
AS	Aortic stenosis
BAV	Bicuspid aortic valve
BMI	Body mass index
CABG	Coronary artery bypass grafting
CI	Confidence interval
CT	Computed tomograhy
E-CABG	European Coronary Artery Bypass Grafting study
EACTS	European Association for Cardio-Thoracic Surgery
eGFR	Estimated glomerular filtration rate
EuroScore II	European System for Cardiac Operative Risk Evaluation II
ECG	Electrocardiography
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
ESC/EACTS	European Society of Cardiology / European Association for Cardio-Thoracic Surgery
HF	Heart failure
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
LAA	Left atrial appendage
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow track
NYHA	New York Heart Association
PBAV	Percutaneous balloon aortic valvuloplasty
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
SAVR	Surgical aortic valve replacement
STS	The Society of Thoracic Surgeons

SVD	Structural valve deterioration
TAVR	Transcatheter aortic valve replacement
VARC-2	Valve academic research consortium-2

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 Mäkikallio T, Jalava MP, Husso A, Virtanen M, Laakso T, Ahvenvaara T, Tauriainen T, Maaranen P, Kinnunen EM, Dahlbacka S, Jaakkola J, Airaksinen J, Anttila V, Savontaus M, Laine M, Juvonen T, Valtola A, Raivio P, Eskola M, Niemelä M, Biancari F. Ten-year experience with transcatheter and surgical aortic valve replacement in Finland. *Ann Med.*, 2019;51(3-4):270–279.

II Jalava MP, Laakso T, Virtanen M, Niemelä M, Ahvenvaara T, Tauriainen T, Maaranen P, Husso A, Kinnunen EM, Dahlbacka S, Jaakkola J, Airaksinen J, Anttila V, Rosato S, D'Errigo P, Savontaus M, Laine M, Mäkikallio T, Valtola A, Raivio P, Eskola M, Biancari F. Transcatheter and Surgical Aortic Valve Replacement in Patients With Recent Acute Heart Failure. *Ann Thorac Surg*., 2020;109(1):110–117.

III Jalava MP, Savontaus M, Ahvenvaara T, Laakso T, Virtanen M, Niemelä M, Tauriainen T, Maaranen P, Husso A, Kinnunen EM, Dahlbacka S, Jaakkola J, Rosato S, D'Errigo P, Laine M, Mäkikallio T, Raivio P, Eskola M, Valtola A, Juvonen T, Biancari F, Airaksinen J, Anttila V. Transcatheter and Surgical Aortic Valve Replacement in Patients with Left Ventricular Dysfunction. *Submitted*.

1 Introduction

Aortic stenosis (AS) is one of the most common heart valve disease with a prevalence of 2% of people over 65 years old (Iung and Vahanian, 2011). AS covers 34% of all native valve disease and 43% of all single valve disease (Saikrishnan *et al.*, 2014). The natural course of AS is characterized by a long and asymptomatic latent phase of progressive valvular degeneration. After becoming symptomatic the AS leads to death within a few years if left untreated and is associated with a 1-year mortality rate of >30% (Iung and Vahanian, 2011). For decades, open heart surgery with surgical aortic valve replacement (SAVR) was the only definitive treatment option. Since 2002, transcatheter aortic valve replacement (TAVR) has become a reasonable treatment option initially for high operative risk patients and subsequently also for intermediate operative risk patients. The number of patients undergoing TAVR procedure has increased rapidly over the last few years and TAVR treatment has surpassed SAVR as the most common treatment for severe AS.

A decrease in exercise tolerance is often the first symptom of AS, followed by exertional angina and/or syncope. Heart failure (HF) is a late manifestation of severe AS and is associated with a poor prognosis. Acute heart failure (AHF) may complicate the course of AS and is the main cause of death in these patients. It is also known that left ventricular dysfunction, even without clinical symptoms of HF, associates with inferior outcomes. The prognosis of AS patients with HF is mostly dependent on left ventricular recovery after aortic valve replacement. Only a limited number of studies have evaluated whether TAVR is associated with a more favourable outcome when compared to SAVR in these patients.

The FinnValve registry was created to evaluate and compare the outcomes of AS patients treated by TAVR and SAVR from 2008 to 2017. This study focuses on AS patients with reduced left ventricular ejection fraction (LVEF) and those with HF.

2 Review of the Literature

2.1 Aortic stenosis

2.1.1 Normal aortic valve structure

The aortic valve is a semilunar tri-leaflet structure located between the left ventricular outflow tract and the aorta (Fig. 1). Its purpose is to enable blood flow from the left ventricle to systemic circulation during systole and to prevent backflow form the aorta to the left ventricle during diastole. The leaflets are composed of three layers: fibrosa, spongiosa, and ventricularis (Czarny et al. 2014, Rajamannan et al. 2011). The fibrosa contains strong collagen fibers. The spongiosa contains mucopolysaccharides and functions to resist compressive forces and to facilitate movements between the fibrosa and ventricularis during leaflet motion. The ventricularis contains flexible elastin. Valve interstitial cells are found in each of these layers. The leaflet is covered on the aortic surface with aortic endothelium and on the ventricular surface with ventricular endocardium and endothelium. Aortic annulus is a non-anatomical three ring structure consisting of a basal circular attachment of the leaflets, the ventriculoarterial junction, and the sinotubular junction. Three leaflets form a crown-like structure. The basal leaflet attachment to the aortic root is the structure that is referred to as the surgical annulus.

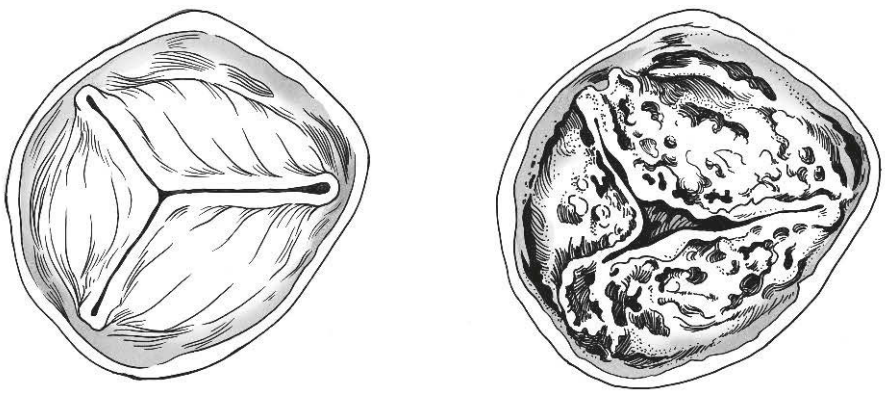

Figure 1. Normal and stenotic aortic valve.

2.1.2 Epidemiology, pathophysiology and clinical significance of aortic valve stenosis

Aortic valve stenosis (AS) is one of the most common valvular condition and it affects 2–7% of the population age >65 years worldwide, with a marked increase at ≥75 years of age (Otto *et al.*, 1999; Iung and Vahanian, 2011). An increased afterload caused by the stenotic valve ultimately leads to structural cardiac changes causing both systolic and diastolic dysfunction. When the symptoms of left ventricular (LV) dysfunction emerge, the prognosis is poor: the survival drops to 2–3 years without aortic valve intervention (Turina *et al.*, 1987) with a 1-year mortality rate of >30% (Iung and Vahanian, 2011).

The most common etiology of AS in the aging western population is degeneration of a normal tri-leaflet valve by calcification (Fig. 1). The second most common cause are congenital valve abnormalities, such as bicuspid and unicuspid valves with a prevalence of 2% (Czarny and Resar, 2014). Cardiac lesions caused by rheumatic fever are rare in the Western world due to widespread antibiotic use, though they remain frequent in the developing nations.

For a long time, it was thought that AS was only a degenerative process that leads to an accumulation of calcium on the leaflets. However, there is now also evidence that AS might be a result of inflammatory processes that involve biochemical, humoral and genetic factors (Rajamannan *et al.*, 2011). Another theory suggests that the process of atherosclerosis secondarily causes AS. The histology of stenotic aortic valves includes active inflammation with lipid accumulation, inflammatory cell infiltration and calcification. Low-density-lipoprotein cholesterol and lipoprotein A undergo oxidative processes in the valve and stimulate the inflammatory processes and mineralization (Lerman, Prasad and Alotti, 2015). In addition, the bone formation markers may play a role in the pathogenesis of AS. Specific markers of bone formation, such as bone matrix proteins (e.g., osteopontin, osteocalcin, and bone sialoprotein) (Kaden *et al.*, 2004; Rajamannan *et al.*, 2011), osteoblast transcription factors, and mature bone lamellar tissue have been found in calcified aortic valves. In view of these recent studies, AS may be seen as a fibrocalcific disease (Luft, 2015).

The risk factors for AS are similar with those for atherosclerosis and other cardiovascular diseases. Hypertension, dyslipidemia, chronic renal insufficiency, diabetes, male gender and smoking are widely established risk factors for AS. However, by treating these risk factors it not possible to affect the natural course of AS. As demonstrated in the randomized SEAA and ASTRONOMER trials, the lipid-lowering therapy does not stop or decelerate the progression of calcific AS or induce its regression despite a significant reduction in plasma cholesterol levels and inflammatory markers (Cowell *et al.*, 2005; Chan *et al.*, 2010).

The exact cause of AS remains yet to be discovered. Due the complex etiology, it is difficult to develop an effective medical treatment for AS.

2.1.3 Bicuspid and unicuspid aortic valve

Bicuspid aortic valve (BAV) is the second most common aortic valve morphology and the most common congenital cardiac defect (Hoffman and Kaplan, 2002; Roberts and Ko, 2005). In most cases, the cusps of BAV are asymmetrically orientated with 3 sinuses of Valsalva and 3 raphes. A symmetrical BAV without raphe and only two identifiable sinuses of Valsalva is rare. Differences in the valve function, compared to tricuspid aortic valve, increase stress in the raphal area of the merged cusp, and cause uneven systolic flow patterns and stenosis even without calcification. AS has been observed in 12–37% of patients with BAV (Masri *et al.*, 2017). Majority of these patients require intervention within 25 years of their initial diagnosis and the need for intervention occurs nearly 20 years earlier than in patients with a tricuspid aortic valve (Michelena *et al.*, 2014). When compared to tricuspid stenotic aortic valve, stenotic BAV is more likely to have heavily calcified leaflets and raphes, and it is associated with more frequent dilatation of the aortic annulus and root and aortic dissection.

Generally, patients with BAV were excluded from randomized SAVR and TAVR trials due to anatomical challenges related to its morphological features and association with aortopathy. Data on TAVR patients with BAV is based on observational studies and case series (Michelena *et al.*, 2014). Husso et al. reported the outcomes of 1023 (15.8%) patients with BAV from the FinnValve registry, 920 patients underwent SAVR and 103 patients TAVR, respectively (Husso *et al.*, 2021). The older generation TAVR devices were found to associate with paravalvular regurgitation more often compared to SAVR. Newer generation TAVR valves and SAVR had comparable rates of paravalvular leakage. In addition, they found that type 1 N-L (37.5%) and type 2 L-R/R-N (100%) BAV morphologies had high incidence of paravalvular regurgitation compared to other morphologies. In an observational study of 1034 CT-confirmed BAV patients, calcified raphe and excess leaflet calcification were identified as independent risk factors for aortic complications, permanent pacemaker implantation, paravalvular regurgitation and two year mortality after TAVR (Yoon *et al.*, 2020). The long term survival after SAVR up to 25 years after operation is similar in BAV patients compared to general population (Michelena *et al.*, 2014). Current valvular guidelines do not provide general recommendations on the use of TAVR in BAV patients (Baumgartner *et al.*, 2017; Otto *et al.*, 2021).

Unicuspid aortic valve is a congenital cardiac defect in general population with prevalence of 0.02%. However, in patients treated for AS the prevalence is 5% (Roberts and Ko, 2005). It causes heavy calcification of the aortic valve at young age: 72% of unicuspid AS patients need intervention for AS before the age of 60 years (Roberts and Ko, 2005).

2.1.4 Definition and diagnosis of aortic stenosis

2.1.4.1 Echocardiography

The diagnosis of AS is based on echocardiography (Baumgartner *et al.*, 2009). Transthoracic echocardiography (TTE) is generally sufficient in defining the type and severity of the disease. Anatomic evaluation includes the identification of the number of leaflets, and a description of leaflet mobility, thickness and calcification. The severity of the AS is then evaluated by combining Doppler and 2D data. AS jet velocity is defined as the highest velocity through the aortic valve orifice. Mean transaortic pressure gradient is defined as the difference in pressure between the pressures of the left ventricular and aorta during systole. The transvalvular aortic gradient is a standard measure of severity of the stenosis (Tab. 1). Doppler velocity and pressure gradients are flow dependent: for a given orifice area, velocity and gradient increase with an increase in the transaortic flow rate, and, similarly, decrease with a decrease in the flow rate. The assessment of the stenotic orifice area or aortic valve area is needed to evaluate the severity of AS, when flow rates are exceptionally low or remarkably high, although the degree of the valve opening varies to some degree with the flow rate. Accuracy of stroke volume calculations depend on how precisely the left ventricular outflow tract (LVOT) diameter and velocity are measured.

Table 1. Defining aortic stenosis by echocardiography.

Type of AS	V_{max}	AVA	ΔPm	EF	SVi	Other considerations
High-gradient AS	≥4 m/s	<1 cm^2	>40 mmHg	any	any	
Low-flow, low-gradient AS with reduced EF	<4 m/s	<1 cm^2	<40 mmHg	<50%	≤35 mL/m^2	Dobutamine stress echo-cardiography shows AVA <1.0 cm^2 with V_{max} ≥4m/s at any flow rate.
Low-flow, low-gradient AS with preserved EF	<4 m/s	<1 cm^2	<40 mmHg	≥50%	≤35 mL/m^2	Typically elderly patients. Associated with a small LV size and hypertrophy and a history of hypertension. Define the degree of valve calcification by MSCT.
Normal-flow, low-gradient AS with preserved EF		<1 cm^2	<40 mmHg	≥50%	>35 mL/m^2	These patients, in general, only have moderate AS.

Vmax, peak transvalvular velocity; ΔPm, mean transvalvular pressure gradient; AS, aortic stenosis; AVA, aortic valve area; MSCT, Cardiac imaging by multi-slice computed tomography; EF, ejection fraction; LVEF, left ventricular ejection fraction; Svi, stroke volume index. Modified from 2017 ESC/EACTS Guideline for valvular heart disease.

Transesophageal echocardiography (TEE) is needed when a more accurate evaluation of the cardiac and aortic valve structure and function is desired, and TTE is nondiagnostic. The TEE analysis includes a detailed evaluation of the aortic root, ascending and descending aorta, the left atrial appendage, prosthetic valves, valve masses and paravalvular abscesses, and an evaluation of critically ill patients. TEE is performed pre- and perioperatively. (Hahn *et al.*, 2013; Nishimura *et al.*, 2014; Baumgartner *et al.*, 2017).

2.1.4.2 Computed tomography

Computed tomography (CT) is used for preoperative assessment prior to TAVR, and, sometimes, prior to SAVR too (Baumgartner *et al.*, 2017). In TAVR-CT the patient is scanned from the subclavian artery to the femoral arteries, including an ECG-gated imaging of the aortic root (Francone *et al.*, 2020).

The assessment of the aortic root includes measurements of the left ventricular outflow tract, annulus, sinus of Valsalva, sinotubular junction and ascending aorta, and distances between coronary ostia and the aortic annulus. The valve cuspicity and calcification are assessed for diagnostic and procedure planning purposes (Francone *et al.*, 2020). For TAVR, an aortic annular diameter of 16–30 mm is required. Other than tricuspid anatomy may cause problems in TAVR sizing and fitting, and low positioned ostia poses a risk of coronary ostium occlusion. The threshold for a safe minimal distance from annulus to ostia is considered to be at least >12–14mm (Soon *et al.*, 2017).

Equally important to aortic root imaging is the evaluation of vascular access (Francone *et al.*, 2020). The possible aortic atherosclerosis, atheromas, wall thrombi and calcifications are assessed. Diameters of femoral and iliac arteries should be more than the outer diameter of the delivery sheath used. Prominent tortuosity of the iliac arteries and aorta are a contraindication for femoral TAVR. In this case, the alternative vascular access should be evaluated in the CT report.

Observing non-vascular findings is a significant advantage obtained by the routine CT evaluation, as clinically significant incidental findings have been reported in up to 25% of TAVR-CT imaging studies (Trenkwalder *et al.*, 2018).

For the valve-in-valve procedures, the size of the existing aortic valve prosthesis determines the type and size of TAVR valve that can be implanted. This can be estimated from TAVR-CT, especially if the exact size of the valve is unknown (Francone *et al.*, 2020). The main concern with valve-in-valve procedures is the possible obstruction of the coronary artery ostia by the leaflets or struts of the existing aortic valve prosthesis and is more frequent following valve-in-valve procedures than after primary TAVR procedures.

2.1.4.3 Additional evaluations

Exercise testing is recommended in physically active patients with asymptomatic severe AS for unmasking symptoms and for risk stratification (Czarny and Resar, 2014). Exercise stress echocardiography may provide prognostic information in asymptomatic severe AS by assessing the increase in the mean pressure gradient and the change in LV function during exercise (Kang *et al.*, 2020).

Cardiac magnetic resonance imaging provides additional information on the dimensions and geometry of the aortic root and ascending aorta, and the extent of calcification. More importantly, it is used to detect and quantify myocardial fibrosis (Baumgartner *et al.*, 2017).

Retrograde LV catheterization with invasive pressure gradient measurements to directly assess the severity of AS is not routinely recommended in the current guidelines. Its use is mostly restricted to patients with inconclusive non-invasive investigations. Right side catherization is recommended for evaluation of the extent of the cardiac damage and pulmonary and right side pressures in selected patients (Weber *et al.*, 2019).

Natriuretic peptides are hormones of which atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are released from cardiac atria and ventricles (Potter *et al.*, 2009). ANP acts to decrease blood pressure and cardiac hypertrophy. ProANP secretion is stimulated by pressor hormones and stretch of the atrial wall. BNP acts to decrease ventricular fibrosis. Generally, the plasma levels of ANB and BNP are low, but markedly increased levels are established in response to atrial and ventricular stress, such as volume overload. In addition, natriuretic peptides inhibit cardiac remodelling. Natriuretic peptides predict symptom-free survival and long-term outcomes in normal and low-flow severe AS and may be useful in asymptomatic patients to determine the optimal timing of intervention (Baumgartner *et al.*, 2017; Nishimura *et al.*, 2017).

2.1.5 Management of aortic stenosis

There is no effective medical treatment for severe AS and aortic valve replacement (AVR) remains the only definitive therapy. For decades, open heart surgery with a surgical aortic valve replacement (SAVR) and percutaneous balloon aortic valvuloplasty (PBAV) were the only definitive treatment options. Over the last years, TAVR has rapidly become the most frequent intervention. The development of less invasive surgery and rapid deployment valves has also expanded surgical intervention alternatives. A multidisciplinary Heart Team decision is recommended to decide on the most suitable intervention for each patient individually, according to the current guidelines (Nishimura *et al.*, 2014; Baumgartner *et al.*, 2017).

2.1.5.1 The history and evolution of heart valve prostheses

Mechanical valves

The groundbreaking introduction of the heart-lung machine in 1953 enabled the development of modern cardiac surgery. The first valvular heart prosthesis, the Hufnagel cage ball valve, was implanted in the descending aorta in 1952 (Butany *et al.*, 2002). The first subcoronary implantation with a Harken-Soroff cage ball valve was made in 1960 (Gott, Alejo and Cameron, 2003). These cage ball valves were composed of a metallic cage and a silicon ball. Several models of Starr-Edwards prostheses were introduced in the 1960's (Rose, 1987). The Starr-Edwards model 6120 mitral valve is still used in third world countries owing to its reasonable cost, satisfactory hemodynamic function and good durability. Fabrication with pyrolytic carbon for the DeBakey-Surgitool cage ball valve in 1969 was invented by the materials engineer Dr Jack Bokros (Debakey and Lawrie, 1987). Pyrolytic carbon later became the preferred material for all mechanical heart valves (Gott, Alejo and Cameron, 2003).

Non-tilting disc valves were developed and used in the late 1960's and in 1970's. The development continued with two types of Bjork-Shiley valves, Lillehei-Kaster valve, Omniscience and Omnicarbon valves (Gott, Alejo and Cameron, 2003). These tilting disc valves and the bileaflet valves were introduced in the 1970's and offered better hemodynamical function, when compared with cage ball and non-tilting valve prostheses. The widely used Hall-Kaster tilting pyrolyte disc valve was first implanted in 1977. In 1987, Medtronic continued the manufacturing, with some minor modifications. Since 1977, over 300.000 Hall-Kaster and Medtronic-Hall valves were implanted before discontinuation of the production (Antunes, 2015).

