Tampere University

MARKO VIRTANEN

Treatment of Severe Aortic Stenosis with a Transcatheter or Surgical Bioprosthesis

Results from the FinnValve Registry

Tampere University Dissertations 411

Tampere University Dissertations 411

MARKO VIRTANEN

Treatment of Severe Aortic Stenosis with a Transcatheter or Surgical Bioprosthesis

Results from the FinnValve Registry

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the auditorium F115
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 21 May 2021, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Finland

Responsible supervisor	Docent Markku Eskola Tampere University Finland	
Supervisor	Professor Fausto Biancari University of Turku and University of Oulu Finland	
Pre-examiners	Docent Kari Kervinen University of Oulu Finland	Professor Karl Lemström University of Helsinki Finland
Opponent	Docent Heikki Miettinen University of Eastern Finland Finland	
Custos	Professor Kjell Nikus Tampere University Finland	

The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-1941-0 (print)
ISBN 978-952-03-1942-7 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-1942-7

PunaMusta Oy – Yliopistopaino
Joensuu 2021

To the pioneers in the field of transcatheter aortic valve implantation.

ACKNOWLEDGEMENTS

This study was conducted at the Tays Heart Hospital, Tampere University Hospital, and at the Faculty of Medicine and Health Technology (formerly the Faculty of Medicine and Life Sciences), Tampere University, in collaboration with the University Hospitals of Helsinki, Kuopio, Oulu, and Turku.

I am full of gratitude to my supervisors, Docent Markku Eskola, M.D. and Professor Fausto Biancari, M.D., for their invaluable support during this project. I have learned a lot from you both. Markku, you have greatly supported my work on this thesis, organized many practical issues, and enabled me to devote the effort required and have provided vital comments on planning and executing the actual scientific work. It has also been fun to work with you in the catheterization laboratory performing valvular heart interventions during the past ten years. Fausto, I honestly believe that your phenomenal talent is the key factor making the FinnValve study possible. Your expertise in setting up, conducting, and supervising scientific work has helped us run this nationwide study on the treatment of valvular heart disease in Finland. I am especially grateful for your guidance on analysing and interpreting data. I also thank you for the inspiring discussions during this project.

My warmest thanks also go out to a great team of the FinnValve collaborators: board members Professor Juhani Airaksinen, M.D.; Docent Matti Niemelä, M.D.; Docent Peter Raivio, M.D. and Antti Valtola, M.D.; and coauthors Tuomas Ahvenvaara, M.D.; Docent Vesa Anttila, M.D.; Paola D'Errigo, M.Sc.; Sebastian Dahlbacka, M.D., Ph.D.; Annastiina Husso, M.D., Ph.D.; Jussi Jaakkola, M.D., Ph.D.; Maina Jalava, M.D.; Professor Tatu Juvonen, M.D.; Eeva-Maija Kinnunen, M.D., Ph.D.; Teemu Laakso, M.D.; Docent Mika Laine, M.D.; Pasi Maaranen, M.D.; Docent Timo Mäkikallio, M.D.; Stefano Rosato, M.Sc.; Docent Mikko Savontaus, M.D.; Tuomas Tauriainen, M.D., Ph.D.; Tuija Vasankari, R.N.; and Docent Antti Vento, M.D. It has been a great pleasure to see how efficiently and thoroughly this study has been conducted!

I truly appreciate the opportunity to practice clinical cardiology and research at Tays Heart Hospital and thus wish to express my thanks to Professor Kari Niemelä, M.D., former CEO and Chief Medical Officer; Pasi Lehto, M.D., Ph.D., CEO and Chief Medical Officer; Docent Vesa Virtanen, M.D., Medical Director; Professor

Kjell Nikus, M.D.; and Docent Saila Vikman, M.D., former Head of Research Unit, at Heart Hospital.

My special thanks belong to the highly skilled and helpful research personnel at Tays Heart Hospital: Kati Helleharju, R.N., research coordinator; Katri Mikkonen, R.N.; Hannaleena Näppilä, R.N.; and Virpi Palomäki, R.N.

I am grateful to my thesis pre-examiners Docent Kari Kervinen, M.D.; and Professor Karl Lemström, M.D. for your great comments on my thesis.

I also want to thank all my colleagues and co-workers at Tays Heart Hospital for the pleasant collaboration. Special thanks to Docent Olli Kajander, M.D.; Pasi Maaranen, M.D.; and Anna Tahvanainen, M.D., Ph.D. for support and friendship.

No words are enough to express the gratitude that I feel having my beloved ones near me. Johanna, I thank you for your sympathy and love. Aino and Helka, you are so precious. Thank you for your love and the energy you bring along with you.

This study was financially supported by Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital and by research grants from the Aarne Koskelo Foundation, Paavo Ilmari Ahvenainen Foundation, and Finnish Medical Foundation.

6.3.2021 Marko Virtanen

ABSTRACT

Symptomatic severe aortic valve stenosis is associated with high mortality rate, even up to 50% at 1 to 2 years, unless treated operatively. Transcatheter aortic valve implantation (TAVI) has emerged as a valid alternative to surgical aortic valve replacement (SAVR) in patients with high surgical risk. However, there are insufficient data comparing TAVI and SAVR in patients with low surgical risk.

This thesis is based on three original publications that are referred to by the Roman numerals **I**, **II** and **III**. The aim of this study was to compare operative mortality, estimated 3- to 4-year mortality and procedural safety in patients with severe aortic stenosis who underwent TAVI or SAVR with a bioprosthesis and who were **I** at low risk for surgery, **II** at low risk for surgery without having concomitant coronary artery disease, or **III** treated with a transcatheter balloon-expandable or surgical bioprosthesis made of bovine pericardial leaflets.

Data of patients included in the retrospective FinnValve registry were used (n=6463). A total of 2841 patients in study **I**, 1006 patients in study **II**, and 2000 patients in study **III** fulfilled the inclusion criteria. Propensity score matching was performed to balance the baseline variables and provided 304 (**I**), 140 (**II**) and 308 (**III**) matched pairs. Primary endpoints: Operative mortality between matched pairs was 1.3% vs. 3.6% (p=0.12) (**I)**, 2.1% vs. 2.1% (p=1.000) (**II**), and 1.3% vs. 3.6% (p=0.092) (**III**) for TAVI vs. SAVR. The estimated mortality at 3 years after TAVI vs. SAVR was 14.3% vs. 12.3% (p=0.45) in study **I** and 17.0% vs. 14.6% (p=0.805) in study **II**. The estimated mortality at 4 years was 20.6% after TAVI vs. 25.9% after SAVR (p=0.910) in study **III**. Secondary endpoints: No significant differences were observed in the postoperative rate of stroke or acute kidney injury in study **I** or **II**. In study **III,** TAVI was associated with lower rates of stroke (1.3% vs. 3.6%, p=0.006) and acute kidney injury (0.3% vs. 7.8% p< 0.0001) than SAVR. In all studies, TAVI was associated with a higher incidence of major vascular complications (e.g., **II** 7.9% vs. 0.7%, p=0.006), lower rates of atrial fibrillation (e.g., **III** 33.1% vs. 64.9%, p<0.0001) and severe bleeding (e.g., **II** 2.3% vs. 16.9% p<0.001), and a four-day-shorter hospital stay (p<0.001 in all) than SAVR. Paravalvular regurgitation was more common after TAVI, but the incidence of moderate/severe paravalvular regurgitation was similar (1.9% vs. 1.3%, p=0.754

III). Permanent pacemaker implantation was more often needed after TAVI (9.5%) than after SAVR (4.6%) (p=0.03) in study **I**, but this was not observed in study **II** or **III**. The rates of late coronary revascularization, prosthetic valve endocarditis and aortic valve reintervention at 3 to 4 years were low and were similar between TAVI and SAVR. TAVI was associated with increased risk of permanent pacemaker implantation at 4 years (HR 2.16; 95% CI 1.27–3.68) compared to SAVR in study **III**, but not in study **II**.

Conclusions: TAVI is associated with similar mid-term survival at 3 to 4 years compared to SAVR in low-risk patients with aortic stenosis who undergo valve intervention with bioprosthesis. Postoperative complications are typical for both treatments. Its lower frequencies of bleeding, acute kidney injury, atrial fibrillation, stroke, and shorter hospital stay favour TAVI, while the lower incidences of major vascular complications, permanent pacemaker implantations and paravalvular regurgitation favour SAVR. TAVI can be offered as an alternative to SAVR in low-risk patients, but longer-term follow-up studies are essential to assess the durability of TAVI prostheses.

TIIVISTELMÄ

Oireiseen vaikea-asteiseen aorttaläpän ahtaumaan liittyvä kuolleisuus on jopa 50% 1-2 vuoden kuluessa, ellei sairautta hoideta operatiivisesti. Aorttatekoläpän asentaminen katetrilla (TAVI) on tullut hyväksi hoitovaihtoehdoksi kirurgiselle hoidolle (SAVR) potilailla, joiden leikkausriski on suurentunut. Katetrimenetelmän käytöstä verrattuna kirurgiaan on riittämättömästi tietoa potilailla, joiden leikkausriski on pieni.

Tämä väitöskirja perustuu kolmeen alkuperäisjulkaisuun, joihin viitataan myöhemmin roomalaisin numeroin **I**, **II** ja **III**. Tämän tutkimuksen tarkoituksena oli verrata toimenpidekuolleisuutta, arvioitua 3-4 vuoden kuolleisuutta sekä toimenpiteen turvallisuutta vaikeaa aorttaläpän ahtaumaa sairastavilla potilailla, joiden aorttaläppätoimenpide oli tehty joko katetrimenetelmällä tai kirurgisesti, ja heillä oli joko **I** matala leikkausriski, **II** matala leikkausriski ilman samanaikaista sepelvaltimotautia, tai **III** heidät oli hoidettu joko katetrimenetelmällä tai kirurgisesti asentamalla naudan sydänpussikudoksesta valmistettu biologinen tekoläppä.