The first bileaflet valve, Gott-Daggett valve with a heparinized carbon coating, was introduced in 1963 (Gott, Daggett and Young, 1989). The first valve entirely fabricated from pyrolytic carbon, the original St. Jude Medical bileaflet valve, was implanted in 1977. The St. Jude Regent valve was introduced in 1999 to enlarge the orifice size of smaller aortic prostheses (Walker, Brendzel and Scotten, 1999). St. Jude valves are the most widely used prosthetic valves in the world with over 1.3 million implantations (Gott, Alejo and Cameron, 2003). Dr. Bokros continued developing heart valves, and the Carbomedics bileaflet valve was introduced in 1986 (Aagaard, 2004). The structure enables valve rotation following/during implantation. To date, more than 500.000 Carbomedic valves have been implanted. Dr. Bokros accompanied Mr. Villafana to further develop new bileaflet pyrolytic carbon valves, such as On-X and ATS (later known as Medtronic Open Pivot aortic valve) valves.

Biological valves

The evolution of biological valves has required development in biochemistry, mechanical engineering and biology. The first tissue valves, cadaveric homografts, were implanted by Donald Ross in 1962 in the pulmonary position (Ross, 1962, 1995). Cadaveric homograft valves were complex to obtain eventually leading to the advent of xenografts.

The first generation xenografts were porcine valves due to their similarities with human valves (Russo *et al.*, 2017). Tissue valve engineering began with the use of formalin to sterilize and fixate the tissue. A major issue was early calcification and fibrosis which limited their durability. Carpentier was the first one who started to use glutaraldehyde to prevent inflammatory reactions and anticalcification treatments to improve valve durability (Carpentier, 1977). Later, in 1966, Carpentier made an innovation to set a porcine valve into a stent frame to obtain an original valve structure and to simplify the implantation procedure. Still, mechanical stress and biological responses eventually led to structural valve deterioration (SVD). Examples of such native porcine valves are the Mosaic, Hancock II, and Epic valves (Kueri *et al.*, 2019).

The first pericardial glutaraldehyde treated valve, the Ionescu-Shiley valve, was implanted in 1971 (Ionescu *et al.*, 1977). Unfortunately, SVD was already detected after a 5 year follow up due to leaflet movements within the stent damaging them. Learning from earlier failures, different types of stents and leaflet suturing techniques were introduced, allowing supra-annular implantation improving hemodynamical performance. In addition, several antimineralization methods were developed. Bovine pericardium was found to offer better long term performance compared to porcine valves (Gao *et al.*, 2004).

The third generation bioprostheses (St. Jude Trifecta, Sorin Mitroflow, Carpentier-Edwards Perimount Magna) were designed to achieve a larger effective orifice area and to prevent the risk of patient-protheses mismatch. Currently, newer generation, including St. Jude Trifecta GT, and Carpentier-Edwards Perimount Magna Ease and Inspiris Resilia, valves are in use (Fig. 2). Long-term durability data beyond 10 years are still lacking on the most recent models. Resilia tissue is a new innovation in which the pericardial leaflets are treated with a new sterilization procedure to further reduce calcification, improve hemodynamic performance and to allow dry valve storage (Shala and Niclauss, 2020). In this Edwards Integrity-Preservation (EIP™) technology, the tissue calcium-binding sites are permanently blocked and a better performance is expected (De La Fuente *et al.*, 2015).

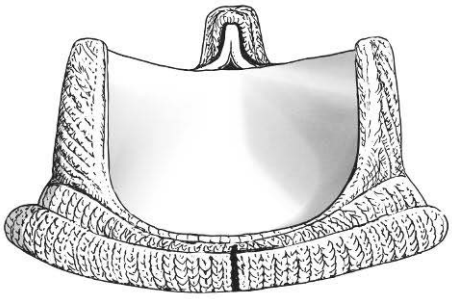

Figure 2. Biological surgical prostheses.

Stentless valves were introduced by Dr. Tirone David in 1988 (David *et al.*, 1998). They were xenograft, both porcine and pericardial, without any stent or sewing cuff. However, the good results were challenged by the requirement for aortic root surgery. The use of these valves decreased in the late 1990's as no superiority over stented valves was detected. Still, the technology was a foundation for both sutureless and transcatheter valve development.

Sutureless valves

A recent development in the surgical field is the invention of sutureless rapid-deployment valves. Three sutureless valves have been introduced and accepted into clinical use: the Livanova Perceval S, the Edwards Intuity and the ATS Medical Enable 3F. The compressed bioprosthetic valve is delivered to replace the resected aortic valve via aortotomy. This approach aims to shorten the cross-clamp and cardiopulmonary bypass times and, thereby, decrease surgery-related risks, to facilitate minimally invasive surgery (Williams *et al.*, 2020), as well as in optimizing hemodynamic results in patients with small aortic annuli (Karangelis *et al.*, 2017). The long-term durability is still unknown. The strong development of transcatheter valve technologies has decelerated the evolution of rapid deployment valves. Their current role and future are somewhat unclear. Possible indications may include small aortic roots, multiple valve surgery, or use in minimally invasive surgery.

Transcatheter valves

Over the last twenty years, transcatheter valve procedures have dramatically changed the treatment of AS. TAVR-valve is a bioprosthetic valve that is compressed to a sheath for a percutaneous implantation, mainly by a transfemoral approach (Cribier *et al.*, 2002). TAVR is then positioned and launched to the aortic valve orifice. Their evolution is based on decades of experience on valve prosthesis development and

the development of mini-invasive instruments and catheter-based devices to enable an endovascular approach. Two types of stents were developed: a stainless-steel balloon-expandable stent and a self-expanding nitinol stent.

The first implantation of a transcatheter valve was performed in 2000 by Bonhoeffer into the pulmonary position (Khambadkone and Bonhoeffer, 2006). In 2002, the first implantation into the aortic position with the Cribier-Edwards valve (formerly Percutaneous Valve Technologies, PVT) was performed (Cribier *et al.*, 2002). The valve was made of equine pericardium and a stainless-steel frame. To improve the sealing, a polyethylene terephthalate fabric skirt was added to the first high profile Edwards SAPIEN model introduced in 2006. The first generation SAPIEN XT valve was introduced in 2009 and was designed with a lower-profile cobalt-chromium stent to enable a safer transfemoral approach. The newest of the SAPIEN valves is the SAPIEN 3, in which the outer skirt and delivery sheath were redesigned to increase the sealing and to decrease peripheral vascular injuries, but it carries out an increased risk of an atrioventricular block (Facchin *et al.*, 2014; Russo *et al.*, 2017). SAPIEN valves are balloon-expandable devices. Low stent frame allows easier coronary access after TAVR (Claessen *et al.*, 2021).

The first self-expandable TAVR device, the Medtronic Corevalve, was introduced in 2005. It consists of pericardial leaflets within a nitinol frame. The first-generation valves had bovine pericardium leaflets. A switch to porcine pericardium and redesigning the outflow helped to lower the device profile, creating the EVOLUT R valve that was repositionable, resheathable and recapturable. The Evolut PRO valve is designed with further improved valve sealing features (Mahtta, Elgendy and Bavry, 2017). Other self-expandable devices include the Acurate neo2 (Boston Scientific) and Portico (Abbott Structural Heart) valves. The Acurate neo 2 is non-repositionable and requires predilatation of the stenotic valve, but the supra-annular design and special deployment system allows good control of implant depth. The Portico valve has a high stent frame with an intra-annular design. It is retrievable and repositionable (Claessen *et al.*, 2021). The Lotus Edge (Boston Scientific) valve is a mechanically expandable valve that is retrievable and repositionable. The optimal device for each patient is chosen by individual assessment of the patient characteristics and known possible pitfalls of each device (Claessen *et al.*, 2021)(Fig. 3).

The development of TAVR generations from first to present has changed the use and indications of TAVR. At the early stage, TAVR use was limited to high risk and inoperable patients, but the results from recent studies with newer generation devices suggest expanding the indications for TAVR (Durko *et al.*, 2018). The design of TAVR valves offers optimal hemodynamic function and the TAVR future will be determined by valve durability and performance in younger low-risk patients (Arora *et al.*, 2017). Typical complications for transcatheter procedures have been

paravalvular leakage, peripheral vascular complications, stroke and an atrioventricular conduction block.

"Valve-in-valve" procedures represent the newest area in the valve procedure field (Edelman *et al.*, 2019). Valve-in-valve TAVR offers an alternative to surgical reoperations in patients with deteriorated bioprostheses, both surgical and TAVR. The anatomical characteristics and the size of the previously implanted valve constitutes the major limiting factors for the implantation of the valve-in-valve TAVR. Valve-in-valve procedures have created a need for redesigning bioprostheses and the possibility of later valve-in-valve procedures should be considered in contemporary primary procedures.

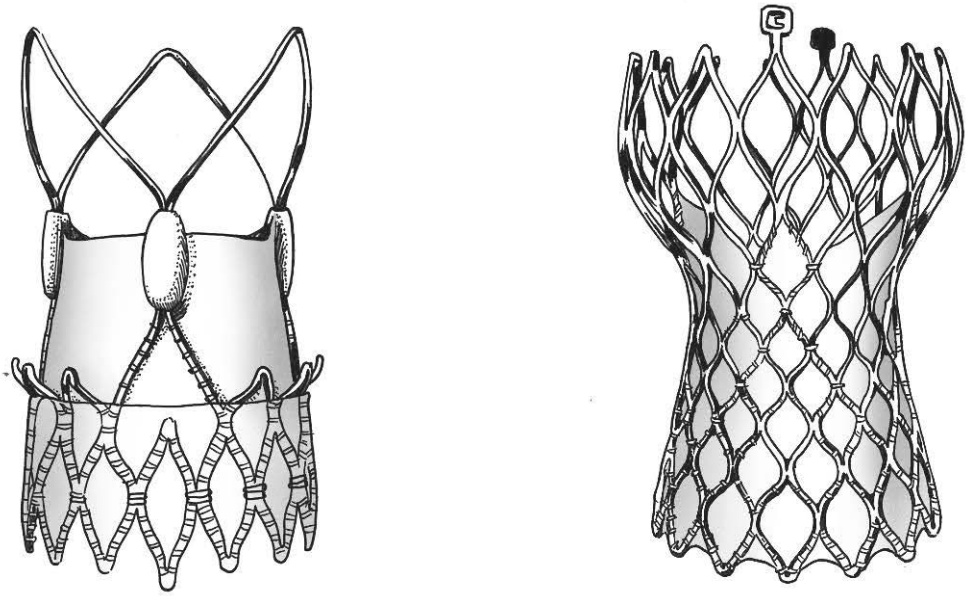

Figure 3. Transcatheter aortic valve prosthesis.

2.1.5.2 Indications for intervention and choice of intervention mode

Table 2. 2017 ESC/EACTS guideline recommendation for management of severe aortic stenosis.

	Class of recommendation	Level of evidence
Intervention is indicated in patients with symptomatic high-gradient AS	I	B
Intervention is indicated in symptomatic patients with low-flow low-gradient AS with HFrEF and existing flow reserve	I	C
Intervention should be considered in symptomatic patients with low-flow low-gradient confirmed severe AS and normal EF	IIa	C
Intervention should be considered in symptomatic patients with low-flow low-gradient AS and HFrEF without flow reserve, especially with coexisting heavily calsified aortic valve	IIa	C
Intervention is not recommended in patients in whom the intervention unlikely improves quality of life or survival	III	C

Levels of evidence: A, Data derived from multiple randomized clinical trials or meta-analyses; B, Data derived from a single randomized trial or large non-randomized trials; C, Expert opinion/consensus and/or data derived from small studies, retrospective studies and/or registries.

Symptomatic aortic stenosis

The indications for intervention in symptomatic severe AS are summarized in Table 2. Treatment options for symptomatic AS include SAVR and TAVR. The choice of the procedure type is based on the characteristics of the patient, the individual risk of surgery, the feasibility of SAVR and TAVR, and the local experience, which are assessed by the Heart Team (Nishimura *et al.*, 2014, 2017; Baumgartner *et al.*, 2017). To date, TAVR has been proven to be superior to medical therapy in extreme-risk patients, non-inferior or superior to surgery in high-risk patients, and non-inferior to surgery for intermediate-risk patients and superior via transfemoral access in intermediate-risk octogenarians (Baumgartner *et al.*, 2017). In the current European and North American guidelines, SAVR is the preferred treatment option for patients < 75 years and for surgical low-risk patients, for whom data on TAVR is limited. SAVR is also recommended for patients with endocarditis and for those who require other cardiac surgery procedures, i.e., concomitant surgery of other heart valves, aorta, and/or revascularization for advanced coronary artery disease. PBAV may be considered as a bridge to SAVR or TAVR. The use of PBAV as a definite therapy is questionable as resent data

indicates that even emergency TAVR is a preferrable option to PBAV (Debry *et al.*, 2018; Kolte *et al.*, 2018; Kawsara *et al.*, 2020).

Asymptomatic aortic stenosis

In patients with asymptomatic AS, the risk of sudden cardiac death is reported to be low, approximately 1% per year, and the overall mortality <4% per year (San Román *et al.*, 2020). While the existing literature is somewhat controversial, the current guidelines recommend SAVR for patients with very severe AS (peak aortic jet velocity (Vmax) ≥5.0 m/s or mean aortic pressure gradient ≥60 mmHg), or LVEF<50% (Rosenhek *et al.*, 2010; Baumgartner *et al.*, 2017). Predictors of developing symptoms and adverse outcomes include echocardiographic findings, such as Vmax ≥4.5–5.0 m/s (cut off point varies between studies) (Kang *et al.*, 2010, 2020) or mean aortic gradient ≥60 mmHg, LVEF <50%, increase in mean gradient >20 mmHg in exercise testing, excessive valve calcification, LV hypertrophy, LV diastolic dysfunction, pulmonary hypertension (PH) and elevated plasma levels of natriuretic peptides. However, these markers mainly predict the development of symptoms rather than post-AVR outcome (San Román *et al.*, 2020). The main predictors of developing adverse events are the maximal jet velocity and valve calcification (Rosenhek *et al.*, 2010; Lancellotti *et al.*, 2018). Lancellotti and Rosenhek also suggest that very severe AS leads to a similarly increased risk of death pre- and postoperatively. The staging classification by Généreux et al. based on the extent of cardiac damage may prove to be helpful for an individual assessment on the treatment pathway choice (Généreux *et al.*, 2017). If early surgery is considered in asymptomatic patients, the operative risk should be low, especially when exercise performance remains normal (Baumgartner, Iung and Otto, 2020).

TAVR is not recommended in asymptomatic patients, although this might change in the future (Baumgartner, Iung and Otto, 2020). On the other hand, in a recent review by San Román et al., they conclude that unless data on ongoing randomized trials change the current evidence, an intervention in asymptomatic patients with severe AS cannot be recommended in general (San Román *et al.*, 2020). The management of asymptomatic severe AS remains controversial.

2.1.5.3 Surgical aortic valve replacement

Surgical aortic valve replacement is the golden standard in treating AS. The development of perioperative treatment and intensive care have led the reduced morbidity and shorter hospital stay (Aya *et al.*, 2013). The short term mortality in patients undergoing isolated AVR is currently averaging 2.6–5% (Malaisrie *et al.*, 2010; Thourani *et al.*, 2015; Groh *et al.*, 2017; Thyregod *et al.*, 2019). Studies in low

risk patients have shown in-hospital mortality rates as low as 1–2% post-AVR (Frerker *et al.*, 2017; Virtanen *et al.*, 2019; Kundu *et al.*, 2020). Patients undergoing SAVR have a significantly better survival rate than predicted in risk models, especially in the higher risk populations (Thourani *et al.*, 2015). Improved patient selection and understanding of the disease along the TAVR experience has had a positive effect on the SAVR results. To date, SAVR still offers superior long term results compared to TAVR (Zhang *et al.*, 2020).

Indications for the use of mechanical valve prosthesis

Both American College of Cardiology / American Heart Association (AHA/ACC) and European Society of Cardiology / European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines for the management of valvular heart disease recommend the use of mechanical aortic valve prostheses in patients younger than 60 years of age on the basis of the risk/benefit ratio of mechanical and bioprosthetic valves. The decision between mechanical and biological valve prosthesis is made with informed patient preference and by estimating the risk of anticoagulation-related bleeding, thromboembolism with a mechanical valve, and the risk of SVD with a bioprosthesis (Baumgartner *et al.*, 2017). Mechanical valve prostheses are associated with lower mortality, lower reoperation-rate, and lower occurrence of infective endocarditis when compared to bioprostheses within 10 years after SAVR in patients aged 50 to 70 years (Kytö *et al.*, 2020). Similarly, in a systematic review by Borger et al (Borger *et al.*, 2019), they state that data does not support the expanding use of biological valves in patients <65–70 years.

Indications for the use of biological valve prosthesis

European guidelines recommend bioprosthetic valves for patients >65 years of age and American guidelines for patients >70 years of age (Nishimura *et al.*, 2014; Baumgartner *et al.*, 2017). The use of biologic prostheses is increasing, although the average lifespan of an estimated 15 years remains a limitation. Dunning et al. reported an increase in the use of bioprostheses from 65.4% to 77.8% between 2004 and 2009 in Great Britain (Dunning *et al.*, 2011). In their analysis, patients in categories of <55 years and 55–60 years showed a similar increase when compared to patients in older age categories, despite the current guideline recommendations. The same globally seen trend is present in Finland: Myllykangas et al. reported that the implantation rate of biological valves increased from 42.9% to 75.5% from 2001 to 2016 (Myllykangas *et al.*, 2020).

Compared to the elderly, the risk for SVD is higher in younger patients. The risk of reoperation after implantation of biological SAVR is 45% for patients aged 50

years, and 10% for patients aged 70 years (van Geldorp *et al.*, 2009). The most common reason for a reoperation is SVD, while the risk of non-SVD reoperation is equally low when compared to mechanical valves. In younger patients, the risk of SVD is increased due to a more active immunologic response to foreign biological material and accelerated calcification of the prostheses. In addition, elderly patients, due to a shorter life expectancy, require reoperations less often (Head, Çelik and Kappetein, 2017).

Indications for the use of sutureless bioprosthetic valves

A recent review by Williams et. al presented that 42.4% of patients underwent the sutureless aortic bioprosthetic valve procedure via full sternotomy, with 30.1% undergoing other concomitant cardiac procedures. Survival rates at 1- and 5-year follow-ups were 94.9% and 84.2%, respectively. The incidence of stroke (4.8%), severe paravalvular leak (1.5%) and permanent pacemaker insertion (8.2%) at the 5-year follow-up were acceptable, as were hemodynamic outcomes. There is a growing interest in minimally invasive procedures and sutureless technology offers a less time consuming technique (Phan *et al.*, 2015; Williams *et al.*, 2020). The first trials randomizing patients between sutureless valve and SAVR, like the PERSIST-AVR trial, are underway (Lorusso *et al.*, 2020).

2.1.5.4 Transcatheter aortic valve replacement

Over the last decade, a large series of randomized trials have shown TAVR to be non-inferior or even superior to SAVR in patients with an intermediate- or high surgical risk as well as feasibility in patients not eligible for surgery (Baumgartner *et al.*, 2017; Nishimura *et al.*, 2017). TAVR is currently recommended for elderly intermediate- and high-risk patients, but indications are spreading towards younger and lower-risk patients (Arora *et al.*, 2017; Durko *et al.*, 2018; Virtanen *et al.*, 2019). Developments in reoperation technics with valve-in-valve procedures have made TAVR a valuable option in patients with degenerated surgical or TAVR bioprostheses (Edelman *et al.*, 2019).

2.1.5.5 Medical therapy

Medical therapy does not affect the natural course of AS, and patients with LV dysfunction and AS should undergo intervention for the valve itself. Patients with symptomatic HF who are inoperable or waiting for intervention are medically treated according to HF and valvular guidelines (Yancy *et al.*, 2013; Nishimura *et al.*, 2014).

As stated in the ESC/EACTS and ACC/AHA guidelines, all patients with AS should undergo guideline-directed medical therapy for other cardiovascular risk factors, including diabetes mellitus and hyperlipidemia. Patients with HF should also receive medication for LV systolic dysfunction, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers and beta-adrenergic blockers. Hypertension should be treated, avoiding hypotension. Medical treatment should aim for maintenance of sinus rhythm.

2.1.6 Patient-prostheses mismatch

Prosthesis-patient mismatch (PPM) is a condition in which the effective orifice area of the prosthetic valve is too small in relation to patients size. This leads to increased gradient through the inserted prosthetic valve. Prevalence of PPM varies from 8% to 80% in the literature with a decreasing trend with time (Bilkhu, Jahangiri and Otto, 2019). In a recent review by Bilkhu et al., severe PPM was found to associate with mortality. However, the prognosis of patients with moderate PPM was not different compared to patients with no PPM. PPM was associated with lesser LV mass regression and increased risks of perioperative stroke and renal insufficiency (Bilkhu, Jahangiri and Otto, 2019). Among the patients included in the FinnValve registry, the incidence of PPM was 46.0% (Dahlbacka et al., 2021). Moderate PPM was detected in 38.8% and severe in 7.2% patients, respectively. The incidence of PPM decreased from 74% in 2009 to 18% in 2017 ($p<0.01$). Severe PPM was associated with increased 5-year all-cause mortality. Earlier generation prostheses, valve size ≤21 mm, female sex and larger body surface area and BMI were associated with PPM. Preventing PPM is the most effective way to treat it. Enlargement of the aortic root may be necessary to enable the implantation of an adequate sized prostheses.