Tutkimus tehtiin takautuvasti kerätyn FinnValve -rekisterin potilasaineistosta (n=6463). Tutkimuksen sisäänottokriteerit täyttyivät 2841 potilaalla tutkimuksessa **I**, 1006 potilaalla tutkimuksessa **II**, ja 2000 potilaalla tutkimuksessa **III**. Propensiteettipistemäärään perustuvaa hoitoryhmien kaltaistamista käytettiin tasaamaan lähtötilanteen muuttujien eroja. Tämä perusteella luotiin 304 (**I**), 140 (**II**) ja 308 (**III**) kaltaistettua paria. Ensisijaiset päätetapahtumat: toimenpidekuolleisuus oli kaltaistetuissa hoitoryhmissä TAVI ja SAVR 1.3% vs. 3.6% (p=0.12) (**I**), 2.1% vs. 2.1% (p=1.000) (**II**), ja 1.3% vs. 3.6% (p=0.092) (**III**). Arvioitu kuolleisuus kolmen vuoden kohdalla toimenpiteestä oli 14.3% (TAVI) vs. 12.3% (SAVR) (p=0.45) tutkimuksessa **I** ja 17.0% (TAVI) vs. 14.6% (SAVR) (p=0.805) tutkimuksessa **II**. Arvioitu kuolleisuus neljän vuoden kohdalla toimenpiteestä oli 20.6% (TAVI) vs. 25.9% (SAVR) (p=0.910) tutkimuksessa **III**. Toissijaiset päätetapahtumat: leikkauksen jälkeen ilmaantuneen aivoverenkierron häiriön ja äkillisen munuaisten vajaatoiminnan esiintyvyyksissä ei ollut eroa hoitoryhmien välillä tutkimuksissa **I** ja **II**. Tutkimuksessa **III** katetrimenetelmään liittyi vähemmän toimenpiteen jälkeisiä aivoverenkiertohäiriöitä (1.3% vs. 3.6%, p=0.006) ja akuuttia munuaisten vajaatoimintaa (0.3% vs. 7.8% p< 0.0001) verrattuna kirurgiaan. Kaikissa

tutkimuksissa katetrimenetelmään liittyi enemmän merkittäviä verisuonivaurioita (esim. **II** 7.9% vs. 0.7%, p=0.006), vähemmän eteisvärinää (esim. **III** 33.1% vs. 64.9%, p<0.0001), vakavia verenvuotoja (esim. **II** 2.3% vs. 16.9% p<0.001), sekä neljä vuorokautta lyhyempi sairaalahoitojakso (p<0.001 kaikissa) verrattuna aorttatekoläpän asentamiseen kirurgisesti. Tekoläpän viereinen läppävuoto oli yleisempää katetrimenetelmään liittyen, mutta keskivaikean/vaikean vuodon ilmaantuvuudessa ei ollut eroa hoitoryhmissä (esim. **III** 1.9% vs. 1.3%, p=0.754). Pysyvä sydäntahdistin tarvittiin useammin katetrilla asennetun tekoläpän jälkeen tutkimuksessa **I** (9.5% vs. 4.6%, p=0.03), mutta ei tutkimuksissa **II**, **III**. Myöhäisten sepelvaltimoiden toimenpiteiden, tekoläpän infektioiden sekä aorttaläpän uusintatoimenpiteiden esiintyvyys oli alhainen ja samankaltainen hoitoryhmissä kolmen ja neljän vuoden kuluttua toimenpiteestä. Katetrimenetelmällä hoidettujen potilaiden ryhmässä todettiin suurentunut riski pysyvän sydäntahdistimen asentamiseen neljän vuoden kuluessa verrattuna kirurgisesti hoidettuihin potilaisiin (HR 2.16; 95% CI 1.27–3.68) tutkimuksessa **III**, mutta suurentunutta riskiä ei todettu tutkimuksessa **II**.

Johtopäätökset: Katetrimenetelmällä hoidettujen matalan leikkausriskin omaavien aorttaläppäahtaumaa sairastavien potilaiden eloonjäämisen todennäköisyys on samanlainen kuin kirurgisesti hoidetuilla potilailla 3–4 vuoden kohdalla toimenpiteestä. Leikkauksen jälkeen ilmaantuvat komplikaatiot ovat kummallekin toimenpiteelle tyypillisiä. Vähäisempi verenvuotojen, äkillisen munuaisten vajaatoiminnan, eteisvärinän ja aivoverenkiertohäiriön ilmaantuvuus, sekä lyhyempi sairaalahoidon kesto puoltavat katetrimenetelmän käyttöä, kun taas vähäisempi verisuonivaurion ja tekoläpän viereisen läppävuodon ilmaantuvuus, sekä vähäisempi pysyvän sydäntahdistimen asentamisen tarve puoltavat kirurgisen hoidon käyttöä. Katetrimenetelmällä asennettavaa aorttatekoläppää voidaan käyttää kirurgisen hoidon sijaan potilailla, joiden leikkausriski on pieni. Lisätutkimukset pidempiä seuranta-aikoja käyttäen ovat kuitenkin välttämättömiä katetrilla asennettavien tekoläppien kestävyyden arvioimiseksi.