2.1.7 Economic aspects

Economic aspects are strongly tied to the selection of different procedure types and also have an effect on future budgeting. Incremental cost-effectiveness ratio (ICER) measures the average addition of costs associated with health status gain and is defined by the difference in cost between two interventions, divided by the difference in their effectiveness. In a cost-effectiveness analysis, the ICER describes the cost per quality-adjusted life year (QALY) gained. QALY measures both the quality and the quantity of life: one QALY equals one healthy year.

TAVR prosthesis costs $32,000 and SAVR prosthesis $5000 in the USA (Baron *et al.*, 2018). In the PARTNER 1 Cohort A study (mean STS score 11.7%), TAVR was reported to provide an intermediate to high economic value compared with

SAVR with an ICER of $76.877/QALY gained. In the randomized PARTNER 2 trial (mean STS score 5.8%), TAVR reduced long-term costs by $9.000 compared to SAVR. Index procedure costs were >$20.000 higher with TAVR (Baron *et al.*, 2018). In addition, in the PARTNER S3i registry, the TAVR long-term cost reduction was even greater, >$11.000 per patient. The reduction in the total cost is mostly composed of shorter lengths of ICU and hospital stays during the index hospitalization, reduced operation room times and the demand of staff, and less resource requirements during follow-up. SAVR was more cost-effective in the patients who were ineligible for transfemoral access. Because of the lack of TAVR long term durability data, TAVR associated lifetime costs might be greater if there is need for more frequent repeat valve procedures (Baron *et al.*, 2018). In Germany, ICER is most favorable for patients older than 85 years (ICER €154.839, 95% CI €89.163–€302.862), followed by patients at higher pre-operative risk (ICER €413.745, 95% CI €258.027–€952.273). A shift from SAVR towards transfemoral TAVR among the intermediate operative risk patients is associated with a less favorable ICER (€1.486.118, 95% CI €764.732–€23.692.323). The risk-adjusted mortality benefit is small, while the additional cost is still 14.464€. The additional costs per life saved due to TAVR is most favorable for patients older than 85 years and/or at a higher pre-operative risk (Kaier *et al.*, 2019). Modi et al. reported episode payments for TAVR and SAVR patients between 90 days before the intervention and 90 days after hospital discharge. After adjusting for patient characteristics, episode payments were $55.545 for TAVR and $59.467 for SAVR. Episode payments increased along with increasing risk, with a stronger association with SAVR (rate ratio, 1.18, 95% CI, 1.17–1.19) than with TAVR (rate ratio, 1.11, 95% CI, 1.11–1.12; $p<0.001$ for interaction) (Modi *et al.*, 2019).

Osnabrugge et al. report an increase in total costs in isolated elective SAVR from low- to intermediate- to high-risk patients: $35.021±$22.642 vs. $46.101±$42.460 vs. $51.145±$31.655; p<0.001. The same trend was seen in the length of hospital stays (Osnabrugge *et al.*, 2013). Sutureless valve prostheses seem to be less costly, compared to TAVR. In a study by Povero et al. both in-hospital and long-term costs were lower for sutureless valves with total savings of $4.158 in France and $20.930 in United States. In addition, patients treated with sutureless valves were expected to live 1.25 years longer, compared to TAVR, with a mean gain of 1.14 QALY (Povero *et al.*, 2018).

The overall costs for AS intervention in Turku University Hospital average 20.440€ for TAVR and 14.320€ for SAVR, as calculated by 2018 catalogue prices (including preoperative visits, pre-, peri- and postoperative treatment). Valve prostheses were included, TAVR being more expensive when compared to SAVR prostheses, 15.000€ vs 1.600€, respectively. Annual frequencies for TAVR were 120 and 100 for SAVR in 2018, but it is estimated that in 2030, 200 TAVR and 50 SAVR prostheses will be

implanted. Without a decrease in TAVR prostheses prices, the annual overall intervention costs will increase from 3.88M€ to 4.8M€ in Turku. (Personal note by Vesa Anttila, Chief of Cardio-thoracic surgery, Turku University Hospital).

When HF is complicating the course of AS, the costs also rise drastically. The economic burden of HF alone accounts for >2.0% of total health care expenses in Western countries, mostly due to related hospitalizations. Costs are reported to be $3.780–34.233 per hospitalization and as high as $84.434 annually (Shafie, Tan and Ng, 2018). In the US, the estimated annual cost of $40 billion is predicted to increase to almost $69.7 billion by 2030 (Elgendy, Mahtta and Pepine, 2019). In this perspective, any procedure that prevents the development of HF is most likely to be cost-effective.

2.2 Heart failure

2.2.1 Epidemiology and pathophysiology of heart failure

Worldwide, the burden of HF has increased to an estimated 23 million people. HF is a clinical syndrome characterized by dyspnea or exertional limitation due to diastolic or systolic dysfunction or both (Yancy *et al.*, 2013; Elahi *et al.*, 2014). The pathophysiology of HF includes structural, neurohumoral, cellular, and molecular mechanisms, which cause inflammation, myocyte hypertrophy, myocyte death, apoptosis and fibrosis. Due to these changes, volume overload, increased sympathetic activity and fluid redistribution result in negative remodeling, worsening of ventricular function and in clinical symptoms of HF (Tanai and Frantz, 2015).

HF activates neurohumoral systems to maintain vital organ perfusion. HF causes a decreased carotid baroreceptor response, which activates the sympathetic nervous system and leads to increased cardiac contractility and tachycardia, vasoconstriction and increased afterload. In normal circumstances, renal blood flow is 20% of cardiac output and mainly determined by differences in renal arterial and venous pressure. Renal blood flow and glomerular filtration rate are regulated by three major mechanisms: the myogenic response, the tubuloglomerular feedback and renin secretion. These processes aim to maintain the glomerular filtration rate constant, but in HF simultaneously activate the renin-angiotensin-aldosterone system. Activation of the renin-angiotensin-aldosterone system causes fluid retention and increases preload. In addition, this activation increases angiotensin I conversion to angiotensin II, leading to vasoconstriction, fluid retention and pathological fluid redistribution, which further increase preload and accelerate remodeling.

Preload, myocardial contractility and afterload control the LV function and stroke volume. The Frank-Starling law represents the relationship between stroke

volume/cardiac output and left ventricle end-diastolic pressure/pulmonary capillary wedge pressure, with a positive correlation between increased cardiac filling pressures and increased stroke volume/cardiac output: the greater the stretch of the ventricle wall is, the greater is its ability to contract. In HF, the reduced ventricle wall compliance results in an inadequate ventricular filling and a decrease in the end-diastolic volume, and, as a result, leads to a decreased stroke volume (Borlaug and Reddy, 2017).

2.2.2 Diagnosis and classification of heart failure

HF is divided into three subgroups, according to LVEF: a) HF with preserved ejection fraction (EF) (HFpEF) LVEF≥50%, b) HF with moderately reduced EF (HFmrEF) LVEF 40–49%, and c) HF with reduced EF (HFrEF) LVEF<40%. The current LVEF-based HF classification does not take into account the underlying etiology of HF and its influence on the prognosis (Branca *et al.*, 2020). LVEF measurement is considered to be the corner stone prognostic and classification method for patients with acute and chronic HF. Biomarkers, echocardiographically measured left atrial size, myocardial global longitudinal strain and myocardial fibrosis measured by magnetic resonance imaging are important prognostic predictors that may guide the management of HF in addition to LVEF (Lauritsen, Gustafsson and Abdulla, 2018).

2.2.2.1 Left ventricular ejection fraction

EF is a fraction of the volume content ejected from a ventricle per contraction. It is calculated by dividing the stroke volume (SV) by the end-diastolic volume (EDV). The volume of blood left at the end of systole is the end-systolic volume (ESV).

$$EF(\%) = \frac{SV}{EDV} x100$$

$$SV = EDV - ESV$$

LVEF is used to estimate the severity HF. The problem is that LVEF is reduced in only half of the patients. In a clinical use, EF is most commonly measured by echocardiography, although cardiac magnetic resonance imaging is currently considered to be the best method. Cardiac CT, ventriculography and SPECT/PET scans may also be used. Measurements by different modalities are not directly comparable.

2.2.2.2 Heart failure with preserved ejection fraction

ESC and ACC/AHA guideline definitions for HFpEF are: 1) clinical signs or symptoms of HF, 2) evidence of preserved or normal LVEF, 3) evidence of abnormal LV diastolic dysfunction, 4) elevated levels of natriuretic peptides, and either 5a) a relevant structural heart disease (left ventricular hypertrophy and/or left atrial enlargement) and/or 5b) diastolic dysfunction. The EF cut-off point for defining HFpEF previously ranged between ≥40% and ≥50%. Herein that range is further referred to as HF with a mildly reduced ejection fraction (HFmrEF) (Yancy *et al.*, 2013) (Kelly *et al.*, 2015).

HF with a preserved ejection fraction (HFpEF) is a clinical challenge with limited treatment options and poor outcomes, frequently remains unrecognized and untreated. No medical therapy has yet been shown to decrease morbidity and mortality (Kelly *et al.*, 2015; Kalogirou *et al.*, 2020). The symptom burden and outcomes in HFpEF are as poor as the outcomes in patients with HF with reduced EF (HFrEF) (Kelly *et al.*, 2015). Half of all patients with HF have preserved EF. Patients with HFpEF are more likely to be old, female and have multiple co-morbidities. Multiple mechanisms usually coexist within the same patient to cause symptomatic HF, but the extent in which each factor causes and correlates with symptoms and treatment differs widely (Borlaug, 2014). Current recommendations for the management of HFpEF focus on controlling cardiovascular and non-cardiovascular co-morbidities and recommend the use of diuretics to regulate fluid balance. Although multi-disciplinary team work boards, including geriatric assessment, aim to reduce the risk of hospitalization and mortality, there is little information about their effectiveness, specifically in HFpEF (Kalogirou *et al.*, 2020).

2.2.2.3 Heart failure with mildly reduced ejection fraction

In 2016, a new category of mid-range/mildly reduced LVEF (HFmrEF) was introduced and established specific characteristics of the patients with HFmrEF compared to patients with HFpEF and HFrEF (Branca *et al.*, 2020). HFmrEF patients have a similar clinical profile and co-morbidity burden as HFpEF and HFrEF patients, but with the lower mortality rartes (Lauritsen, Gustafsson and Abdulla, 2018). Despite a better prognosis, HFmrEF patients still have only a slightly better all-cause and cardiovascular survival at a 3 year follow-up than HFrEF patients (Lauritsen, Gustafsson and Abdulla, 2018). The limitations of LVEF as the sole criterion to categorize patients with HF is recognized, especially when LVEF is >40% (Branca *et al.*, 2020). To better define the exact HFmrEF phenotype, there is a need to consider other parameters, such as HF etiology, co-morbidity burden, LVEF changes during the follow up period and other imaging parameters. Only one-

third of the HFmrEF patients remain in this category during a long-term follow up (Savarese *et al.*, 2019).

There is increasing evidence that many patients with HFrEF experience an improvement in their LVEF following HF treatment. This group of patients with improved LVEF has been suggested to constitute a category called HF with improved EF (HFiEF) (Yancy *et al.*, 2013). Patients with HFiEF have similar characteristics with HFmrEF patients, as they are more often younger females and have less ischemic heart disease than HFrEF patients (Lauritsen, Gustafsson and Abdulla, 2018).

2.2.2.4 Heart failure with reduced ejection fraction

HFrEF is defined as LVEF ≤40% and a progressive LV dilatation and adverse cardiac remodeling. Approximately 50% of the patients with HF have a reduced EF (Murphy, Ibrahim and Januzzi Jr, 2020). Risk factors for HFrEF are multifactorial and complex. The risk of developing HFrEF can be decreased by treating the known cardiovascular risk factors, such as hypertension, diabetes and obesity. Early treatment strategies (i.e., early revascularization, valvular heart disease treatment) appear to be effective in reducing the risk and severity of acute myocardial infarction (Murphy, Ibrahim and Januzzi Jr, 2020). This may explain a reduction in the incidence of HFrEF and an increasing incidence of HFpEF and HFmrEF. Still, 5-year survival is reported to be as low as 25% after hospitalization for HFrEF. (Murphy, Ibrahim and Januzzi Jr, 2020).

2.2.3 Cardiomyopathies

Cardiomyopathies are a diverse group of diseases of the myocardium associated with cardiac dysfunction. Cardiomyopathies are categorized as primary cardiomyopathies and secondary cardiomyopathies. The primary cardiomyopathies are subdivided into genetic, mixed (predominantly nongenetic) and acquired diseases. The genetic cardiomyopathies include hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and unclassified cardiomyopathies. The mixed cardiomyopathies include dilated cardiomyopathy and restrictive cardiomyopathy. The acquired cardiomyopathies include myocarditis, stress-induced (Takotsubo), peripartum and tachycardia-induced cardiomyopathies. The most common cardiomyopathies are hypertrophic, dilated and restrictive cardiomyopathy. The classification of cardiomyopathies is challenging due to mixing anatomic and functional designations (Yancy *et al.*, 2013)

2.2.3.1 Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is usually inherited and is the most common genetic cardiac disorder (Maron, 2018). In the most common phenotype, the anterior septum and anterior free wall below the aortic valve become hypertrophic causing increased LVOT gradient, whereas minimal or no hypertrophy occurs on the LV posterior wall. Hypertrophic cardiomyopathy rarely is acquired and is then associated with acromegaly, pheochromocytoma and neurofibromatosis. In hypertrophic cardiomyopathy, the ventricular hypertrophy leads to diastolic dysfunction as a result of a noncompliant and small LV. Increased end-diastolic pressure decreases cardiac output and increases pulmonary venous pressure. Also, systolic anterior motion of the mitral valve during systole causes obstruction of flow and decreases cardiac output. Mitral regurgitation can occur as the result of systolic anterior motion. At first, LV contractility and EF are usually normal. Later, EF elevates to maintain cardiac output. Coronary artery flow may be impaired due to inadequate capillary density or narrowed intramyocardial coronary artery lumen diameter by intimal and medial hyperplasia and hypertrophy. Simultaneously, the demand of oxygen is increased in the hypertrophic myocardium. Hypertrophic cardiomyopathy is a common cause of sudden death in young athletes and chronic HF occurs less often (Maron, 2018).

Treatment of hypertrophic cardiomyopathy is based on the phenotype. Patients without significant obstruction perform well, although diastolic dysfunction can cause symptomatic HF. In patients with LVOT obstruction, the treatment aims to improve diastolic function. Calcium channel blockers, beta-blockers and disopyramide are used to reduce the LVOT gradient. Symptomatic patients with LVOT gradients ≥50 mmHg, despite adequate medical therapy, are candidates for invasive treatment. Surgical myectomy has good outcomes with low operative mortality in experienced centers (Nishimura, Seggewiss and Schaff, 2017). Percutaneous catheter alcohol septal ablation is an alternative to surgery in selected young patients and in patients at high surgical risk (Nishimura, Seggewiss and Schaff, 2017). Drugs reducing preload (including nitrates, diuretics, ACE inhibitors, and angiotensin II receptor blockers) are not recommended. Vasodilators increase the LVOT gradient and cause a reflex tachycardia. Inotropic drugs increase LVOT obstruction, do not decrease the high end-diastolic pressure and may induce arrhythmias (Maron, 2018). Promising results are reported of an oral cardiac myosin inhibitor mavacamtem, that reduces actin-myosin cross-bridge formation. It relieves symptoms, reduces LVOT obstruction and increases exercise tolerance (Olivotto *et al.*, 2020). If syncope or sustained ventricular arrhythmias or aborted sudden cardiac arrest has occurred, an implantable cardioverter-defibrillator should be considered (Maron *et al.*, 2019).

2.2.3.2 Dilated cardiomyopathy

In dilated cardiomyopathy, ventricular dysfunction, LV dilatation and increased end-diastolic filling pressures cause systolic and diastolic dysfunction. Dilated cardiomyopathy is one of the most common causes of heart failure with estimated prevalence ranging from 1 : 250–400 to 1 : 2500 (Reichart *et al.*, 2019). Causes of dilated cardiomyopathy are classified as genetic and nongenetic. The etiology is genetic in 35% of cases. Most common etiology is reactive changes in myocardium due to multiple possible pathologies, such as inflammation (viral myocarditis and autoimmune disease), toxic influences (alcohol, drugs and chemotoxines), prolonged tachycardia and metabolic disorders (Reichart *et al.*, 2019). Hypertensive, valvular, congenital and ischemic heart disease as etiology should be excluded. Most patients become symptomatic at 20-60 years of age. Rarely also children can be affected and dilated cardiomyopathy constitutes 60% of pediatric cardiomyopathies (Reichart *et al.*, 2019). If left untreated, the 1- and 5- year survival are 70% and 50%, respectively (Dec and Fuster, 1994). 60% of patients die due to HF and 30% by sudden cardiac death (Weintraub, Semsarian and Macdonald, 2017). Low EF and severe diastolic dysfunction are associated with worse prognosis.

Guideline-based HF medication and device therapies reduce the frequency of HF hospitalizations and improve survival (Yancy *et al.*, 2013). Adequate treatment induces reverse remodeling and leads in 25% of patients with acute onset dilated cardiomyopathy to improvements in LVEF. Patients with symptoms lasting >3 months and initially severe HF are more unlikely to recover (Reichart *et al.*, 2019). The treatment includes nonpharmacologic therapies, such as reduction of salt and water intake and moderate physical exercise. Medical treatment follows the recommendations for HFrEF (Yancy *et al.*, 2013). In patients with severe HF, angiotensin-neprilysin inhibitor significantly reduces risks of mortality and hospitalization. Disease progression causes dyssynchronous ventricular contraction and conduction disturbance. Cardiac resynchronization therapy (CRT) aims to synchronize contraction of the left and right ventricle thus reducing morbidity, mortality and improving LVEF. CRT-pacemaker, CRT-P, can be upgraded to defibrillator, CRT-D, in the risk of or present ventricular tachyarrhythmias. Implantation of left ventricular assist devices and heart transplantation are treatment options in the end-stage HF in younger patients. Dilated cardiomyopathy is the most common indication for heart transplantation worldwide (Weintraub, Semsarian and Macdonald, 2017).

2.2.3.3 Restrictive cardiomyopathy

Restrictive cardiomyopathy is a rare form of cardiomyopathy. The disease may be infiltrative and/or obliterative with fibrosis of the endocardium and subendocardium.

Restrictive cardiomyopathy can result from systemic and genetic disorders, such as amyloidosis, sarcoidosis, hemochromatosis, Fabry disease and Löffler syndrome, although the etiology usually remains unknown. Iatrogenic causes include chemotoxines. Cardiac amyloidosis is discussed in section 2.2.3.4. Restriction results from endocardial thickening, myocardial infiltration, myocyte death, papillary muscle infiltration, compensatory myocardial hypertrophy and fibrosis. This also leads to atrial enlargement and mitral and/or tricuspid valves regurgitation. Restriction may occur diffuse or non-diffuse, typically on the left side. If nodal and conduction tissues are affected, sinoatrial and atrioventricular block may occur. Symptoms and signs of restrictive cardiomyopathy resemble those of constrictive pericarditis. Sudden death is common and the prognosis is poor as the diagnosis is often made at advanced stage. Differential diagnosis with hypertrophic cardiomyopathy may be difficult.

No curative treatment is available for most patients and the treatment aims at symptom relief. Standard medical therapy used in HF is poorly tolerated in restrictive cardiomyopathy. Diuretics may be considered and may ease pulmonary edema and congestion. However, decrease in preload in patients with noncompliant LV may also compromise cardiac output. Beta-blockers and calcium channel blockers may be used to treat tachycardia in selected patients. Nitrates and other medication decreasing afterload may cause hypotension and usually are not well tolerated. In a case of an early diagnosis, specific treatment options of amyloidosis, sarcoidosis, hemochromatosis, and Löffler syndrome may improve the prognosis. There is a high rate of conduction disorders requiring a pacemaker or an implantable cardioverter-defibrillator. In a progressed stage of the disease, left ventricular assist devices and cardiac transplantation may be considered (Muchtar, Blauwet and Gertz, 2017).

2.2.3.4 Cardiac amyloidosis

Cardiac amyloidosis is a condition where extracellular deposit of amyloid fibrils accumulate into cardiac structures, i.e. myocardium and in the conduction system. The most prevalent proteins involved are transthyretin and light chain immunoglobulin (Ternacle *et al.*, 2019). The coexistance of AS and cardiac amyloidosis complicates the diagnosis, management and prognosis of both conditions (Cappelli *et al.*, 2020). Impairment of both diastolic and systolic function result in reduced LV filling and stroke volume and lead to HFpEF and low cardiac output. In addition, right heart failure is common due to right side affision. The conduction disturbance caused by amyloidosis often occurs during the early state of the disease.

It is estimated that ≤15% of the AS patients and ≤30% of the subset with low-flow, low-gradient AS may have cardiac amyloidosis (Ternacle *et al.*, 2019).

Myocardial amyloidosis is found at endomyocardial biopsy or autopsy in the general population increasingly in conjunct with advancing age: 25% at the age >85 years and 63% age >100 years (Tanskanen *et al.*, 2008). The incidence of cardiac amyloidosis in SAVR patients is reported to be 5.6% (Treibel *et al.*, 2016).