CONTENTS

ABBREVIATIONS

6MWT	6-minute walk test
AF	Atrial fibrillation
AKI	Acute kidney injury
AS	Aortic valve stenosis
AUC	Area under the curve
AVA	Aortic valve area
AVR	Aortic valve replacement
BAV	Balloon aortic valvuloplasty
BVF	Bioprosthetic valve failure
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CKD	Chronic kidney disease
CLD	Chronic lung disease
COPD	Chronic obstructive pulmonary disease
E-CABG	European Coronary Artery Bypass Grafting
LVEF	Left ventricular ejection fraction
eGFR	Estimated glomerular filtration rate
EuroSCORE	European System for Cardiac Operative Risk Evaluation
GARY	German Aortic Valve Registry
GSS	Geriatric Status Scale
HR	Hazard ratio
KDIGO	Kidney Disease Improving Global Outcomes
LVOT	Left ventricular outflow tract
MACCE	Major adverse cardiac and cerebrovascular events
MSCT	Multislice computed tomography
NOTION	Nordic Aortic Valve Intervention
NSVD	Non-structural valve dysfunction
NYHA	New York Heart Association
OBSERVANT	Observational Study of Effectiveness of SAVR-TAVI Procedures for Severe Aortic Stenosis Treatment

O:E	Observed to expected ratio
PARTNER	Placement of Aortic Transcatheter Valve
PCI	Percutaneous coronary intervention
PPMI	Permanent pacemaker implantation
PVR	Paravalvular regurgitation
RBC	Red blood cell
SAVR	Surgical aortic valve replacement
STS-PROM	Society of Thoracic Surgeons predicted risk of mortality
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
SVD	Structural valve dysfunction
TAVI	Transcatheter aortic valve implantation
TIA	Transient ischaemic attack
VARC-2	Valvular Academic Research Consortium 2

ORIGINAL PUBLICATIONS

Publication I Virtanen MPO, Eskola M, Jalava MP, Husso A, Laakso T, Niemelä M, Ahvenvaara T, Tauriainen T, Maaranen P, Kinnunen EM, Dahlbacka S, Jaakkola J, Vasankari T, Airaksinen J, Anttila V, Rosato S, D'Errigo P, Savontaus M, Juvonen T, Laine M, Mäkikallio T, Valtola A, Raivio P, Biancari F. Comparison of Outcomes After Transcatheter Aortic Valve Replacement vs Surgical Aortic Valve Replacement Among Patients With Aortic Stenosis at Low Operative Risk. JAMA Netw Open. 2019;2(7):e198352. doi:10.1001/jamanetworkopen.2019.5742.

Publication II Virtanen MPO, Airaksinen J, Niemelä M, Laakso T, Husso A, Jalava MP, Tauriainen T, Maaranen P, Kinnunen EM, Dahlbacka S, Rosato S, Savontaus M, Juvonen T, Laine M, Mäkikallio T, Valtola A, Raivio P, Eskola M, Biancari F. Comparison of Survival of Transfemoral Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement for Aortic Stenosis in Low-Risk Patients Without Coronary Artery Disease. Am J Cardiol 2020;125(4):589-596. doi:10.1016/j.amjcard.2019.11.002.

Publication III Virtanen MPO, Eskola M, Savontaus M, Juvonen T, Niemelä M, Laakso T, Husso A, Jalava MP, Tauriainen T, Ahvenvaara T, Maaranen P, Kinnunen EM, Dahlbacka S, Laine M, Mäkikallio T, Valtola A, Raivio P, Rosato S, D'Errigo P, Vento A, Airaksinen J, Biancari F. Mid-term outcomes of Sapien 3 versus Perimount Magna Ease for treatment of severe aortic stenosis. J Cardiothorac Surg. 2020;15(1):157. doi:10.1186/s13019-020-01203-1.