The treatment of cardiac amyloidosis aims to mitigate the consequences of the disease. Medical treatment recommendations follow current HF guidelines. Digoxin may cause arrhythmias in patients with cardiomyopathy due to amyloidosis, and digitalis sensitivity is common. Specific, amyloidosis type targeted, therapies aim to prevent and reduce amyloidosis and recent studies offer promising results (Ternacle *et al.*, 2019). Still, heart and liver transplantations are a valid option in younger patient population.

2.2.3.5 Ischemic cardiomyopathy

Coronary artery disease, hypertension and valvular heart disease are causes of secondary cardiomyopathies. HF patients are reported to have 60–70% an ischemic etiology, about 10% of all patients (28.8% of nonischemic patients) to have a hypertensive etiology and 8% a valvular etiology (Balmforth *et al.*, 2019; Elgendy, Mahtta and Pepine, 2019). Valvular disease related HF is discussed in the view of AS in the section 2.3.

In ischemic heart disease the myocardial necrosis and fibrosis leads to dilated ventricles and cardiac dysfunction resembling dilated cardiomyopathy. Patients with coronary artery disease are more likely to have HFrEF rather than HFpEF. The prevalence of ischemic cardiomyopathy is predicted to increase 46% by 2030 due to the declining acute myocardial infarct death rates and aging population (Elgendy, Mahtta and Pepine, 2019). The prognosis is worse than in patients with dilated cardiomyopathy and nonischemic etiology (Weintraub, Semsarian and Macdonald, 2017).

The development of ischemic cardiomyopathy is a continuum from thrombotic acute coronary syndrome or chronic ischemia to a clinical HF. In an acute ischemia, loss of cardiomyocytes results in myocardial stunning, myocardial necrosis, myocardial inflammation, hypertrophy and fibrosis. These changes activate the neurohormonal processes that result in adverse LV remodeling causing dilation and dysfunction. This also affects the noninfarcted myocardium. Secondary mitral regurgitation and tachyarrhythmias worsen the course of the disease process. LV remodeling, LV dilatation and ischemic mitral regurgitation lead to development of the HF. Patients with LVEF≤35% and prior myocardial infarction have twice as high hospitalization rates for HF and fourfold mortality rates versus patients without a prior cardiac infarctation (Elgendy, Mahtta and Pepine, 2019). Chronic ischemia may result in similar condition even without acute ischemia. The pathophysiological

mechanisms for developing HFpEF secondary to ischemia are more complex than those leading to HFrEF. HFpEF has been thought to develope secondary to myocardial stress resulting of long-standing hypertension or AS. However, recent evidence suggests that microvascular dysfunction involving the smaller coronary vessels in noninfarcted regions leads to recurring ischemia, endothelial dysfunction increases vascular stiffness and resistance leading to decreased tissue perfusion. This leads to extracardiac multiorgan dysfunction and to an increased cardiac afterload. The presence of comorbidities, such as diabetes, obesity, inactivity, chronic kidney disease and chronic obstructive pulmonary disease, increase the systemic inflammation. Inflammation further compromises endothelial function leading to ischemia and diastolic dysfunction even in the absence of an obstructive coronary artery disease and an ischemic event (Elgendy, Mahtta and Pepine, 2019).

In the randomized STICH (Surgical Treatment for Ischemic Heart Failure) trial, coronary artery bypass grafting (CABG) reduced all-cause mortality and hospitalizations in patients ischemic cardiomyopathy and LVEF <35% compared to medical treatment (Howlett *et al.*, 2019). The reduction in mortality included both sudden death and fatal HF. Long-term survival benefit was most apparent in the youngest patients enrolled in the trial. The short-term CABG-related mortality and adverse event rate was 5%. Repeated hospitalizations were responsible for >70% of hospitalizations at 10 year follow up and were associated with increased mortality and worse symptoms of HF. Half of the hospitalizations were due to HF. The long-term benefit from CABG was evident 1 year after enrolment, with more clear difference the longer the follow up. Guideline-based HF medication also decreased both mortality and HF hospitalization in medical treatment cohort (Howlett *et al.*, 2019). There is a lack of evidence in percutaneous coronary intervention (PCI) for patients with ischemic cardiomyopathy, but results from REVIVED-BCIS2 trial may be expected in a few years (Perera *et al.*, 2018). Wolff et all conclude on their meta-analysis on patients with HFrEF and coronary disease, that revascularization with either CABG or PCI improves the long-term survival over medical therapy. CABG was associated with better survival compared to PCI. Also, CABG compared with PCI was associated with a significant reduction in the risk of myocardial infarction and need for repeated revascularization, although the risk for stroke was increased.

2.2.4 Acute heart failure

Acute heart failure (AHF) is defined as de novo HF or worsening of chronic HF (Yancy *et al.*, 2013; Arrigo *et al.*, 2020). The clinical presentation of AHF is typical regardless of its etiology and pathophysiology. LV dysfunction results in an increased preload and afterload, which further leads to pulmonary congestion. Fluid retention and redistribution result in systemic congestion. The majority of

hospitalizations are due to acute decompensated HF, rather than de novo AHF (Arrigo *et al.*, 2020). Cardiogenic shock is rare, but when present, it leads to a higher in-hospital mortality and is associated with poor outcomes. The substantial majority of adverse events occur after discharge of AHF patients and the risk stays increased for 2–3 months (Greene *et al.*, 2015). The 90-day readmission rate is reported to be 30% and 1 year survival 65%, with majority of deaths occurring within the first 2–3 months after initial hospitalization. (Gheorghiade *et al.*, 2012; Greene *et al.*, 2015)

2.2.4.1 Pathophysiology of acute heart failure

Multiple underlying structural or functional cardiac conditions can predispose for AHF. The underlying cardiac disease leads to a simultaneous activation of several pathophysiological pathways that decrease peripheral perfusion. As in a chronic setting, these pathways lead to systemic congestion and ventricular remodeling, and, ultimately, to vital organ dysfunction (Arrigo *et al.*, 2020). In addition to cardiac conditions, other acute diseases can trigger AHF by directly impairing cardiac function or by causing systemic congestion (Arrigo *et al.*, 2020). In the majority of patients, AHF is induced by systemic congestion caused by fluid retention and/or redistribution, particularly in patients with a pre-existing diastolic dysfunction (Zile *et al.*, 2008). Systemic congestion is a major determinant of multi-organ dysfunction occurring in AHF (Arrigo, Nijst and Rudiger, 2018). The responses to treatment vary greatly depending on the underlying pathophysiology.

Any acute change in cardiac function which leads to an increase in LV filling pressures can result in AHF. Acute myocardial ischemia and new onset atrial fibrillation (AF) are among the most common conditions (Anter, Jessup and Callans, 2009; Bahit, Kochar and Granger, 2018). LV filling is a two phase process, in which the early phase is mostly dependent on rapid myocardial relaxation and the later phase on atrial contraction and the atrial-to-ventricular pressure gradient (Arrigo *et al.*, 2020). Myocardial relaxation is an active energy-requiring process, and in an acute setting the reduction in oxidative ATP generation in cardiomyocytes impairs the relaxation (Doenst, Nguyen and Abel, 2013). The LV end-diastolic function is impaired due to the LV end-diastolic volume changes, structural cardiac damage and delayed relaxation. Even without hypervolemia, an increased extracellular volume and/or a change in the compliance of peripheral veins can lead to an increase in cardiac filling pressures. Sympathetic activation can induce a sudden displacement of volume from the splanchnic and peripheral venous system to the pulmonary circulation (Fudim, Hernandez and Felker, 2017).

2.2.4.2 Management of acute heart failure

AHF results in an increased risk of death from both cardiovascular failure and the consequences of vital organ dysfunction due to congestion and hypoperfusion. The treatment of AHF mostly focuses on treating decongestion and consists of non-invasive ventilation, intravenous diuretics and short-acting vasodilators. Patients with AHF have a similar congestion profiles regardless of their LVEF, so the treatment is similar in patients with HFrEF or HFpEF (Arrigo, Nijst and Rudiger, 2018; Arrigo *et al.*, 2020). The decongestive therapy should be guided by the hemodynamic conditions and the underlying pathophysiology of AHF. To further resolve AHF and to prevent recurrencies, the underlying cardiac disease and other precipitating factors should be resolved.

2.2.5 Pulmonary artery pressures and hypertension

In severe AS, the maladaptive processes leading to LV hypertrophy are associated with myocardial fibrosis, diastolic dysfunction, cause an increase in the left atrial pressures and lead to pulmonary hypertension (PH). PH is defined as mean pulmonary artery pressures (mPAP) ≥25 mmHg and mean pulmonary capillary wedge pressure >15 mmHg (Maeder *et al.*, 2018; Weber *et al.*, 2019). Systolic pulmonary artery pressures (sPAP) are usually estimated based on the peak tricuspid regurgitation velocity on echocardiography, using the Bernoulli equation (Kiely *et al.*, 2019). Direct measurement of the mean PAP by right heart catheterization, which is required for an exact diagnosis of PH, is performed infrequently nowadays and is mainly used to assess tricuspid regurgitation. In patients with AS, PH is usually post capillary, as a consequence of AS and its impact on left ventricular and atrial function (Maeder *et al.*, 2018). PH has been found in cardiac catheterizations in 48–75% of severe AS patients undergoing AVR (O'Sullivan *et al.*, 2015; Weber *et al.*, 2019). The prevalence of rest sPAP >50 mmHg is 15–30%, according to Martinez et al. (Martinez *et al.*, 2016). In a meta-analysis of surgical patients, Rocha et al. reported that 65% of symptomatic AS patients and 80% of octogenarians have PH (Rocha *et al.*, 2019). If left untreated, PH ultimately leads to a right ventricle failure, accounting for 70% of deaths in patients with PH.

Patients with combined post- and pre-capillary PH have the lowest LVEF, the smallest aortic valve area, and most severe mitral regurgitation, as well as the worst survival rates (Maeder *et al.*, 2018). Also, in a meta-analysis of TAVR patients with preoperative PH, PH was found to be a predictor of an increased early (OR, 1.52; 95%CI, 1.28–1.80; p=0.50) and late (OR, 2.00; 95%CI, 1.49–2.69; p=0.23) mortality, compared to patients with no PH (Tang *et al.*, 2017). It seems that pre-capillary and combined post- and pre-capillary, but not isolated post-capillary PH, are associated with the worst intermediate- and long-term survival rates. (O'Sullivan

et al., 2015; Maeder *et al.*, 2018). On the other hand, Alushi et al. found that the reduction in post-TAVR sPAP was more important than the pre-TAVR sPAP in predicting 30-day and 1-year survival (Alushi *et al.*, 2019).

In AS with preserved LVEF, PH is common and causes HF similar to that seen in patients with HFpEF. These patients have various abnormalities in LV systolic function despite LVEF >50%, and in this subset of patients, a stroke volume index of <35 ml/m^2 is caused by impaired filling and contractility, causing a low flow-low gradient severe AS (Maeder *et al.*, 2018). For these patients, comorbidities including AF, pulmonary disease, obesity, anemia, and renal failure are key determinants of PH.

In patients undergoing SAVR, PH increases the risks of adverse events and death. In a meta-analysis of 70.676 patients by Rocha et al. patients with any PH had a higher in-hospital mortality when compared to patients with no PH (OR, 1.65; 95%CI, 1.28–2.14; p<0.01), and particularly severe PH was associated with a higher risk (OR, 5.68; 95%CI, 2.54–12.70; p<0.01) (Rocha *et al.*, 2019). Similarly, in a median follow-up of 4 years, any PH was associated with increased long-term mortality when compared with no PH (RR, 1.67; 95%CI, 1.32–2.12; p<0.01) and severe PH again associated with a greater risk (RR, 2.44; 95%CI, 1.60–3.72; p<0.01). On the other hand, mild to moderate PH was associated with higher unadjusted long-term mortality, but the in-hospital mortality was not different when compared with no PH. The EuroSCORE II (Nashef *et al.*, 2012) risk score includes moderate and severe PH as a risk factor for operative morality; but they are not included in the Society of Thoracic Surgeons (STS) risk score (*The Society of Thoracic Surgeons. Online STS adult cardiac surgery risk calculator. 2017. http://riskcalc.sts. org/stswebriskcalc/#/. Accessed October 7, 2018.*). Patients with PH undergoing SAVR had longer cardiopulmonary bypass times, increased need for prolonged mechanical ventilation, and longer hospital stays. Rocha et al. also found that patients with severe AS and PH had a lower LVEF compared to those with no PH. These findings may be related to older age and a higher prevalence of comorbidities in patients with PH, as well as respiratory failure secondary to PH. Long-term survival following SAVR in patients with PH is impaired: the 10-year survival is 45% and 31% in patients with moderate and severe PH, respectively (Roselli *et al.*, 2012). Both SAVR and TAVR reduce PAP in approximately 60% of patients, but the reduction in PAP is relatively modest, with the greatest reduction in patients with the highest preoperative PAP, at least among TAVR patients (Alushi *et al.*, 2019).

The 2017 ESC guidelines for the management of valvular heart disease give a IIa indication for SAVR in asymptomatic patients with severe AS and sPAP >60 mmHg (Baumgartner *et al.*, 2017). The guideline further states that PH should be confirmed by cardiac catheterization if PH is the main indication for surgery. In this case, PH indicates an extensively advanced stage of AS with a

significantly worse prognosis than severe AS without PH, and complete recovery of LV diastolic function and the resolution of PH is unlikely. Patients with PH have an increased risk for operative mortality, adverse outcomes, and poor long-term survival following SAVR compared to patients with no PH. The correlation is more evident with more severe PH. Further research is needed to better understand the impact of PH in relation to the TAVR operative risk, the timing of the intervention and the long-term outcomes after TAVR in these patients. An individual risk assessment and Heart Team decision guide the timing and type of intervention in patients with AS and PH.

2.2.6 Management of heart failure

2.2.6.1 Medical treatment

Angiotensin-converting enzyme inhibitors

ACE inhibitors inhibit the production of angiotensin II. This leads to reduced resistance in renal vessels, increased venous capacity, vasodilatation and decreased cardiac output, stroke work and stroke volume. ACE inhibitors improve survival in patients with LV systolic dysfunction. A significant reduction in mortality, alleviation of symptoms and improvement in clinical status is well established in multiple studies (Yancy *et al.*, 2013; Balmforth *et al.*, 2019). A lower total mortality, lower rate of readmission for HF and a lower incidence of myocardial infarction were detected (Flather *et al.*, 2000). The mortality benefit was achieved due to decreased death rate from progressive HF.

Beta blockers

Patients with HFrEF with no or minimal volume overload should receive carvedilol, metoprolol or bisoprolol. Even low doses are effective. Randomized trials of specific beta blockers (carvedilol, metoprolol and bisoprolol) were analyzed by The Beta-Blockers in Heart Failure Collaborative Group and demonstrated a reductions in mortality and hospitalization rates in patients with HFrEF and New York Heart Association (NYHA) classes II-IV (Kotecha *et al.*, 2017; Cleland *et al.*, 2018). Also, an improvement in LVEF, NYHA functional class and exercise tolerance has been observed. The benefits were achieved with concurrent ACE inhibitor use. When comparing the effects of vasodilating beta blockers (primarily carvedilol) with non-vasodilating beta blocker (mainly bisoprolol), the vasodilating beta blockers associated with better survival. The difference was primarily seen in patients with

nonischemic cardiomyopathy. Indirect evidence suggests that carvedilol may produce greater improvement in LVEF than metoprolol. The beneficial effect of beta blockers in HFrEF may be a class effect.

Aldosterone receptor blockers, angiotensin II receptor blockers

Aldosterone receptor blockers may reduce total mortality, but generally do not decrease hospitalization rates compared to placebo in HF patients. However, in patients with symptomatic HF and LVEF ≤40% who did not tolerate ACE inhibitors, cardiovascular death and HF related hospitalization were reduced in the candesartan group (Young *et al.*, 2004). Data comparing aldosterone receptor blockers with ACE inhibitors in patients with HFrEF shows slightly better survival associating with ACE inhibitors (Heran *et al.*, 2012). There were no differences in rates of stroke, myocardial infarction, hospitalizations. Aldosterone receptor blockers are better tolerated compared to ACE inhibitors.

Angiotensin II receptor blocker and neprilysin inhibitor

Sacubitril/valsartan is an angiotensin receptor neprilysin inhibitor that provides inhibition of neprilysin and the angiotensin receptor (McMurray *et al.*, 2014). In PRARDIGM-HF trial, the HF patients with NYHA II-IV and LVEF ≤40% were randomized to receive either ACE or angiotensin receptor neprilysin inhibitor (McMurray *et al.*, 2014). The trial was closed after two year follow up due to sacubitril-valsartan being superior to ACE inhibitors for improving the prognosis of HF patients. Angiotensin receptor neprilysin inhibitors are associated with reduced all cause mortality, cardiovascular death, the risk of hospitalization for HF and decreased the symptoms of HF, compared to ACE inhibitor. Patients experienced more often hypotension and nonserious angioedema and less often renal insufficiency, hyperkalemia and cough (McMurray *et al.*, 2014). Also, sacubitril/valsartan reduce central aortic systolic pressure, central aortic pulse pressure and nocturnal hypertension (Kario, 2018). Sacubitril/valsartan may alleviate the development of hypertension to HF. PROVE-HF and EVALUATE-HF trials suggest that angiotensin receptor neprilysin inhibitors associate with cardiac reverse remodeling in patients with HFrEF (Drazner, 2019). Angiotensin receptor neprilysin inhibitors are now recommended in HF guidelines for patients with reduced LVEF.

Diuretics

Diuretic agents, particularly loop diuretics, are fundamental in HF treatment (Felker *et al.*, 2020). Loop diuretics have steep dose-response curves. Diuretic resistance is a complex clinical problem with poor prognosis and ill-defined treatment options. The evidence base for optimal use of loop diuretics is scarce compared to many other areas of HF therapies (Yancy *et al.*, 2013). Increase in serum creatinine level during diuretic treatment is common and does not always require stopping or decreasing loop diuretic dosing, especially if congestion is persistent. Diuretic resistance is a relevant clinical problem. Identification of the resistance mechanisms is crucial to improve diuretic response. Combining nephron blockade by adding a thiazide-like diuretic agent, most often metolazone, often results in voluminous diuresis, but is associated with a risk of electrolyte disturbances. The results from studies combining loop diuretics with acetazolamide (ongoing ADVOR trial), diuretic doses of mineralocorticoid receptor antagonists, spironolactone (ATHENA-HF trial), low-dose dopamine in HFpEF (ROSE-AHF trial), low-dose nesiritide, tolvaptan or SGLT-2 inhibitors did not prove to be beneficial.

Most patients with chronic HF require loop diuretics to maintain normovolemia and clinical stability. The ideal choice of the loop diuretic agent is uncertain. Most commonly used loop diuretic agents, furosemide and bumetanide, are short acting (<3 h). Therefore, minimum twice a day dosing is needed to shorten the periods of low concentration in the tubular fluid, which may induce post-diuretic sodium retention. Torsemide and bumetanide have better and more predictable pharmacological profiles than furosemide. Torsemide may also have other favorable effects, such as mitigation of cardiac fibrosis. Preliminary data suggests that torsemide may be associated with improved outcomes compared to furosemide in patients with HF, but the data from large trials, such as ongoing TRANSFORM-HF, are needed to confirm the finding.

Mineralocorticoid receptor antagonist

Mineralocorticoid receptor antagonists are recommended for patients with HFrEF. Spironolactone is the primary mineralocorticoid receptor antagonist to begin with. Eplerenone is recommended, if endocrine side effects occur with spironolactone. Two major mineralocorticoid receptor antagonist trials, the RALES for spironolactone and EMPHASIS-HF for eplerenone, were discontinued after an about 2 years follow up because of significant risk reductions in the index medication arm: both were associated with lower overall mortality, decreased death rates from HF, decreased sudden death rates and reduction in hospitalizations for HF (Pitt *et al.*, 1999; Zannad *et al.*, 2011). Other effects of spironolactone were improved NYHA class, reductions in blood pressure, reduced incidence of hypokalemia and a dose-

related increase in the risk of hyperkalemia. Endocrine side effects of spironolactone (gynecomastia, breast pain, menstrual irregularities, impotence and decreased libido) result from nonselective binding to androgen and progesterone receptors. Eplerenone has better specificity for the mineralocorticoid receptor, resulting in a lower incidence of MRA associated side effects.

SGLT2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce blood glucose by increasing urinary glucose excretion and reduce the risk of progression of diabetic kidney disease. Other myocardial and vascular effects are under investigation. Contraindications for SGLT2 inhibitor use are type 1 diabetes mellitus and type 2 diabetes mellitus with prior or predisposing diabetic ketoacidosis, low eGFR, end-stage kidney disease and rapidly declining renal function. The most studied SGLT2 inhibitors are dapagliflozin, empagliflozin and canagliflozin. The dapagliflozin, added to optimal pharmacologic and device therapy, reduces both all-cause and cardiovascular mortality and worsening of HF in patients with NYHA II-IV HFrEF with or without diabetes (McMurray *et al.*, 2019). The empagliflozin, similarly added to optimized therapy, reduced hospitalizations for HF as well as a composite outcome of cardiovascular death or hospitalizations for HF in adults with NYHA II-IV HFrEF with or without diabetes (Packer *et al.*, 2020). Cardiovascular and all-cause mortality were not significantly different compared to a placebo group. However, a meta-analysis combining DAPA-HF and EMPEROR trials found no significant differences in these outcomes between the two trials and the pooled analysis showed significant reductions in mortality and cardiovascular death also for empagliflozin (Zannad *et al.*, 2020). Other SGLT2 inhibitors include canagliflozin, ertugliflozin and sotagliflozin.