1 INTRODUCTION

Aortic valve stenosis (AS) is a progressive disease characterized by increased inflammation and lipid accumulation in valve tissue leading to fibrosis and calcification of the leaflets, which eventually results in limited valve opening (Otto et al., 1994a). The prevalence of AS is 4.3% in individuals aged ≥70 years (Danielsen et al., 2014). Lindroos et al. reported a prevalence of critical AS in 2.9% of subjects aged 75 years or older (Lindroos et al., 1993). Symptomatic severe AS carries an increased risk of death, and valve replacement is the only effective treatment for this condition (Leon et al., 2010). Typically, aortic valve replacement has been performed surgically by cardiopulmonary bypass. However, surgical aortic valve replacement (SAVR) is associated with excess mortality and morbidity risk in some patients with advanced age and comorbidities. Transcatheter aortic valve implantation (TAVI) has been introduced as a treatment for patients not eligible for SAVR and has emerged as a valid option in patients with high, intermediate, and low risk for surgery (Leon et al., 2010, 2016; Mack et al., 2019; Smith et al., 2011). Both treatments are associated with risks due to patient comorbidities and to the invasive nature of these procedures. Several randomized trials have demonstrated comparable mid-term outcomes after TAVI and SAVR in patients with increased risk for surgery (Gleason et al., 2018; Mack et al., 2015; Makkar et al., 2020). In contrast, TAVI is associated with inferior mid-term outcomes compared to SAVR in observational studies of real-life AS patients with low to intermediate and high surgical risk (Armoiry et al., 2018; Barbanti et al., 2019a). However, data on the outcomes in low-risk patients are still scarce. In these studies, we aimed to investigate the short- and mid-term outcomes in low-risk patients from the nationwide FinnValve Registry.

2 REVIEW OF THE LITERATURE

2.1 AORTIC VALVE STENOSIS

2.1.1 Aetiology and pathogenesis

AS can be either acquired or congenital. In the Euro Heart Survey on Valvular Heart Disease in 2001, the aetiology of AS was degenerative in 82%, rheumatic in 11%, congenital in 5%, and other (e.g., endocarditis, inflammatory) in 2% of the patients (Iung et al., 2003). Most recently, in 2017, the EURObservational Research Programme Valvular Heart Disease II Survey showed that ~90% of the patients with severe AS were classified as having degenerative disease, and congenital AS was more common than rheumatic AS, in contrast to a previous report (Iung et al., 2019). Congenital and rheumatic AS are more common aetiologies than degenerative AS in patients <50 years of age, and a degenerative aetiology is the main cause of AS in older patient groups (Iung et al., 2007). Aortic valve cusps are exposed to repeated mechanical stress in millions to billions of pulsatile cycles during their lifetime. The cusps are composed of several microscopically arranged layers (Aikawa & Schoen, 2014). The layer below the aortic side of the valvular endothelium, the fibrosa, is rich in collagen and is responsible for tissue integrity and maintenance of valve durability. In addition, the deformation of the cusps during the cardiac cycle is made possible by the elastin fibres, which are mainly arranged on the ventricular side of the cusps. Third, the central proteoglycan-rich spongiosa layer reduces the forces to the tissue during blood flow (Aikawa & Schoen, 2014). It has been hypothesized that endothelial injury caused by increased mechanical load, reduced shear stress and inflammatory reaction, as evidenced by abnormal accumulation of lipoproteins, macrophages, T-lymphocytes, mast cells and calcium, initiates the development of AS (Otto et al., 1994a; Pawade et al., 2015). Increased oxidative stress, activation of the renin-angiotensin system and inflammatory cytokines induce the differentiation of valvular interstitial cells into osteoblasts and further calcification and bone formation at the later stages of the disease (Pawade et al., 2015).

Male sex and long-term exposure to traditional atherosclerotic risk factors such as hypertension, dyslipidaemia, diabetes and smoking are associated with a

significantly higher risk for the development of AS (Capoulade et al., 2012; Kaltoft et al., 2020b; Katz et al., 2009; Owens et al., 2010; Thanassoulis et al., 2010; Yan et al., 2017). Interestingly, certain lipoprotein(a) single-nucleotide polymorphisms (SNPs) are associated with calcified aortic valves but not with coronary calcium, and lipoprotein(a) and associated oxidized phospholipids are linked to AS in Mendelian randomization studies (Thanassoulis, 2016). Other risk factors associated with AS include elevated serum phosphate, chronic kidney disease (CKD) and obesity (Kaltoft et al., 2020a; Linefsky et al., 2011; Vavilis et al., 2019).

The bicuspid aortic valve is a major predisposing pathology for AS. The prevalence of bicuspid aortic valves is 0.65-1.37% based on two large autopsy series of 2,000 and 21,417 individuals (Larson & Edwards, 1984; Pauperio et al., 1999). Congenitally uni- or bicuspid aortic valves create excessive folds and creases during the cardiac cycle, and this irregular shape and restricted opening function of the valve together with turbulent blood flow are thought to predispose the valve to earlier tissue damage and degenerative processes compared to normal tricuspid aortic valves (Beppu et al., 1993; Robicsek et al., 2004). More than half of the valves excised surgically for aortic stenosis are congenitally malformed with considerable unequal distribution in different age groups. In the age cohort of <50 years, more than 90% of valves are uni- or bicuspid. The corresponding proportions are 63%, 43% and 28% in the age cohorts of 61-70, 71-80 and 81-91 years, respectively (Roberts & Ko, 2005).