Digoxin

The 2016 ESC HF guidelines included a weak recommendation for use of digoxin in s patients with HFrEF with persistent NYHA class III-IV despite evidence-based therapy. The ACC/AHA HF guidelines give a more general recommendation that digoxin can be beneficial in patients with HFrEF to decrease hospitalizations for HF (Yancy *et al.*, 2013). Randomized controlled trials (RCT) in patients with HFrEF have shown that digoxin improves clinical symptoms, quality of life, exercise tolerance and decreases hospitalization rates for HF but it does not improve survival. The effect of digoxin on patient survival and hospitalization rates was evaluated in the Digitalis Investigation Group (DIG) trial (Aguirre Dávila *et al.*, 2019). Thus, digoxin differs from other inotropic agents, including milrinone,

that decrease survival in patients with HFrEF. In an analysis of high-risk subgroups of patients with HF with LVEF<45% in the DIG trial, digoxin improved outcomes compared with placebo in all. However, in a low-risk group, digoxin improved HF related morality and HF hospitalizations, but did not improve all-cause mortality and all-cause hospitalizations. Digoxin is contraindicated in patients with sinoatrial or atrioventricular block and in patients with cardiac amyloidosis. Toxic digitalis-effects include arrhythmias, conduction disturbances, nausea, vomiting and visual disturbances. Digoxin toxicity is a clinical concern irrespective of circulating levels.

Levosimendan

Levosimendan is a calcium sensitizer and potassium channel-opener that is used to treat decompensated heart failure (Bouchez *et al.*, 2018). It is an inodilatator that causes inotropy, vasodilatation and cardiac protection without increasing myocardial oxygen consumption. Levosimendan improves coronary blood flow and right ventricular and endothelial function (Pölzl *et al.*, 2017). It prevents myocardial apoptosis and remodeling. Cardiorenal syndrome is often complicating the course of decompensated and/or acute HF. Levosimendan appears to improve renal perfusion and reverse kidney dysfunction. In clinical trials, such as the LEVOREP, repetitive intra venous use of levosimendan in patients with advanced HF is reported to offer symptom relief, improvements in hemodynamics, re-hospitalization rates and biomarkers and survival (Altenberger *et al.*, 2014). The impact on mortality in large RCTs has been alternating. However, in contrary to conventional inotropes, no impression of increased mortality has been detected and there are signals of improved HF-related quality of life (Bouchez *et al.*, 2018). Prophylactic levosimendan dosing was associated with a reduced mortality, low cardiac output syndrome and acute kidney injury (AKI) rates in a large meta-analysis of patients with severe LV dysfunction undergoing cardiac surgery (Weber *et al.*, 2020). Levosimendan is well tolerated. The most common adverse events include hypotension, AF, hypokalemia and tachycardia.

2.2.6.2 Pacemakers

Conduction distubances and bradycardia can be treated with pacemakers. In patients with cardiomyopathy and known risk for severe ventricular arrhythmias, an implantable cardioverter-defibrillator may be used to prevent sudden death. Patients with a widened QRS interval, low LVEF and severe symptoms despite optimal medical treatment benefit from cardiac resynchronization therapy (CRT), CRT with pacemaker, CRT-P, or with defibrillator as CRT-D.

2.2.6.3 Other treatment options

Patients with refractory HF despite adequate medical treatment and treatment for specific cause of HF may be candidates for left ventricular assist devices and heart transplantation.

2.3 Heart failure in patients with aortic stenosis

In patients with AS, AS initially causes concentric LV hypertrophy and HF developes secondarily. To preserve the stroke volume, according to the Laplace equation, an increase in wall thickness in the presence of increased LV pressure normalizes the wall stress. This process leads to LV diastolic dysfunction with an increase in the end-diastolic pressures to achieve a normal end-diastolic volume. Finally, left atrial pressure increases to enable adequate LV filling (Maeder *et al.*, 2018). Therefore, the clinical manifestation of HF in patients with AS is often comparable to that seen in patients with HFpEF. In patients with AS, LVEF<52% in men and <54% in women should be considered to be reduced (Dahl *et al.*, 2019).

2.3.1 Medical therapy for severe AS and HFrEF

Medical therapy recommendation for patients with severe AS and HFrEF follows the HF guidelines. However, medical therapy does not improve the poor outcome: the mortality rates are 58%, 70% and 80% during 1-, 3- and 5-year follow up (Varadarajan *et al.*, 2006; Passeri *et al.*, 2015). Current guidelines recommend intervention over medical therapy for patients with HFrEF and severe AS who are eligible for intervention (Yancy *et al.*, 2013; Baumgartner *et al.*, 2017). Medical therapy is focused on optimizing the cardiac function, fluid balance and other cardiovascular conditions (Steiner *et al.*, 2017).

2.3.2 Surgical treatment for severe AS with HFrEF

SAVR in AS patients with HFrEF is associated with increased perioperative and long-term mortality, when compared to patients with normal LV function (Pai, Varadarajan and Razzouk, 2008). The outcomes are still significantly better than with medical therapy alone: Pai et al. reported 30-day, 1-year, and 5-year survival rates of 91%, 80%, and 58%, respectively, in the surgical cohort, compared to 79%, 47%, and 23% for those who had no AVR ($p < 0.0001$). Perioperative mortality is reported to be 8–21% in patients with AS and HFrEF after SAVR; however, recent studies show better survival after SAVR, possibly owing to an individualized patient selection, modern perioperative treatment and improved cardiac protection (Steiner *et al.*, 2017). Patients with poor flow reserve have the worst prognosis, as discussed

in the review by Steiner et al. 2017. Reduced LVEF significantly increases the operative risk, and is included in the STS Predicted Risk of Mortality (STS-PROM) score and EuroSCORE II risk prediction models. Based on this, most patients with AS and HFrEF are rather referred to TAVR due to increased surgical risk.

In the European guidelines for the management of valvular heart disease, AVR is recommended for AS patients with LVEF <50% as a Class I(C) recommendation. Patients with severe AS and HFrEF have a poor prognosis, with or without AVR, even if asymptomatic (Henkel *et al.*, 2012). Operative treatment should be offered before the onset of HF. The better the postoperative recovery of both systolic and diastolic function is, the better is the patient's long-term survival. In addition, LV recovery prevents later HF.

2.3.3 TAVR for severe AS and HFrEF

TAVR has proven to be a feasible and safe option for patients with AS and HFrEF, even in patients who have been previously denied SAVR (Smith *et al.*, 2011; Hirji *et al.*, 2017). In the PARTNER Cohort B Trial Passeri et al. evaluated patients with LVEF <50%, and the 1-year mortality after TAVR was 34.8% vs. 59.3% in patients treated by optimal medical therapy (Passeri *et al.*, 2015). TAVR is currently considered to be the golden standard of care for very high risk patients with severe AS and HFrEF (Steiner *et al.*, 2017). TAVR has proven to also be feasible in patients with LVEF <20% and is the preferred choice over SAVR for patients with STS/EuroSCORE II >4% and in patients older than 75 years in European valvular guidelines (Baumgartner *et al.*, 2017). Patients with AS and HFrEF are generally not categorized as low-risk patients and, thus, current and oncoming data from trials such as PARTNER 3 and NOTION-2 is expected to remain scarce in this subset of patients.

Clavel et al. reported, that despite a higher operative risk, TAVR is associated with better LVEF recovery than SAVR: LVEF >50% after a 1-year follow up was detected in 58% of TAVR patients, compared to 20% of SAVR patients (Clavel *et al.*, 2010). However, early mortality was similar in both groups. The possible benefits of TAVR over SAVR are unclear for intermediate-risk patients with HFrEF (Reardon *et al.*, 2017; Langer *et al.*, 2019); and the procedure type did not affect LVEF recovery in the PARTNER trial including patients with moderate LV dysfunction (Elmariah *et al.*, 2013). HFrEF is associated with an increased risk of sudden cardiac death and all-cause mortality after TAVR, despite LVEF postprocedural improvement (Steiner *et al.*, 2017). New-onset conduction disturbances and/or the need for a new pacemaker after TAVR are associated with a failure of LVEF recovery after TAVR (Nazif *et al.*, 2014).

2.3.4 Percutaneous balloon aortic valvuloplasty

Percutaneous Balloon aortic valvuloplasty (PBAV) is not indicated as a definitive therapy for AS due to the risks involved and it may also cause or significantly increase the severity of aortic regurgitation (Steiner *et al.*, 2017). PBAV might stabilize the patients hemodynamics to facilitate SAVR or TAVR with a lower risk at a less emergency setting (Theiss *et al.*, 2014; Nagao *et al.*, 2017). These recent studies by Theiss et al. and Nagao et al. suggest that rescue or emergency TAVR is associated with a similar risk profile to PBAV, but offers better procedural outcomes, simultaneously serving as a definite treatment.

3 Aims

1. First, to review the trends and changes in the treatment of severe aortic stenosis in a nationwide setting between 2008–2017. Second, to examine changes in survival and adverse outcomes during the study period.
2. To investigate the influence of recent acute heart failure in survival and adverse outcomes after SAVR or TAVR in patients with severe aortic stenosis.
3. To ascertain the influence of reduced ejection fraction (LVEF≤50%) in survival and adverse outcomes after SAVR or TAVR in patients with severe aortic stenosis.

4 Materials and Methods

4.1 Study design and patient population

4.1.1 The FinnValve registry

The FinnValve registry is a nationwide registry (ClinicalTrials.gov Identifier: NCT03385915), which retrospectively collects data from patients who underwent TAVR or SAVR with a bioprosthesis for severe AS in the five Finnish university hospitals (Helsinki, Kuopio, Oulu, Tampere and Turku) from January 2008 to November 2017. During the study period, all five university hospitals performed both TAVR and SAVR procedures. Data from patients treated in central hospitals were not included to this registry.

The inclusion criteria for this registry were: 1) Severe AS with or without aortic valve regurgitation; 2) patients aged >18 years; 3) primary TAVR or SAVR with a bioprosthesis with or without concomitant coronary revascularization. The exclusion criteria were: 1) any prior TAVR or surgical intervention on the aortic valve; 2) concomitant major cardiac procedure on the ascending aorta and/or other heart valves or structures; 3) transcatheter or surgical procedure for isolated aortic valve regurgitation; 4) acute heart valve endocarditis.

The registry was planned by the main investigators representing both cardiologists and cardiac surgeons from all attending hospitals. Data was collected into an electronic case report form which was filled by clinicians and research nurses. No data from prior institutional datasets contributed to this registry. The FinnValve registry includes a consecutive and unselected series of patients, whose operating code referring to TAVR and/or SAVR with a bioprosthesis were retrieved from institutional administrative registries. The definition criteria of baseline, operative and postoperative variables were prespecified and listed in a table with a similar output of the electronic case report for rapid consultation by the researchers, who were instructed before starting the data collection. Data on mortality was retrieved from the Finnish institute for Health and Welfare. All adverse events except mortality were recorded during the index hospitalization. The postprocedural echocardiographic findings of paravalvular regurgitation were not adjudicated by a core lab and its severity was graded before discharge by the treating physicians. The

follow-up was complete for all patients, but for two patients who were not residing in Finland and whose follow-up was truncated at hospital discharge. The last date of follow-up was December 31, 2018.

Definitions of baseline risk factors

Baseline variables were defined according to the EuroSCORE II criteria. The operative risk of these patients was stratified according to the EuroSCORE II and STS risk scores. Frailty was defined according to the Geriatric Status Scale (GSS) (Rockwood *et al.*, 1999). Coronary artery disease was defined as any stenosis >50% of the main coronary branches. Stroke was defined as a focal or global neurological deficit lasting at least 24 hours with a new brain infarct or hemorrhage detected at neuroimaging, or a neurological deficit resulting in death. Critical preoperative state was defined as ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anesthetic room, preoperative inotropes or intra-aortic balloon pump (IABP) insertion and/or preoperative acute renal failure. Patients with critical preoperative state were included in patients with recent AHF.

Outcome measures

European Coronary Artery Bypass Grafting (E-CABG) bleeding grades 2-3 were defined as a transfusion of more than 4 units of red blood cells and/or (re)sternotomy for excessive bleeding (Biancari *et al.*, 2015). Valve Academic Research Consortium-2 consensus document (VARC-2) major bleeding was defined as overt bleeding, either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring a transfusion of two or three units of whole blood/red blood cells, or causing hospitalization or permanent injury, or requiring surgery (Kappetein *et al.*, 2012). VARC-2 life threatening bleeding was defined as any bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery or an overt source of bleeding with a drop in hemoglobin ≥5.0 g/dL or a transfusion of more than three units of red blood cells or causing death. AKI was defined according to the KDIGO classification criteria, i.e., an increase in serum creatinine ≥1.5 times the baseline level or a serum creatinine increase of ≥26.5 μmol/l and/or de novo renal replacement therapy within seven days after surgery. Stage 3 AKI was defined as any increase in serum creatinine ≥3.0 times the baseline level or serum creatinine increase ≥353.65 μmol/l within seven days after surgery and/or de novo renal replacement therapy within seven days after surgery (Kellum *et al.*, 2012). Stroke was defined according to the VARC-2 definition criteria as any focal or global neurological deficit lasting 24h or longer with a new brain infarct or hemorrhage

detected at neuroimaging, or a neurological deficit resulting in death during the index hospitalization. The length of stay in the intensive care unit was not considered in these analyses as an endpoint because of inter-institutional differences in the organizational program of postoperative care of TAVR patients.

4.1.2 Study I – Ten-year experience with transcatheter and surgical aortic valve replacement in Finland

The primary outcome of this study was 30-day mortality. The secondary outcomes were stroke, postoperative mechanical circulatory support as use of IABP and/or extracorporeal membrane oxygenation (ECMO), conversion to cardiac surgery, coronary artery occlusion, aortic annulus rupture, aortic dissection/rupture, major vascular complication, red blood cell transfusion, severe bleeding, (re)sternotomy for bleeding, moderate-to-severe paravalvular regurgitation, implantation of a permanent pacemaker, severe AKI, AF, postoperative length of stay in the hospital where the index procedure was performed and 2-year survival (including only patients operated from 2008 and 2015, i.e. those with at least 2 years of follow-up).

4.1.3 Study II – Transcatheter and surgical aortic valve replacement in patients with recent acute heart failure

Patients with data on a recent hospitalization for treatment of AHF are the subjects of this study. Patients with an episode of AHF >60 days before the index procedure were excluded from the study, because such a delay to invasive treatment did not show a difference in mortality in our preliminary analyzes compared to no HF. Patients who underwent transapical TAVR were excluded from this analysis because of the invasiveness and suboptimal results of this treatment strategy, when compared to less invasive vascular approaches. Recent AHF was defined as any new-onset or worsening of symptoms and signs of HF requiring hospital admission and rapid escalation of therapy within 60 days prior to TAVR or SAVR. Critical preoperative state at the time of admission for a TAVR or SAVR procedure was considered as a condition comparable to AHF. The primary outcomes of this study were in-hospital and late all-cause mortality. The secondary outcomes were stroke, use of IABP and/or ECMO, E-CABG bleeding grades 2–3, major and life threatening VARC-2 bleeding, sternotomy or resternotomy for bleeding, reoperation for peripheral bleeding, implantation of a permanent pacemaker and AKI.

4.1.4 Study III – Transcatheter and surgical aortic valve replacement in patients with left ventricular dysfunction

LV dysfunction was defined as LVEF≤50%. Reduced LVEF was further divided to subclasses of LVEF 30–50% and LVEF<30% according to EuroScore II criteria. Patients who underwent transapical TAVR were excluded from this analysis because of the invasiveness and suboptimal results of this treatment strategy, when compared to less invasive vascular approaches. The primary outcomes were 30-day, 1-year and 4-year survival. The secondary outcomes were defined similarly with the AHF study. Cardiac death was defined as any death occurring from coronary artery disease, valvular heart disease, heart failure, conduction disturbances, endocarditis, sudden cardiac death or death during the index procedure.

4.2 Ethical considerations and funding

4.2.1 Ethical considerations

This study was approved by the Institutional Review Board of each participating center. No written informed consent was required from the participants.

4.2.2 Funding

Maina Jalava has received grants from The University of Turku Department of Clinical Medicine, The Finnish Foundation for Cardiovascular Research and The Finnish Cultural Foundation.

4.3 Statistical Analysis

4.3.1 Study I

Statistical analysis was performed by using SAS statistical package, version 9.2 (SAS Institute Inc, Cary, NC) and SPSS v. 25.0 statistical software (IBM Corporation, p, USA). Comparative analysis of the TAVR and SAVR cohorts was performed by using the Mann-Whitney U-, the Chi-squared and the Fisher exact tests. Trends over time were plotted and analyzed across the 10-year intervals by using the Mantel-Haenszel linear-by-linear association chi-squared test for trend and linear regression with year categories regressed as an ordinal variable. The long-term survival differences were evaluated by the Kaplan-Meier method with the log-rank test. A $p<0.05$ was set for statistical significance.

4.3.2 Study II

Statistical analysis was performed using SAS statistical package, version 9.2 (SAS Institute Inc, Cary, NC) and SPSS v. 25.0 statistical software (IBM Corporation, New York, USA). Mann-Whitney *U*-test, Fisher's exact test and Chi-square test were used for univariate analysis in the unmatched population. Logistic regression and Cox proportional hazards analyses with backward selection were employed for the risk estimation of 30-day and long-term mortality in patients with and without recent AHF adjusted for multiple baseline covariates: age, gender, anemia (<1.2 g/dL in women, <1.3 g/dL in men), estimated glomerular filtration rate (eGFR), diabetes, stroke, pulmonary disease, extracardiac arteriopathy, LVEF ≤50%, porcelain aorta, AF, frailty GSS grades 2–3, active malignancy, PAP, coronary artery disease, prior PCI, prior cardiac surgery and urgent or emergency operation. These regression analyses were performed separately for the TAVR and SAVR cohorts.

Patients with recent AHF were the subjects of a propensity score matching analysis comparing the outcomes after TAVR or SAVR. The propensity score was estimated by using a non-parsimonious logistic regression model including the above listed covariates. One-to-one propensity score matching was performed by employing the nearest neighbor method and a caliper width of 0.2 of the standard deviation of the logit of the propensity score. To evaluate the balance between the matched groups, the t-test for paired samples for continuous variables, the McNemar test for dichotomous variables and the analysis of the standardized differences after matching were used. Standardized differences lower than 0.10 were considered to be an acceptable imbalance between the treatment groups. To evaluate any difference in the adverse events of propensity score matched pairs the following tests were used: Early outcomes in the propensity score matched cohorts were evaluated by using the t-test for paired samples for continuous variables and the McNemar test for dichotomous variables. Differences in the long-term survival was evaluated by the Kaplan-Meier method with the Klein-Moeschberger stratified log-rank test. All tests were two-sided and $p<0.05$ was set for statistical significance.

4.3.3 Study III

Statistical analysis was performed by using SAS statistical package, version 9.2 (SAS Institute Inc, Cary, NC), SPSS v. 26.0 statistical software (IBM Corporation, New York, USA) and Stata v. 15.0 (SAS Institute Inc., Cary, NC, USA). Continuous variables were summarized as mean and standard deviation and categorical variables as counts and percentages. Normal distribution of continuous variables was assessed with the Shapiro-Wilk's test. In the unmatched main cohort, Chi-squared test, Fisher's exact test and Mann-Whitney *U*-test were used for univariable analysis. The Kaplan-Meier method was used to estimate late survival. Outcomes were adjusted

in logistic regression and Cox proportional hazards models, using the enter mode and including the following covariates: age, gender, BMI, eGFR, LVEF≤50%, diabetes, dialysis, prior stroke, recent myocardial infarction, pulmonary disease, oxygen therapy, AF, extracardiac arteriopathy, frailty, recent AHF, systolic pulmonary artery pressures, NYHA class IV symptoms, urgency of the procedure, severe coronary artery disease, left main disease, number of diseased coronary arteries, prior cardiac surgery, prior PCI, planned concomitant revascularization, active malignancy, prior pacemaker, mitral regurgitation (mild, moderate and severe individually) and anemia. These regression analyses were performed separately for the unmatched TAVR and SAVR cohorts.