Rheumatic heart disease is a consequence of haemolytic group A *Streptococcus* infection leading to inflammatory processes affecting the peri-, myo- and endocardium (Yanagawa et al., 2016). Fortunately, the prevalence of rheumatic AS is decreasing due to the almost complete eradication of rheumatic heart disease in developed countries (Matsumura et al., 2002; Passik et al., 1987). However, it remains a challenge in some developing countries (Watkins et al., 2017).

2.1.2 Pathophysiology

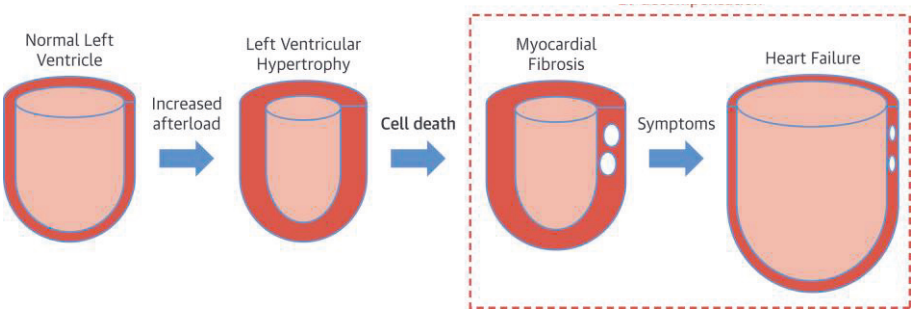
Significant narrowing of the aortic valve orifice hinders blood flow into systemic circulation resulting in pressure overload of the left ventricle. The natural response to increased afterload is left ventricular hypertrophy (Danielsen et al., 2014; Nkomo et al., 2006). Hypertrophy is often seen as a compensatory mechanism to increased afterload in order to normalize ventricular wall stress and systolic function. However, on an individual level, the magnitude of the hypertrophic response is not fully understood, and hypertrophy can be absent or inappropriately increased (Carabello

& Paulus, 2009; Cioffi et al., 2011). Additionally, systemic hypertension is a major contributor to the development of ventricular hypertrophy in non-severe aortic stenosis (Garcia et al., 2007).

Although left ventricular hypertrophy is beneficial in normalizing wall stress, the transition to myocardial damage can occur after prolonged pressure overload. In a study by Musa et al., half of the patients with severe AS undergoing operative treatment had signs of myocardial fibrosis on cardiac magnetic resonance imaging (Musa et al., 2018). Unfavourable progression of myocardial fibrosis predicts significantly decreased survival in AS patients (Azevedo et al., 2010; Chin et al., 2017; Dweck et al., 2011; Everett et al., 2020; Milano et al., 2012; Musa et al., 2018; Vassiliou et al., 2017).

Hypertrophy and fibrosis are the leading mechanisms of diastolic dysfunction in AS (Kampaktsis et al., 2017), and in more advanced states of AS, diastolic dysfunction is more pronounced (Strange et al., 2019). Increasing fibrosis is also associated with lower left ventricular systolic function and other markers of ventricular decompensation (Everett et al., 2020). Some 15-20% of patients with severe AS have evident left ventricular systolic dysfunction, which is also a predictor of decreased survival (Dahl et al., 2015; Ito et al., 2018). The process of left ventricular failure in AS is illustrated in Fig. 1.

Figure 1. Left Ventricular Decompensation in Aortic Stenosis. Reproduced with permission of Elsevier from Lindman et al. JACC Cardiovasc Imaging. 2020;13(2 Pt 1):481-493



Several different cardiac phenotypes can be recognized in patients with severe AS. Some of the patients may have only left ventricular impairment at the time of aortic valve replacement (AVR), but in more advanced phenotypic stages, patients may have structural and functional changes in the mitral valve, left atrium, pulmonary circulation, tricuspid valve and/or right ventricle, which are associated with increased risk of death after AVR (Généreux et al., 2017).

2.1.3 Clinical significance

2.1.3.1 Epidemiology

Calcified aortic valve disease (stenosis, regurgitation) is the second most common non-rheumatic heart valve disease, after degenerative mitral valve disease, with an estimated global prevalence of 12.6 million, and the highest prevalence is observed in countries with high socioeconomic status (Yadgir et al., 2020). In a hospital setting, AS is the most common valvular disease encountered (Iung et al., 2003, 2019). A recent prospective study of a primary care cohort aged ≥65 years without previously detected valve disease demonstrated that 34% of 2500 individuals had mild aortic valve calcification on echocardiography (d'Arcy et al., 2016). The prevalence of moderate or severe AS was 0.4% in a pooled analysis of three epidemiological adult cohorts of all ages (Nkomo et al., 2006), and the prevalence of severe AS was 4.3% in individuals ≥70 years of age (Danielsen et al., 2014). Other epidemiological studies from Nordic countries and North America have also pointed out the importance of ageing on the proportion of individuals with AS. The prevalence of severe AS has been reported to be <1.0%, 1.3%, 2.5-3.9% and 7.3-9.8% in the respective age cohorts of <60-65 years, 60/65 to 70/75 years, 70/75 to 80 years and ≥80 years, respectively (d'Arcy et al., 2016; Danielsen et al., 2014; Eveborn et al., 2013; Lindroos et al., 1993; Nkomo et al., 2006).