Patients with LVEF≤50% were the subjects of a propensity score matching analysis comparing the outcomes after TAVR and SAVR. The propensity score was estimated using a non-parsimonious logistic regression model including the covariates as follows: age, gender, BMI, anemia, eGFR, prior dialysis, diabetes, stroke and transient ischemic attack, pulmonary disease, oxygen therapy, extracardiac arteriopathy, porcelain aorta, AF, frailty, active malignancy, LVEF classes, systolic pulmonary artery pressure, mitral regurgitation, coronary artery disease, left main coronary stenosis, number of diseased coronary arteries, prior pacemaker, prior PCI, prior cardiac surgery, recent myocardial infarction, recent AHF, NYHA class 4 symptoms, urgency, planned concomitant revascularization, EuroSCORE II and STS scores. One-to-one propensity score matching was performed employing the nearest neighbor method and a caliper width of 0.2. To evaluate the balance between the matched groups, the t-test for paired samples for continuous variables and the McNemar test for dichotomous were used. Standardized differences <0.10 were considered an acceptable imbalance between the groups. Baseline characteristics and early outcomes in the propensity score matched cohorts were evaluated using the paired t-test and the McNemar test. Differences in the long-term survival of matched pairs was evaluated by the Kaplan-Meier method. Since the proportional hazard assumption did not hold as assessed graphically and based on Schoenfeld's residuals (global test: p=0.080), the impact of treatment method on 4-year survival in propensity score-matched pairs was estimated using the restricted mean survival time (RMST) method. All tests were two-sided and p<0.05 was set for statistical significance.

5 Results

5.1 Ten-year experience with transcatheter and surgical aortic valve replacement in Finland

The FinnValve registry includes data from 6463 consecutive patients who underwent primary TAVR and SAVR with a bioprotheses for severe AS. TAVR was implanted to 2130 patients (33%) and SAVR to 4333 (67%) patients (Fig. 4). Among the SAVR cohort, 4308 (99.5%) were stented valve prostheses and sutureless valves were implanted for 126 (2.9%) patients. Ministernotomy was made for 3.4% of patients undergoing SAVR and right thoracotomy only occasionally. Other than transfemoral TAVR was performed in 288 patients, including transapical TAVR for 196 patients (9.2%). Other less common approaches included ministernotomy (2.5%), minithoracotomy (0.7%) and subclavian artery (0.6%). The clinical characteristics of all patients included in the database are presented in Table 3.

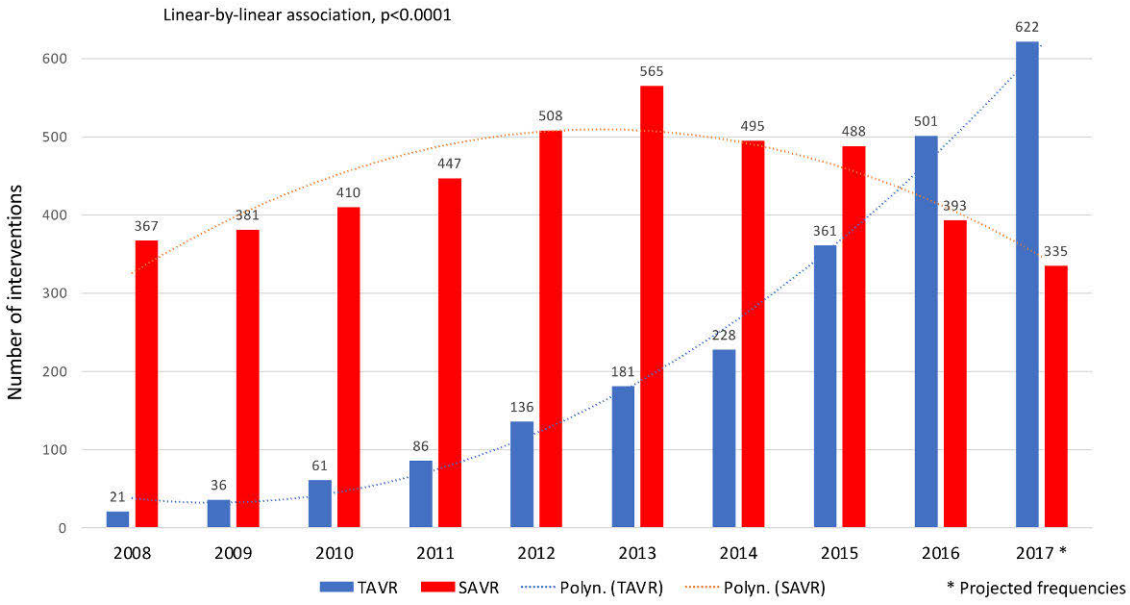

Figure 4. Annual SAVR and TAVR intervention numbers.

Table 3. Characteristics of patients who underwent surgical or transcatheter aortic valve replacement for severe aortic stenosis.

Characteristics	SAVR 4333 patients	TAVR 2130 patients	p-value
Age, years	75.1 ± 6.5	81.2 ± 6.6	<0.0001
Female	2026 (46.8)	1172 (55.0)	<0.0001
Body mass index, kg/m^2	27.7 ± 4.8	27.1 ± 4.8	<0.0001
Hemoglobin, mg/L	132 ± 15	124 ± 4.8	<0.0001
eGFR, mL/min/1.73 m^2	76±22	65 ± 23	<0.0001
Active malignancy	60 (1.4)	84 (3.9)	<0.0001
Diabetes	1154 (26.6)	605 (28.4)	0.133
Stroke	299 (6.9)	247 (11.6)	<0.0001
Pulmonary disease	642 (14.8)	456 (21.4)	<0.0001
Oxygen therapy	16 (0.4)	14 (0.7)	0.109
Frailty GSS grades 2–3	107 (2.5)	318 (14.9)	<0.0001
Extracardiac arteriopathy	539 (12.4)	412 (19.3)	<0.0001
LVEF≤50%	909 (21.0)	596 (28.0)	<0.0001
Atrial fibrillation*	955 (22.0)	932 (43.8)	<0.0001
NYHA 4	453 (10.5)	244 (11.5)	0.223
SPAP			<0.0001
31–55 mmHg	1526 (35.2)	853 (40.0)	
>55 mmHg	305 (7.0)	286 (13.4)	
Moderate-severe mitral valve regurgitation	256 (6.5)	288 (14.3)	<0.0001
Porcelain aorta	15 (0.3)	124 (5.8)	<0.0001
Recent myocardial infarction	312 (7.2)	49 (2.3)	<0.0001
Recent acute heart failure	501 (11.6)	253 (11.9)	0.710
Coronary artery disease	1970 (45.5)	603 (28.3)	<0.0001
Prior PCI	405 (9.3)	467 (21.9)	<0.0001
Prior cardiac surgery	97 (2.2)	431 (20.2)	<0.0001
Permanent pacemaker	174 (4.0)	208 (9.8)	<0.0001
Emergency procedure	59 (1.4)	6 (0.3)	<0.0001
Bicuspid aortic valve	920 (21.0)	114 (5.4)	<0.0001
Concomitant PCI/CABG	1835 (42.3)	119 (5.6)	<0.0001
EuroSCORE II	4.2 ± 5.5	7.2 ± 7.4	<0.0001
STS Score	3.0 ± 2.9	4.6 ± 3.3	<0.0001

Continuous variables are reported as means ± standard deviation and categorical variables as counts and percentages. Clinical variables are according to the EuroSCORE II definition criteria. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; eGFR, glomerular filtration estimated according to the MDRD equation; LVEF, left ventricular ejection fraction; Frailty, GSS grades 2–3; SPAP, systolic pulmonary artery pressure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.
*Any prior atrial fibrillation

During the study period, the mean STS preoperative risk score declined from 6.5 ± 5.7% to 4.1±3.1% in patients treated by TAVR (p<0.001) and from 3.1±2.3 to 2.2 ±

1.5% in patients treated by SAVR (p<0.001)(Tab. 4). However, the overall database STS risk score did not diminish, 3.3% in 2008 and 3.5% in 2017, because of the continuously increasing TAVR numbers. The 30-day mortality rates decreased from 4.8% to 1.2% (p=0.011) following TAVR and from 4.1% to 1.8% (p=0.048) following SAVR during the study period (Tab. 4). Complication rates declined among both procedure types. A significant reduction in paravalvular regurgitation was seen in TAVR patients and a reduction in severe AKI rates was detected among both SAVR and TAVR patients. Also, the need for red blood cell transfusion and reoperations due to bleeding decreased significantly among SAVR and TAVR patients. The mean length of in-hospital stay declined in both cohorts. The outcomes of all patients included in the database are presented in Table 5.

Table 4. Changes in the procedure numbers and outcomes in patients undergoing surgical or transcatheter aortic valve replacement from 2008 to 2017.

Outcomes	SAVR				TAVR			
	2008	2013	2017	p-value	2008	2013	2017	p-value
Procedures, n	367	565	335		21	181	633	
STS Score	3.1	3.2	2.2		6.5	5.0	4.1	
30-day death	4.1	3.7	1.8	0.048	4.8	5.5	1.2	0.011
2-year survival	87.2	91.5	91.6*	0.006	71.4	79.6	83.9*	<0.0001
KDIGO AKI Stage 3	3.3	3.2	1.1	0.012	9.5	1.1	0.2	<0.0001
Stroke	4.1	4.4	2.9	0.828	5.6**	3.3	1.7	0.190
Moderate to severe paravalvular regurgitation	0.8	1.6	0.4	0.827	9.5	7.2	2.3	<0.0001
Hospital stay, days	9.0	8.3	7.8	<0.0001	10.4	6.7	3.7	<0.0001
Severe bleeding***	34.2	23.4	15.7	<0.0001	15.0	5.6	4.1	<0.0001

Continuous variables are reported as means and categorical variables as count and percentages. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; Number of procedures Linear-by-linear association p<0.0001. KDIGO AKI, Kidney Disease: Improving Global Outcomes Acute Kidney Injury.

*2-year survival detected in 2015.

**Outcome detected in 2009, because 0 strokes were reported in 2008.

***Severe bleeding, transfusion of more than 4 units of red blood cells and/or operation for bleeding, according to E-CABG bleeding grades 2–3.

Table 5. Outcomes of patients undergoing surgical or transcatheter aortic valve replacement.

Outcomes	SAVR 4333 patients	TAVR 2130 patients	p-value
30-day death	158 (3.6)	62(2.9)	0.125
Stroke	165 (3.8)	53 (2.5)	0.006
IABP/ECMO	80 (1.8)	4 (0.8)	<0.0001
Conversion to cardiac surgery	-	13 (0.6)	-
Coronary ostium occlusion	10 (0.2)	8 (0.4)	0.320
Aortic annulus rupture	8 (0.2)	10 (0.5)	0.047
Aortic dissection/rupture	31 (0.7)	17 (0.8)	0.716
Major vascular complication	69 (1.6)	191 (9.0)	<0.0001
RBC transfusion	3010 (70.4)	403 (19.2)	<0.0001
units	3.0 ± 3.8	0.6 ± 1.7	<0.0001
>4 units	926 (21.7)	76 (3.6)	<0.0001
(Re)sternotomy for bleeding	351 (8.1)	30 (1.4)	0.109
Severe bleeding*	1033 (24.1)	116 (5.5)	<0.0001
VARC-2 bleeding events			<0.0001
Major	1564 (36.2)	567 (26.7)	
Life-threatening	2597 (60.0)	167 (7.9)	
KDIGO AKI Stage 3	127 (3.0)	21 (1.0)	<0.0001
Dialysis	113 (2.6)	30 (1.4)	0.002
Moderate to severe paravalvular regurgitation	29 (0.7)	79 (3.7)	<0.0001
Atrial fibrillation**	1645 (48.7)	160 (13.4)	<0.0001
Permanent pacemaker	170 (3.9)	185 (8.7)	<0.0001
In-Hospital stay, days	8.3 ± 6.4	5.5 ± 5.0	<0.0001

Continuous variables are reported as means ± standard deviation. Categorical variables as counts and percentages. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; RBC, red blood cells; VARC-2, Valve Academic Research Consortium- 2; KDIGO AKI, Kidney Disease: Improving Global Outcomes Acute Kidney Injury.
*Severe bleeding, transfusion of more than 4 units of red blood cells and/or operation for bleeding.
**Atrial fibrillation, patients with preoperative atrial fibrillation are excluded.

5.2 Prognostic impact of recent acute heart failure in patients undergoing aortic valve replacement for severe aortic stenosis

In the 6463 patients included in the FinnValve registry, there was a clear difference in survival between patients with and without prior AHF (Tab. 6). Patients with an AHF hospitalization within 60 days prior to the procedure had a markedly increased risk of early death, when compared to the outcomes of those patients without a history of AHF. Total of 6096 patients were available for the present analysis after excluding the patients who underwent transapical TAVR and those without data on the timing of hospitalization for AHF.

Table 6. The impact of the timing of the hospitalization for acute heart failure to mortality after aortic valve replacement

Prior AHF	No AHF	0–30 days	31–60 days	61–90 days	>90 days	p-value
30-day mortality, %	2.7	8.2	5.2	2.1	2.8	<0.0001

AHF, Acute heart failure.

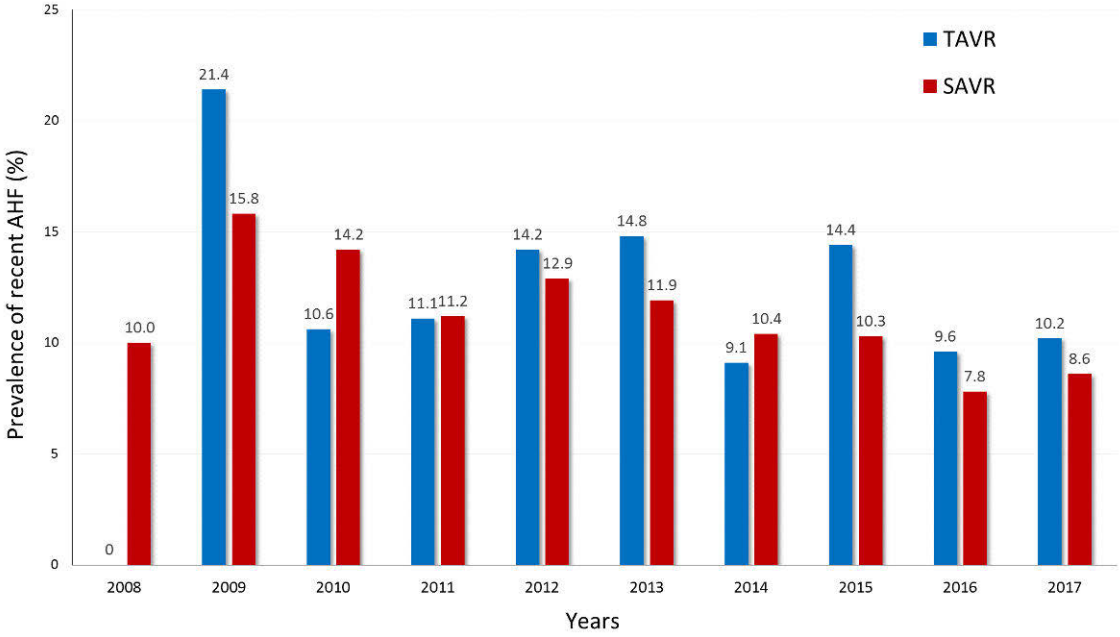

Figure 5. The annual proportion of patients with recent acute heart failure undergoing surgical or transcatheter aortic valve replacement.

Characteristics and outcomes of the patients with and without recent AHF

The prevalence of recent AHF was 11.4% (484 patients) in the SAVR cohort and 11.3% (210 patients) in the TAVR cohort (Fig. 5). In the entire cohort, patients with recent AHF had an increased operative risk, compared to patients with no AHF in both TAVR (STS score 8.1±6.8 vs. 4.0±2.2%, p<0.0001) and SAVR cohort (STS score 7.0±5.8 vs. 2.6±3.2%, p<0.0001). Preliminary analysis of data from patients with recent acute heart failure showed that the gradient of AS and the presence of aortic regurgitation were not associated with adverse outcomes.

In the SAVR cohort, patients with recent AHF had higher rates of in-hospital mortality, mechanical circulatory support with IABP or ECMO, severe bleeding and AKI. Also, recent AHF was associated with a lower 30-day (crude rates, 91.3 vs. 97.0%; adjusted for multiple covariates OR 1.801, 95%CI 1.125–2.882) and 5-year

survival rates (crude rates, 62.5 vs. 81.0%; adjusted for multiple covariates HR 1.482, 95%CI 1.207–1.821) when compared to patients without AHF (Tab. 7) (Fig. 6).

In the TAVR cohort, patients with recent AHF had higher rates of postoperative AKI and a similar frequency of other adverse events. When adjusted for multiple covariates, recent AHF was associated with similar 30-day (crudes rates, 95.2 vs. 97.9%; adjusted for multiple covariates OR 2.028, 95%CI 0.908–4.529) and 5-year survival rates (crude rates, 43.5 vs. 58.5%; adjusted for multiple covariates HR 1.530, 95%CI 1.185–1.976) when compared to patients without AHF (Tab. 7) (Fig. 7).

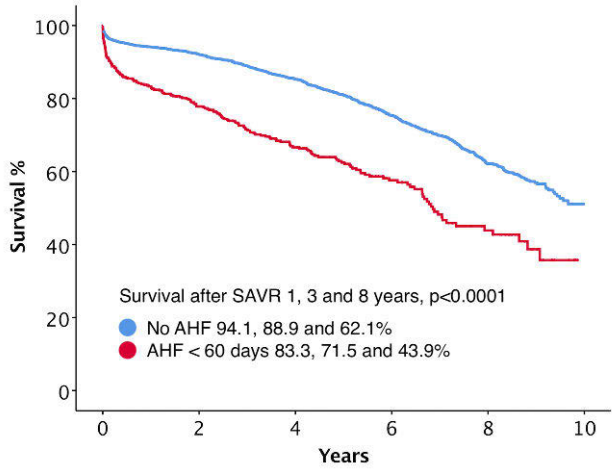

Figure 6. Survival in patients with recent acute heart failure (AHF) after surgical aortic valve replacement (SAVR) vs. no recent AHF.

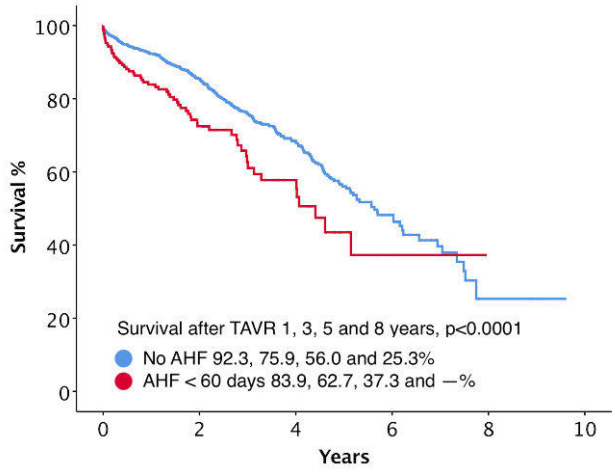

Figure 7. Survival in patients with recent acute heart failure (AHF) after transcatheter aortic valve replacement (TAVR) vs. no recent AHF.

Table 7. Outcomes of unmatched patients with and without recent acute heart failure undergoing surgical or transcatheter aortic valve replacement.

	SAVR				TAVR			
Outcomes	**No AHF 3757 pts**	**AHF 484 pts**	**Univariate analysis p-value**	**Multivariate analysis Risk estimates, 95%CI**	**No AHF 1645 pts**	**AHF 210 pts**	**Univariate analysis p-value**	**Multivariate analysis Risk estimates, 95%CI**
Survival, %			<0.0001				<0.0001	
30-day	97.0	91.3		1.801, 1.125–2.882	97.9	95.2		2.028, 0.908–4.529
1-year	94.1	83.5			92.3	83.9		
3-year	89.0	71.5			75.9	62.7		
5-year	81.2	64.0			58.5	45.3		
Stroke	139 (3.7)	22 (4.5)	0.359	0.840, 0.484–1.456	36 (2.2)	8 (3.8)	0.146	1.849, 0.781–4.377
Postop. ECMO and/or IABP	49 (1.3)	27 (5.6)	<0.0001	2.213, 1.199–4.084	1 (0.1)	0 (0.0)	0.887	-
RBC, units transfused	2.7±3.6	5.0±5.1	<0.0001	1.223, 0.826–1.620	0.5±1.4	0.7±1.6	0.020	0.169, -0.050–0.387
Severe bleeding*	775 (20.9)	225 (46.9)	<0.0001	2.148, 1.682–2.743	69 (4.3)	15 (7.2)	0.056	1.801, 0.950–3.416
VARC-2 bleeding			<0.0001	0.453, 0.213–0.694			0.617	0.382, 0.056–0.709
Major	1402 (37.4)	133 (27.7)			402 (24.5)	56 (26.8)		
Life-threatening	2204 (58.7)	333 (69.2)			101 (6.2)	15 (7.2)		
(Re)sternotomy for bleeding	289 (7.7)	50 (10.3)	0.044	1.217, 0.828–1.787	8 (0.5)	3 (1.4)	0.119	4.191, 0.932–18.838
KDIGO AKI			<0.0001	0.866, 0.360–1.372			<0.0001	0.597, 0.346–0.848
Stage 2	98 (2.6)	29 (6.1)			18 (1.1)	3 (1.5)		
Stage 3	90 (2.4)	30 (6.4)			7 (0.4)	5 (2.5)		
Permanent pacemaker	147 (3.9)	16 (3.3)	0.513	0.856, 0.469–1.562	157 (9.5)	16 (7.6)	0.366	0.808, 0.458–1.423
Moderate to severe paravalvular regurgitation	22 (0.6)	5 (1.0)	0.244	2.555, 0.763–8.548	60 (3.6)	7 (3.3)	0.818	1.073, 0.460–2.507
Hospital stay, days	8.0±5.8	10.7±9.3	<0.0001	2.085, 1.391–2.779	5.0±4.2	6.5±6.0	<0.0001	1.447, 0.769–2.126

Continuous variables are reported as means ± standard deviation, categorical variables as counts and percentages, and clinical variables according to the EuroSCORE II definition criteria. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; AHF, acute heat failure; KDIGO, Kidney Disease: Improving Global Outcomes; ECMO, extracorporeal membranous oxygenation; IABP, intra-aortic balloon pump; RBC, red blood cell units; VARC, Valve Academic Research Consortium; Risk estimates are odds ratios and coefficients with their 95% confidence interval (CI).
*Severe bleeding, Transfusion of >4 RBC units and/or any operation for bleeding, according to E-CABG bleeding grades 2–3.

Comparison of characteristics and outcomes of patients with recent acute heart failure

Propensity score matching resulted in 130 pairs with similar baseline characteristics (Tab 8). Among these matched pairs, SAVR patients had an increased risk of bleeding complications and AKI when compared to TAVR. The risk of postoperative stroke, need of mechanical circulatory support and 30-day mortality rates (5.4 vs. 3.9%, p=0.527) were not significantly different between the study cohorts. After a mean follow-up of 2.9±2.5 years, the 1-year and 3-year survival rates in the TAVR cohort were 89.6% and 66.6%, and 83.8% and 68.6% in the SAVR cohort, respectively (p=0.166) (Tab. 9).

Table 8. Characteristics of propensity score matched patients with recent acute heart failure undergoing transcatheter or surgical aortic valve replacement.

Characteristics	SAVR 130 pts	TAVR 130 pts	Standardized difference	p-value
Age, years	79.7±5.7	79.5±6.9	0.027	0.808
Female	61 (46.9)	64 (49.2)	0.046	0.691
Anemia	84 (64.6)	82 (63.1)	0.032	0.796
eGFR, ml/min/1.73m2	64±21	63±27	0.011	0.928
Diabetes	42 (32.3)	46 (35.4)	0.065	0.564
Stroke	11 (8.5)	12 (9.2)	0.027	0.819
Pulmonary disease	24 (18.5)	27 (20.8)	0.058	0.639
Extracardiac arteriopathy	19 (14.6)	18 (13.8)	0.022	0.862
LVEF ≤50%	74 (56.9)	78 (60.0)	0.062	0.600
Atrial fibrillation	69 (53.1)	68 (52.3)	0.015	0.898
Frailty	10 (7.7)	11 (8.5)	0.028	0.796
Active malignancy	3 (2.3)	5 (3.8)	0.089	0.480
SPAP			0.038	0.991
31–55 mmHg	72 (55.4)	73 (56.2)		
>55 mmHg	31 (23.8)	29 (22.3)		
Coronary artery disease	52 (40.0)	52 (40.0)	0.000	1.000
Prior cardiac surgery	8 (6.2)	12 (9.2)	0.116	0.314
Recent myocardial infarction	25 (19.2)	28 (21.5)	0.057	0.655
Recent balloon valvuloplasty	4 (3.1)	11 (8.5)	0.232	0.052
Urgency of the procedure			0.016	0.992
Urgent	71 (54.6)	72 (55.4)		
Emergency	4 (3.1)	4 (3.1)		
Planned concomitant revascularization	47 (36.2)	11 (8.5)	0.705	<0.0001
Critical preoperative state	20 (15.4)	20 (15.4)	0.000	1.000
EuroSCORE II, %	12.1±10.7	12.8±12.9	0.058	0.635
STS score, %	7.5±5.9	7.9±6.2	0.066	0.591

Continuous variables are reported as means±standard and categorical variables as counts and percentages. Clinical variables were defined according to the EuroSCORE II definition criteria. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; BMI, body mass index; eGFR, glomerular filtration estimated according to the MDRD equation; LVEF, left ventricular ejection fraction; Frailty, GSS grades 2–3; SPAP, systolic pulmonary artery pressure; PCI, percutaneous coronary intervention; Recent AHF, hospitalization for acute heat failure within 60 days; NYHA, New York Heart Association.

Table 9. Outcomes of propensity score matched patients with recent acute heart failure undergoing transcatheter and surgical aortic valve replacement.

Outcomes	SAVR 130 pts	TAVR 130 pts	p-value
Survival, %			0.662
30-day	94.6	96.1	0.527
1-year	83.8	89.6	
3-year	68.6	66.6	
Stroke	6 (4.6)	4 (3.1)	0.480
Post op ECMO and/or IABP	2 (1.5)	0	1.000
RBC units transfused	5.0±4.1	0.7±1.7	<0.0001
Severe bleeding*	67 (51.9)	5 (3.9)	<0.0001
VARC-2 bleeding grades			<0.0001
Major bleeding	41 (31.8)	35 (27.1)	
Life-threatening bleeding	84 (65.1)	9 (7.0)	
(Re)sternotomy for bleeding	12 (9.2)	1 (0.8)	0.002
KDIGO acute kidney injury	43 (35.8)	14 (11.7)	<0.0001
Stage 2	7 (5.8)	2 (1.7)	
Stage 3	7 (5.8)	3 (2.5)	
Moderate to severe paravalvular regurgitation	1 (0.8)	3 (2.3)	0.622
Permanent pacemaker	6 (4.6)	12 (9.2)	0.157
Hospital stay, mean (days)	10.7±7.8	6.8±5.6	<0.0001

Continuous variables are reported as means ± standard deviation, categorical variables as counts and percentages and clinical variables according to the EuroSCORE II definition criteria. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; KDIGO, Kidney Disease: Improving Global Outcomes; ECMO, extracorporeal membranous oxygenation; IABP, intra-aortic balloon pump; RBC, red blood cell units; VARC, Valve Academic Research Consortium; *Severe bleeding, Transfusion of >4 RBC units and/or any operation for bleeding, according to E-CABG bleeding grades 2–3

5.3 The impact of reduced left ventricular ejection fraction in patients undergoing aortic valve replacement for severe aortic stenosis

After excluding patients who underwent transapical TAVR and those without data on the LVEF and sPAP, 5854 patients from the FinnValve registry were available for the present analysis. The prevalence of LVEF ≤50% was 20.8% (876 patients) in the SAVR cohort and 27.7% (452 patients) in the TAVR cohort. In 2008, only four (4.9%) patients with LVEF ≤50% were treated with TAVR. TAVR became the most common procedure for AS in 2016 (Fig. 8). The mean length of follow-up was 2.9±1.8 years after TAVR and 4.4±2.9 years after SAVR. Patients with LVEF ≤50% were the subjects of propensity score matching analyses.

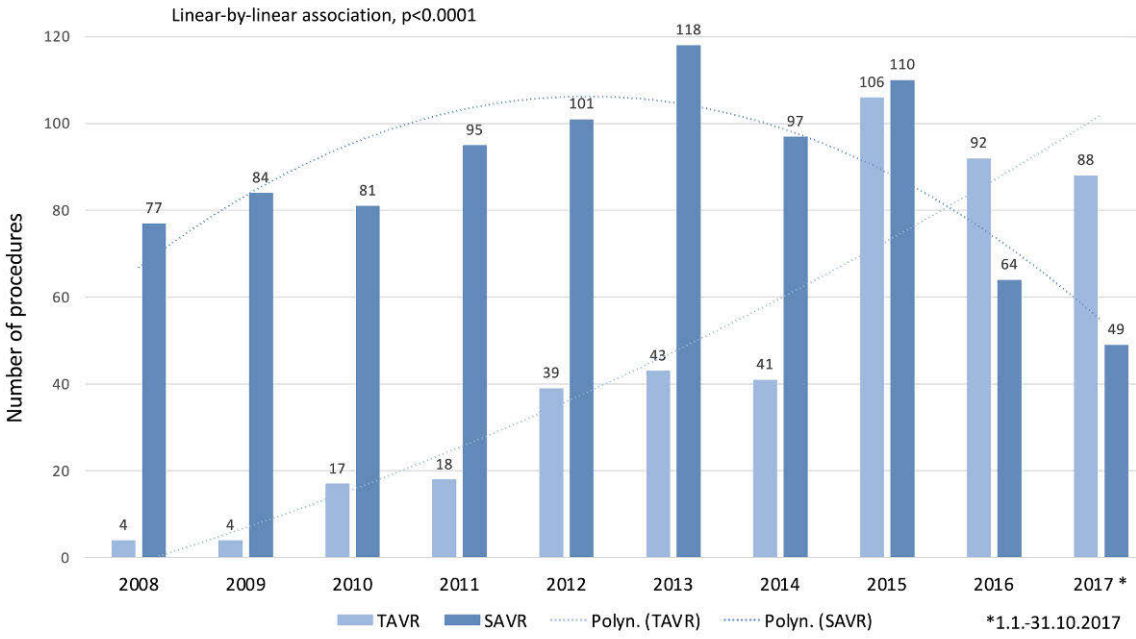

Figure 8. Annual TAVR and SAVR procedure numbers on patients with LVEF≤50%.

In the entire cohort, LVEF≤50% was associated with decreased intermediate survival (adjusted HR 1.215, 95%CI 1.067–1.385). However, when adjusted for baseline variables, LVEF≤50% was not associated with increased 30-day mortality after SAVR (OR 0.999, 95%CI 0.647–1.540, p=1.000) or TAVR (OR 1.171, 95%CI 0.508–2.698, p=0.71). The risk of death at intermediate follow-up was increased after SAVR (HR 1.238, 95%CI 1.060–1.445, p=0.007), but not after TAVR (HR 1.080, 95%CI 0.840–1.388, p=0.548). The outcomes of the entire cohort are summarized in Table 10. There was no difference in baseline LVEF levels between these procedures. Furthermore, the degree of reduction in LVEF did not affect survival in patients with LVEF≤50%

Table 10. Outcomes of patients with LVEF>50% and LVEF≤50% undergoing transcatheter and surgical aortic valve replacement.

Outcomes	SAVR			TAVR		
	LVEF>50% 3344 pts	LVEF≤50% 876 pts	p-value	LVEF>50% 1182 pts	LVEF≤50% 452 pts	p-value
Survival, %						
30-day	97.0	94.1	<0.0001	98.1	96.5	<0.0001
1-year	94.4	86.9		92.9	86.7	
4-year	85.2	74.5		69.8	62.3	
Atrial fibrillation*	1863 (55.7)	532 (60.7)	0.008	452 (38.2)	216 (47.8)	<0.0001
Stroke	121 (3.6)	38 (4.3)	0.319	27 (2.3)	11 (2.4)	0.858
Postop. ECMO and/ or IABP	37 (1.1)	38 (4.3)	<0.0001	1 (0.1)	0 (0.0)	1.000
Vascular complication	46 (1.4)	20 (2.3)	0.054	30 (2.5)	13 (2.9)	0.517
RBC, units transfused	2.8±3.7	3.5±4.2	<0.0001	0.5±1.6	0.5±1.3	0.731
>4 units transfused	652 (19.8)	246 (28.4)	<0.0001	37 (3.2)	13 (2.9)	0.816
Severe bleeding**	739 (22.4)	265 (30.6)	<0.0001	39 (3.3)	16 (3.6)	0.781
Resternotomy for bleeding	266 (8.0)	72 (8.2)	0.797	6 (0.5)	4 (0.9)	0.477
KDIGO AKI			<0.0001			0.118
Stage 2	81 (2.4)	42 (4.9)		14 (1.2)	8 (1.8)	
Stage 3	87 (2.6)	33 (3.8)		6 (0.5)	7 (1.6)	
Dialysis			0.115			0.009
Temporary	58 (1.7)	21 (2.4)		4 (0.3)	8 (1.8)	
Permanent	18 (0.5)	9 (1.0)		8 (0.7)	2 (0.4)	
Permanent pacemaker	131 (3.9)	35 (4.0)	0.916	116 (9.8)	42 (9.3)	0.760
Paravalvular regurgitation			0.085			0.239
Mild	166 (5.0)	50 (5.7)		274 (23.2)	90 (19.9)	
Moderate	18 (0.5)	1 (0.1)		49 (4.1)	20 (4.4)	
Severe	5 (0.1)	4 (0.5)		1 (0.1)	2 (0.4)	
Hospital stay, days	8.1±6.2	9.1±7.0	<0.0001	5.4±4.6	5.5±4.5	0.123

Continuous variables are reported as means ± standard deviation and categorical variables as counts and percentages. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; LVEF, left ventricular ejection fraction; ECMO, extracorporeal membranous oxygenation; IABP, intra-aortic balloon pump; Vascular complication, Major peripheral vascular complication; RBC, red blood cell; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury

*Any postoperative atrial fibrillation during index hospitalization

**Severe bleeding, Transfusion of >4 RBC units and/or any operation for bleeding, according to E-CABG bleeding grades 2–3.

Comparison of characteristics and outcomes of patients with LVEF ≤50%

Patients with LVEF ≤50% were the subjects of propensity score matching analyses resulting in 255 pairs. Planned concomitant coronary artery revascularization was more common within SAVR patients than TAVR patients (29.4 vs. 5.1%, p<0.0001), despite similar prevalence (SAVR 36.5% vs. TAVR 38.4%) and severity of coronary artery disease. Mean aortic valvular gradient was 46±16 mmHg in TAVR patients and 46±14mmHg in SAVR patients (p=0.848). Characteristics of propensity score matched patients with LVEF ≤50% are presented in Table 11.

Table 11. Characteristics of propensity score matched patients with LVEF≤50% undergoing transcatheter and surgical aortic valve replacement.

Characteristics	SAVR 255 pts	TAVR 255 pts	Standardized difference	p-value
Age, years	79.8±5.0	79.2±7.3	0.037	0.690
Female	111 (43.5)	106 (41.6)	0.040	0.729
BMI, kg/m^2	26.5±4.6	26.7±5.0	0.036	0.755
Anemia	137 (53.7)	132 (51.8)	0.039	0.718
eGFR, ml/min/1.73m2	65.3±20.7	64.6±23.8	0.034	0.770
Dialysis	3 (1.2)	3 (1.2)	0.000	1.000
Diabetes	69 (27.1)	73 (28.6)	0.035	0.762
Stroke	26 (10.2)	28 (11.0)	0.025	0.888
Pulmonary disease	60 (23.5)	58 (22.7)	0.019	0.920
Oxygen therapy	1 (0.4)	1 (0.4)	0.000	1.000
Extracardiac arteriopathy	47 (18.4)	40 (15.7)	0.073	0.488
Porcelain aorta	3 (1.2)	4 (1.6)	0.034	1.000
Atrial fibrillation	117 (45.9)	113 (44.3)	0.031	0.794
Frailty	21 (8.2)	26 (10.2)	0.068	0.542
Active malignancy	7 (2.7)	9 (3.5)	0.045	0.804
ProBNP, ng/l	8985±10700	8068±9584	0.090	0.588
Aortic valve area, cm^2	0.62±0.19	0.68±0.18	0.310	0.002
Aortic valve gradient, mmHg				
Mean	46±14	46±16	0.125	0.848
Peak	77±22	74±23	0.018	0.160
Mitral regurgitation			0.086	0.459
Moderate	47 (18.4)	45 (17.6)		
Severe	1 (0.4)	1 (0.4)		
SPAP, mmHg			0.062	0.991
31–55	134 (52.5)	128 (50.2)		
>55	53 (20.8)	52 (20.4)		
Coronary artery disease	93 (36.5)	98 (38.4)	0.040	1.000
Left main stenosis	6 (2.4)	8 (3.1)	0.048	0.791
Number of diseased vessels	0.5±0.8	0.6±0.9	0.064	0.317
Prior pacemaker	24 (9.4)	24 (9.4)	0.000	1.000
Prior PCI	47 (18.4)	42 (16.5)	0.052	0.712
Prior cardiac surgery	22 (8.6)	21 (8.2)	0.014	1.000
Recent myocardial infarction	15 (5.9)	17 (6.7)	0.033	0.850
Recent AHF	78 (30.6)	74 (29.0)	0.034	0.782
NYHA class IV	60 (23.5)	65 (25.5)	0.046	0.707
Urgency of the procedure			0.040	0.992
Urgent	49 (19.2)	49 (19.2)		
Emergency	2 (0.8)	3 (1.2)		
Planned concomitant revascularization	75 (29.4)	13 (5.1)	0.678	<0.0001
EuroSCORE II, %	8.7±7.9	9.3±8.9	0.076	0.416
STS score, %	4.8±3.9	5.1±4.5	0.052	0.668

Continuous variables are reported as means±standard and categorical variables as counts and percentages. Clinical variables were defined according to the EuroSCORE II definition criteria. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; BMI, body mass index; eGFR, glomerular filtration estimated according to the MDRD equation; LVEF, left ventricular ejection fraction; Frailty, GSS grades 2–3; SPAP, systolic pulmonary artery pressure; PCI, percutaneous coronary intervention; Recent AHF, hospitalization for acute heat failure within 60 days; NYHA, New York Heart Association.

Among the matched cohorts, SAVR patients had increased rates of severe bleeding and need for blood transfusions, AKI, need of mechanical circulatory support and prolonged hospital stay compared to TAVR. The risk for permanent pacemaker implantation was higher after TAVR. The incidence of postoperative AF was particularly high after SAVR (SAVR 73.7% vs. TAVR 41.6%). Thirty-day mortality was higher in the SAVR cohort. One-year and 4-year survival in the TAVR cohort were 87.5% and 65.9% and in the SAVR cohort 83.9% and 69.6% (RMST ratio, 1.002, 95%CI 0.929–1.080, p=0.964) (Fig. 9) (Tab. 11). During the first 4 years after intervention, the cause of death was of cardiac nature in 69.1% of patients in the SAVR cohort and 51.7% in the TAVR cohort (p=0.043).

Table 11. Outcomes in propensity score matched patients with LVEF≤50% undergoing SAVR or TAVR.

Outcomes	SAVR 255 pts	TAVR 255 pts	p-value
Survival, %			
30-day	92.2	96.9	0.038
1-year	84.2	87.7	0.649
4-year	69.6	65.9	0.964
Atrial fibrillation*	188 (73.7)	106 (41.6)	<0.0001
Stroke	12 (4.7)	5 (2.0)	0.143
Postop. ECMO and/or IABP	10 (3.9)	0 (0.0)	0.002
Coronary artery occlusion	0 (0.0)	1 (0.4)	1.000
Aortic damage	3 (1.2)	1 (0.4)	<0.0001
Vascular complication	4 (1.6)	35 (13.7)	<0.0001
RBC, units transfused	3.6±3.6	0.5±1.2	<0.0001
Severe bleeding**	77 (30.6)	7 (2.8)	<0.0001
Sternotomy for bleeding	18 (7.1)	3 (1.2)	0.001
KDIGO AKI			<0.0001
Stage 2	12 (4.8)	4 (1.6)	
Stage 3	6 (2.4)	2 (0.8)	
Dialysis	7 (2.7)	2 (0.8)	0.180
Paravalvular regurgitation			0.622
Mild	19 (7.5)	51 (20.0)	
Moderate	0 (0.0)	11 (4.3)	
Severe	1 (0.4)	1 (0.4)	
Permanent pacemaker	9 (3.5)	24 (9.4)	0.009
Hospital stay, days	9.3±6.5	5.4±4.0	<0.0001

Continuous variables are reported as means ± standard deviation and categorical variables as counts and percentages. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; Vascular complication, Major peripheral vascular complication; RBC, red blood cells; E-CABG bleeding grades 2–3, RBC >4 units transfused and/or resternotomy for bleeding; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury.

*Any postoperative atrial fibrillation during index hospitalization.

**Severe bleeding, transfusion of more than 4 units of red blood cells and/or operation for bleeding.

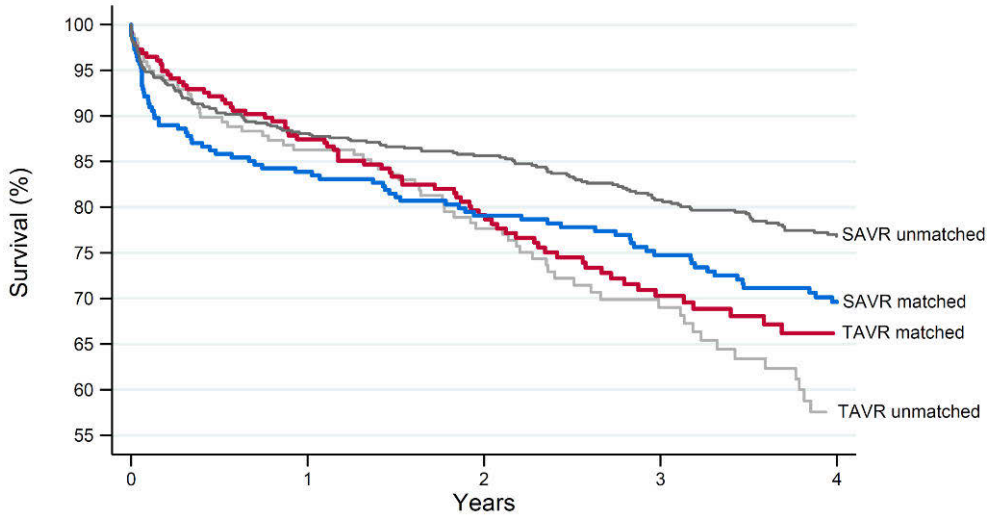

Figure 9. Survival after transcatheter (TAVR) and surgical aortic valve replacement (SAVR) in both matched and unmatched cohorts in patients with reduced ventricular ejection fraction (LVEF≤50%).