In a large nationwide study of the entire Swedish population, the incidences of all valvular heart diseases were recently estimated based on mandatory diagnosis code reporting. The incidence was highest for AS, 37.8 in men and 24.2 in women per 100 000 person-years, with a steep rise in older cohorts being as high as 350 per 100 000 person-years for people ≥85 years of age (Andell et al., 2017). Interestingly, the incidence of AS declined in Sweden between 1989 and 2009 (Martinsson et al., 2015).

2.1.3.2 Natural history and prognosis

Generally, significant heart valve disease portends a poorer survival than an absence of valvular heart disease (Nkomo et al., 2006). AS is a progressive disease. This is evidenced, for example, by an annual increase in aortic valve mean pressure gradient of 2-3 mmHg on Doppler echocardiography or by an increase in aortic valve calcium load on multislice computed tomography (MSCT) (Doris et al., 2020; Eveborn et al., 2013).

Various degrees of AS have an impact on survival, as was shown by Strange et al. from a recent database of more than 200,000 individuals. The age- and sex-adjusted risk for 5-year mortality was 1.63-fold with mild AS, 2.6-fold with moderate AS and 3.05-fold with severe AS cohorts compared to the cohort without AS. Importantly, moderate and severe AS were associated with almost equally dismal prognoses at 5 years, with mortality rates of 56% for moderate AS and 67% for severe AS (Strange et al., 2019).

Asymptomatic patients with mild to moderate AS have a 0.39% annual risk for sudden cardiac death (Minners et al., 2020). A meta-analysis of 29 studies including asymptomatic severe AS patients estimated a rate of 1.1% for sudden death, 3.0% for cardiac death and 18.1% for an indication for AVR per year (Gahl et al., 2020). The risk factors for poorer outcome in asymptomatic patients with AS are moderately or severely calcified aortic valves with rapid progression of stenosis, left ventricular hypertrophy, and left ventricular damage (Gahl et al., 2020; Minners et al., 2020; Nistri et al., 2012; Rosenhek et al., 2000). The group from Vienna demonstrated that an increase in echocardiographic Doppler velocity of more than 0.3 m/s within a year or a Doppler velocity ≥5.0 m/s is associated with poorer survival and the need for AVR during follow-up (Rosenhek et al., 2000, 2010).

Symptomatic AS patients have an expected life span of only a couple of years if left untreated, as was observed by Ross and Braunwald more than 50 years ago, a finding that has been confirmed in several studies (Iung et al., 2007; Ross & Braunwald, 1968; Turina et al., 1987; Varadarajan et al., 2006). In a study by Bach et al., the survival of unoperated symptomatic patients with AS was only 56% at 2 years (Bach et al., 2009). In another study, patients unwilling to undergo recommended AVR for severe AS survived only 23±5 months on average and had 18±7% survival at 5 years (Horstkotte & Loogen, 1988). In the PARTNER study, patients who were not eligible for surgical treatment received medication and 84% of them also underwent balloon aortic valvuloplasty (BAV). All-cause mortality was 50.7%, 68% and 93.6% at 1, 2 and 5 years, respectively (Kapadia et al., 2015a; Leon et al., 2010; Makkar et al., 2012).

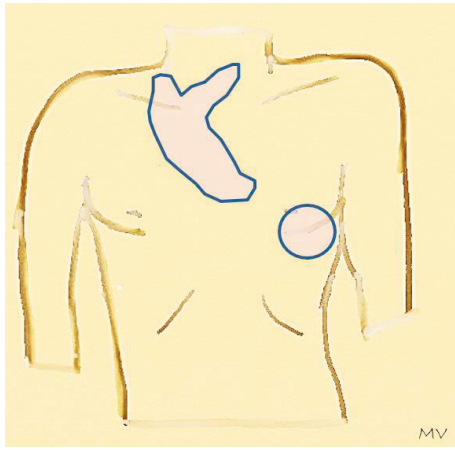
2.1.3.3 Clinical manifestation

In symptomatic severe AS, typical manifestations include dyspnoea (56%), syncope (8%) and angina pectoris (6%) or a combination of these symptoms (29%) (Bach et al., 2009).

A typical finding in AS is a harsh auscultatory systolic murmur, which is audible over the ascending aortic area at the sternal border and radiates to the neck and

sometimes to the cardiac apex (Fig. 2). The second heart sound can be diminished. In the case of markedly reduced left ventricular function, the murmur can be alleviated despite a significant stenotic valve orifice. Carotid pulse upstroke can be delayed and diminished, and the left ventricular apical impulse is amplified when there is severe valve obstruction (Carabello & Paulus, 2009).