6 Discussion

6.1 Ten-year experience with transcatheter and surgical aortic valve replacement in Finland

The main findings are: 1) the early and intermediate mortality in patients with AS has decreased during the last 5-year period among TAVR treated patients, as well as among SAVR treated patients despite unchanged preoperative risk among overall cohort; 2) TAVR is now widely used for patients at high and intermediate surgical risk and it has become the most common treatment for severe AS in 2016; 3) the development of TAVR devices and protocol has led to reduced rates of periprocedural complications, and 4) TAVR is a safe and feasible treatment for most patients with symptomatic severe AS.

Complication rates of both SAVR and TAVR procedures have declined during the past decade. Severe TAVR specific complications are becoming rare due to improved implantation and imaging techniques as well as the development of TAVR devices. However, several issues are yet unresolved and limit the expansion of TAVR procedures into low-risk patients. These include issues like valve durability, paravalvular leak, need for permanent pacemaker and optimal antithrombotic or anticoagulation medication.

The short-term results after TAVR such as procedure-related mortality, low stroke rate, good valve performance and low rates of vascular complications, have been excellent (Arora *et al.*, 2017; Virtanen *et al.*, 2019). The main interest is now on long-term durability of TAVR valves. Current SAVR biological prostheses have 10-year freedom from reoperation rates above 93-97% (Kueri *et al.*, 2019; Biancari *et al.*, 2020; Williams *et al.*, 2020). In a review by Arora et al., good intermediate-long term durability for TAVR is reported (Arora *et al.*, 2017). The TAVR valve durability beyond 10 to 15 years is of extreme importance in younger patients with a life-expectance of over 10 years when TAVR or SAVR options are considered. Heart conduction disturbances are the most common complications following TAVR. Short-term mortality is not increased in patients undergoing TAVR or SAVR who require a permanent pacemaker implantation, but the long-term effects of a permanent pacemaker remain undetermined. With modern devices, low permanent

pacemaker implantation rates have been reported (Nazif *et al.*, 2014; Zhang *et al.*, 2020).

Indications for TAVR are likely to continue to expand (Durko *et al.*, 2018). Over 500.000 TAVR implantations have been made to date and it is estimated that the number of TAVR will rise as high as 280.000 procedures annually. Routine use of TAVR in younger or low risk patients is not currently feasible beyond the limits of randomized controlled clinical trials. SAVR remains the treatment of choice for various patient groups, such as patients needing concomitant coronary artery by-pass grafting, multiple valvular diseases, diseases of the ascending aorta and infective endocarditis.

6.2 Recent acute heart failure

The main findings of the AHF study are: 1) early and intermediate mortality in AS patients with recent AHF was increased after both SAVR and TAVR; 2) in propensity score matched pairs of patients, SAVR was associated with increased risk of major bleeding and severe AKI; and 3) intermediate-term survival in patients with recent AHF was similar after TAVR and SAVR.

When adjusted for multiple covariates, recent AHF was an independent predictor of early and intermediate mortality after SAVR, but not after TAVR. The observed 30-day mortality was markedly lower than predicted by the EuroSCORE II and STS risk scores in the TAVR and to a lesser extent in the SAVR cohort. Similarly, AHF was associated with an increased risk of early adverse events after SAVR, but not after TAVR. In propensity score matched pairs of AHF patients, SAVR was associated with an increased risk of major bleeding and AKI compared to TAVR. Slightly better survival was observed after TAVR, when compared to SAVR, during the first three years after the procedure, but with a trend towards better survival after SAVR beyond 5 years of follow up. Patients requiring urgent procedure were possibly treated by SAVR, at least during the early phase of this study. On the other hand, patients undergoing TAVR were more frequently treated with balloon aortic valvuloplasty, which may indicate that TAVR was more often offered to high-risk patients who were suboptimal candidates for surgery.

Patients hospitalized for AHF experience most of the adverse events and readmissions to hospital during the first 2–3 months after discharge. In literature, this period is called as the vulnerable phase (Greene *et al.*, 2015). Our results support this finding, as short-term mortality was increased in patients operated within 2 months after initial hospitalization for AHF. Such a short delay to intervention indicates a more urgent setting and escalation of a stable or asymptomatic condition to a symptomatic and decompensated HF. We speculate, that hospitalization for AHF

earlier than within 2 months prior the operation is comparable to a condition of a chronic HF.

6.3 Left ventricular systolic dysfunction

This study provides excellent data on the current practice and outcomes of the patients with AS and reduced LVEF in a nationwide setting. The main findings are: 1) early mortality was increased after SAVR; 2) intermediate-term survival was similar after TAVR and SAVR; 3) non-cardiac death was common in this elderly population with multiple co-morbidities.

Patients with LVEF ≤50% have a poor prognosis when compared to patients with normal systolic function and the prognosis is impaired even after aortic valve operation (Dahl *et al.*, 2015; Lancellotti *et al.*, 2018). In the present study population, only 69.6% of SAVR patients and 65.9% of TAVR patients survived beyond 4-year follow up. On the other hand, data from the TVT Registry showed that the low-gradient severe AS, rather than the level of baseline LV dysfunction, associates with an increased 1-year mortality after TAVR (Baron *et al.*, 2016). In the present study, at 4-year follow up the degree of LV systolic dysfunction did not affect survival within the patients with LVEF≤50%. The extent of cardiac damage correlates to the worse outcomes (Généreux *et al.*, 2017). Even LVEF <60% is found to be a risk factor for impaired prognosis (Dahl *et al.*, 2015; Lancellotti *et al.*, 2018; Taniguchi *et al.*, 2018). Van Gils et al. suggest that patients with moderate AS with LV dysfunction are at high risk for adverse events and speculate that earlier AVR might benefit these patients (van Gils *et al.*, 2017).

Based on both our current study and earlier literature, it is evident that the release of the high afterload by AVR should be performed before the development of irreversible pathological changes in myocardium and clinical signs of HF. The prognosis is largely dependent on the LV recovery (Ewe *et al.*, 2010; Une *et al.*, 2015). TAVR has been associated with better LVEF recovery, when compared with SAVR, in some, but not all studies (Clavel *et al.*, 2010; Elmariah *et al.*, 2013). After TAVR, a readmission for cardiac causes, especially HF, predicts high mortality (Goldsweig and Aronow, 2020).

One clinically relevant issue is that only 50% of the AS patients with HF have reduced LVEF and that LVEF reduction in this population is generally not caused by AS, but rather myocardial damage due to ischemic heart disease or other cardiomyopathies (Spitzer *et al.*, 2018). Furthermore, there is controversy in using only LVEF as a measure of LV function, because it does not account for LV thickness and LV cavity size. LVEF correlates with LV concentric remodeling (Taniguchi *et al.*, 2018). Also, several studies have reported that reduced stroke volume, despite normal LVEF in patients with AS, is associated with poor outcomes

(Herrmann *et al.*, 2013). Diastolic dysfunction has already developed when LVEF starts to decrease (Elahi *et al.*, 2014).

6.4 Other considerations

6.4.1 Coronary artery disease

Coronary artery revascularization was performed more often during SAVR than with TAVR, reflecting the contemporary practice and guidelines. The prevalence of coronary artery disease was not different between the matched cohorts in either AHF or LVEF studies and neither was the rate of previous PCI, unlike in the unmatched cohorts.

It is worth noting that leaving coronary disease untreated during SAVR impairs long-term survival, regardless of its severity (Thalji *et al.*, 2015). In SURTAVI trial the patients with a non-complex coronary artery disease (SYNTAX <23) and AS were randomized to undergo either SAVR and CABG or TAVR and PCI. No difference in outcomes was detected. A meta-analysis by Tarus et al. is based on three studies, including the only randomized trial (SURTAVI), comparing TAVR and PCI versus SAVR and CABG (Søndergaard *et al.*, 2019; Tarus *et al.*, 2020). Almost always, CABG was performed concomitantly with SAVR. TAVR patients underwent PCI typically prior TAVR procedure and concomitantly in a lesser scale. A minority of patients had hybrid procedure of CABG and TAVR. There was no difference in 30-day myocardial infarction, stroke rate and survival or 2-year survival in TAVR and PCI versus SAVR and CABG groups. Completeness of revascularization is one of the factors influencing long-term survival in patients with multi-vessel coronary artery disease. There are contradictions in TAVR and revascularization data, with some evidence suggesting incomplete revascularization does not influence TAVR outcomes in patient with coronary artery disease (Faroux *et al.*, 2019). The outcomes after TAVR and PCI on intermediate and low-risk patients with longer life expectancy are not known. SAVR and CABG have shown better long-term results and a higher degree of complete revascularization was achieved in CABG. The results from the randomized ACTIVATION and NOTION 3 trials are likely to provide data on the optimal revascularization strategy choice on TAVR patients with coronary artery disease. Until then, the treatment pathway choice is done by individual patient assessment by the multidisciplinary Heart Team.

In patients with coronary artery disease and HFrEF, revascularization with either CABG or PCI improves the long-term survival compared to medical therapy. CABG is reported to associate with better survival compared to PCI. Also, CABG was found to lead to a significant reduction in the risk of myocardial infarction and need for repeated revascularization when compared with PCI (Wolff *et al.*, 2017). The better

outcomes found in patients with ischemic cardiomyopathy undergoing CABG may be explained by achieving a more complete revascularization with CABG than with PCI.

6.4.2 Atrial fibrillation and anticoagulation

Current guidelines do not recommend anticoagulation for patients with HF and valvular heart disease (Nishimura *et al.*, 2017), (Yancy *et al.*, 2013). Both HF and AF increase the risk for cardiovascular mortality and morbidity. Life-long anticoagulation should be considered in all patients with a history of preoperative AF and these studies reaffirm the high occurrence of AF in HF patients (Nissinen *et al.*, 2020).

We do not have data on left atrial appendix closure rates, but the concomitant closure of the left atrial appendix may be beneficial for SAVR patients. This subject needs further studies, and we look forward to the results of ongoing studies.

6.4.3 Bleeding and vascular complications

Major bleeding complications were identified as the strongest independent predictor of 1-year mortality among the full cohort in the AHF study. SAVR was associated with a significantly higher rate of transfusions, compared with TAVR in our studies. Perioperative bleeding has a negative impact on the early and late outcomes of patients undergoing any cardiac surgery. E-CABG bleeding grading used here has been proven to be valid a method for predicting in-hospital death (Mariscalco *et al.*, 2016). Transfusions cause a dose-dependent risk of mortality and infections after cardiac surgery and TAVR (Maaranen *et al.*, 2019; Ming *et al.*, 2020)

In patients undergoing TAVR, vascular complications have been associated with increased mortality, with a correlation to the anatomical site and the severity of the bleeding (Laakso *et al.*, 2020). Here, the vascular complication rate decreased during the study period after both SAVR and TAVR. LVEF ≤50% did not compose an increased risk for vascular complications. However, AHF patients more often had severe bleeding and reoperations for bleeding after SAVR. The same trend was seen in TAVR patients, although the difference was not statistically significant.

6.4.4 Acute kidney injury

Kidney insufficiency is common in patients with HF. The prevalence is reported to be as high as 32–49%, with higher prevalence among patients with AHF vs. chronic HF (53% vs. 42%, respectively) (Damman *et al.*, 2014). Multiple mechanisms explain the poor outcomes in HF patients with kidney insufficiency. These include

reduced LV systolic function, increased renin-angiotensin-aldosterone system activation and volume overload (Gudsoorkar and Thakar, 2019). Patients with AS and HF are at high risk of developing kidney insufficiency and these conditions affect one another negatively. Renal insufficiency is associated with a high burden of morbidity and mortality in patients with AHF.

Cardiac surgery associated AKI is a significant clinical problem. Its pathogenesis is complex and multifactorial (Bellomo *et al.*, 2008). AKI is also seen in TAVR patients, but to a lesser scale. In the whole FinnValve population the incidence of KDIGO AKI stage 3 was 3.0% after SAVR and 1.0% after TAVR. Among the patients with AHF and reduced LVEF, the incidences were 6.4% and 3.8% after SAVR compared to 2.5% and 1.6% after TAVR. It has been well established that AKI impairs both early and late survival after both SAVR and TAVR (Machado, Nakazone and Maia, 2014; Konigstein *et al.*, 2015; Moriyama *et al.*, 2020). The KDIGO stage 3 patients who did not require dialysis had a mortality rate of 41%, while the mortality of dialysis patients was 62% (Machado, Nakazone and Maia, 2014). Similar poor outcomes have been reported by Aittokallio et al: the ICU and 90-day mortality rates were 47.7% and 58.2%, respectively, in patients with cardiac surgery related AKI requiring dialysis. Only 37.3% of these patients were alive 1 year after surgery (Aittokallio *et al.*, 2020).

Urgent and emergency setting increases the risk for AKI and new dialysis both after TAVR (Gargiulo *et al.*, 2015; Kolte *et al.*, 2018) and SAVR (Moriyama *et al.*, 2020). In addition to urgency, preoperative conditions of hypertension, history of HF, other valvular conditions, use of ACE inhibitors preoperatively, perioperative blood transfusion, prolonged cardiopulmonary by-pass and cross clamp times and inotropic support are known to increase the risk of AKI after SAVR (Ibrahim *et al.*, 2020). Major bleeding and transfusion are predictors of AKI (Liao *et al.*, 2017). Postoperatively cardiogenic shock and both hypovolemia and congestion increase the risk for AKI (Nadim *et al.*, 2018). There is an independent association between central venous pressure, age, pre-operative creatinine level and LV dysfunction in the development of AKI after cardiac surgery, although the significance of LV dysfunction was not clear in all studies (Machado, Nakazone and Maia, 2014; Yang, Ma and Zhao, 2018).

6.4.5 Percutaneous balloon aortic valvuloplasty

Rescue PBAV is a feasible and safe procedure in patients with severe AS who cannot undergo emergency SAVR or TAVR. Most early deaths after rescue PBAV are related to the overall severe baseline condition of the patient. AS patients with AHF may benefit from an early release of the high afterload to the same extent of urgent PBAV in the setting of AS-related cardiogenic shock (Theiss *et al.*, 2014; Debry *et*

al., 2018). In view of the similar risk of adverse events after PBAV and TAVR (Kawsara *et al.*, 2020), patients with AHF secondary to severe AS may be considered for primary TAVR. Although rescue TAVR can be feasible for selected patients, rescue PBAV allows the hemodynamic and clinical condition of the patients to be stabilized and to select those in whom further interventions may improve prognosis (Eugène *et al.*, 2018). Kolte et al. have shown that urgent/emergency TAVR offers good early and intermediate survival, although it requires changes in the diagnostic and treatment pathway (Kolte *et al.*, 2018). Instead of rescue PBAV, rescue TAVR could be an option for patients that are not candidates for SAVR. The cost-effectiveness of a rescue TAVR protocol is still uncertain.

6.4.6 Future and economic considerations

Up to 80% of low risk AS patients are currently treated with SAVR. In the future, if results of ongoing PARTNER 3 and NOTION-2 low-risk trials favor TAVR over SAVR also in that group, they will significantly increase the number of TAVR candidates. One possible scenario is that all intermediate-risk patients receive TAVR while SAVR remains the preferred treatment for low-risk patients; or even that TAVR becomes the choice of treatment for all intermediate-, and for elderly low-risk patients. There are currently an estimated 115.000 and 58.000 potential annual candidates for TAVR in Europe and Northern-America, respectively. These numbers will increase dramatically, up to 177.000 and 90.000, if abovementioned clinical trials prove the feasibility of TAVR for low-risk patients (Durko *et al.*, 2018). In Finland, the proportion of the population aged >65 years was 19.4% in 2015. In 2050 it is estimated to be 27%, and 34% in 2070. The average life expectancy in Finland is estimated to grow from 80.8 years in 2015 to 87 years in 2050. (*Suomen virallinen tilasto (SVT): Väestöennuste. ISSN=1798-5137. 2019. 13.10.2020 Tilastokeskus: http://www.stat.fi/til/vaenn/2019/vaenn_2019_2019-09-30_tie_001_fi.html*; *https://www.demoshelsinki.fi/wp-content/uploads/2015/06/Terveys2050.pdf*).

In the current guidelines, recommendations for AVR in patients with asymptomatic AS are highly selective (Baumgartner *et al.*, 2017; Nishimura *et al.*, 2017). There is growing evidence, that treating severe AS, instead of watchful waiting in patients with asymptomatic severe AS, might be beneficial (Lancellotti *et al.*, 2018; Kang *et al.*, 2020). Evidence favoring early TAVR in this group would result in a marked increase in annual TAVR numbers. In addition, the current trend of increased bioprosthetic surgical heart valve implantations in younger patients will likely lead to growing numbers of valve-in-valve procedures over the next 10–20 years (Durko *et al.*, 2018).

The need for AS interventions is without a doubt growing in the future. TAVR is feasible for a majority of otherwise inoperable patients, high- and intermediate

risk patients and probably for some low-risk patients as well. TAVR valve durability and long-term outcomes have a key role in determining the future development. Recent data from randomized trials present similar rates of SVD with TAVR and SAVR up to 5–6 years (Arora *et al.*, 2017; Baron *et al.*, 2018; Virtanen *et al.*, 2020). The number of SAVR procedures is likely to continue to decrease and surgery will focus on younger patients with long life expectancy. It is possible that the balance will turn back from biological valve prostheses to mechanical valve prostheses in SAVR. Surgery remains the treatment of choice for patients needing other concomitant heart surgery, i.e., aortic surgery, revascularization and other valve interventions. Both TAVR and SAVR reoperation techniques require new and more feasible innovations.

Economic considerations have a notable impact on AS treatment and, especially, on TAVR expansion globally. The cost-effectiveness profile of TAVR vs SAVR in low-risk patients is yet unknown, but the large number of potential TAVR candidates in intermediate- and low-risk patients has a major financial impact on health care systems. Quality of life and survival benefits in low-risk TAVR patients are needed to justify the higher cost (Durko *et al.*, 2018). Within this population, these benefits are only achieved by excellent long-term TAVR valve durability and a decrease in TAVR related complications (e.g., increased rates of mild paravalvular regurgitation and pacemaker implantation), especially in the younger low-risk population (Baron *et al.*, 2018). Treating younger low-risk patients with TAVR may create a need for evaluating long-term outcomes and the cost effectiveness of mechanical SAVR compered to TAVR.

6.5 Limitations

The retrospective nature is the main limitation of these studies. The overall TAVR and SAVR cohorts differ significantly. The procedure type selection was made according to guidelines valid at the time by the multidisciplinary Heart Team and patient preference. Patient selection has changed along the study period. Also, the pre- and perioperative timing and methods for echocardiographic assessment varied between the cohorts and institution. This registry does not include specific data on the type of aortic stenosis such as high-gradient, low-flow low-gradient and normal-flow low-gradient AS. Data on diastolic function were not collected in the FinnValve registry and, therefore, it is not possible to estimate the influences of it in our study population. The impact of BAV and PPM were not separately evaluated in present FinnValve HF studies.

The first publication is mainly descriptive in nature and evaluates TAVR and SAVR outcomes independently. On the second and third study, the limited numbers of patients with AHF and reduced LVEF do not allow a comparative analysis of

patients without coronary artery disease undergoing SAVR or TAVR. The definition of recent AHF is based on history of recent hospitalization for treatment of AHF, but neither the severity of AHF nor information on its treatment were captured in the FinnValve registry. In addition, there is no consensus on defining time limits for recent AHF in the literature. This data does not allow an analysis of the impact of the timing of treatment on the outcome of AHF patients.

The important limitation of propensity score matching is that although it can balance observed baseline covariates between groups, it doesn't balance possible unmeasured confounders. There may be factors or variables which have been driven decisions of treatment. As a result, propensity score analyses have the limitation that remaining unmeasured confounding variables may still be present, thus leading to biased results.

Finally, the relatively small sample size of this study as well as the rather short follow-up are potential biases of this study and limited the validity of comparative analyses of TAVR versus SAVR. On the other hand, this dataset represents a 10-year nationwide experience with these treatment methods and the unselected nature of this series and reliability of data on survival are the strengths of these analysis.

7 Conclusions

1. TAVR has led to a more widespread use of invasive treatment for severe AS. Early outcomes have improved after both SAVR and TAVR. TAVR serves as feasible and definitive treatment for patients not eligible for surgery and high surgical risk patients. In Finland, TAVR surpassed SAVR as the most common procedure for AS in 2016.

2. Recent acute heart failure leads to increased morbidity and mortality in patients with aortic stenosis. TAVR is a valid alternative to SAVR in these patients.

3. Reduced LVEF in AS patients is associated with increased morbidity and mortality. Similar intermediate-term survival is observed with these interventions.

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