Figure 2. Areas of auscultatory systolic murmur in aortic stenosis.



2.1.4 Diagnostic tests

Common examinations used in the evaluation of cardiovascular diseases, such as electrocardiography, chest X-ray and cardiac biomarkers, can provide useful information about left ventricular load but are not sensitive or specific in the diagnosis of AS (Carabello & Paulus, 2009). The most useful and recommended method to diagnose AS is echocardiography.

2.1.4.1 Echocardiography

Echocardiography allows direct visualization of the aortic valve morphology and function as well as evaluation of the cardiac consequences of the valve obstruction: ventricular hypertrophy, diastolic or systolic dysfunction, mitral or tricuspid valve regurgitation, and elevated pulmonary pressure. The quantification of stenosis severity is based on Doppler echocardiography, which makes possible the measurement of the velocity of the jet in the narrowed valve orifice. The pressure drop (i.e., gradient) between the left ventricle and aorta in systole can be obtained

from the continuous Doppler velocity curve by the Bernoulli equation, which originally contains terms for velocity, viscous friction, and flow acceleration (Weyman & Scherrer-Crosbie, 2005). For clinical purposes, the equation can be simplified and expressed as follows: $\Delta P = 4\ x\ (V_{max}^2 - V_{proximal}^2)$, where ΔP is the pressure gradient, V_{max} is the maximal Doppler velocity and $V_{proximal}$ is the Doppler velocity proximal to the narrowed orifice, i.e., in the left ventricular outflow tract (LVOT). Usually this (low) proximal velocity can be neglected, and an even more simplified Bernoulli equation is used: $\Delta P = 4\ x\ V_{max}^2$ provides the maximal pressure gradient, and the respective mean gradient is calculated from the mean of the instantaneous gradients during the ejection period (Baumgartner et al., 2017b; Weyman & Scherrer-Crosbie, 2005).

The peak jet velocity is a robust and easy measurement of stenosis severity if obtained parallel to the blood flow, but more than 20 degrees of angulation of the Doppler beam can introduce a clinically significant error and lead to underestimation of the stenosis (Armstrong & Ryan, 2010). If Doppler velocities are recorded only from the apical window, the severity of the stenosis is underestimated in more than 20% of the patients (de Monchy et al., 2009; Ringle et al., 2018; Thaden et al., 2015).

Calculation of the aortic valve area (AVA) is based on the law of conservation of mass, as the volume and flow measured at the LVOT entering the stenotic valve orifice must remain constant. The stroke volume is calculated as a product of the LVOT area (πr^2) and the velocity-time integral in the LVOT by pulsed Doppler during the ejection period. The velocity-time integral at the stenotic orifice is obtained by continuous Doppler. Then the effective AVA can be calculated as follows: $AVA = \frac{CSA_{lvot}\ x\ VTI_{lvot}}{VTI_{av}}$, where CSA_{lvot} is the cross-sectional area of the LVOT, VTI_{lvot} is the velocity-time integral at the LVOT, and VTI_{av} is the velocity-time integral at the aortic valve orifice (Baumgartner et al., 2017b). Incorrect measurement of the continuity equation components may lead to under- or overestimation of AVA. A common error is made in the measurement of LVOT diameter. The correct level of the measurement is debated, the LVOT geometry is usually elliptical, not circular as assumed by the equation, and LVOT calcifications can sometimes hamper correct measurement (Baumgartner et al., 2017b; Clavel et al., 2015; Gaspar et al., 2012; Hahn & Pibarot, 2017; Saitoh et al., 2012; Utsunomiya et al., 2012).

Direct visualization of the valve opening is possible with transthoracic echocardiography, but planimetric measurement of anatomic AVA is often challenging due to calcified leaflet margins and difficulty obtaining a perpendicular imaging plane at the narrowest orifice. Three-dimensional imaging with

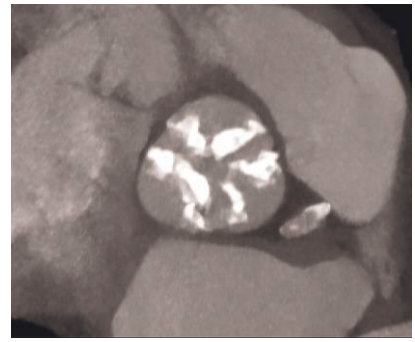
transesophageal echocardiography, MSCT or magnetic resonance imaging can then be helpful. It should be recognized that anatomic AVA is slightly larger than the effective AVA measured by the continuity equation (Baumgartner et al., 2017b). However, planimetric methods have a good correlation with cardiac catheterization-based AVA but do not provide a major benefit over the echocardiographic continuity equation (Rong et al., 2020). Dobutamine stress-echocardiography can be useful in the presence of left ventricular dysfunction to differentiate between severe and non-severe AS (Baumgartner et al., 2017b).

2.1.4.2 Cardiac catheterization

Invasive cardiac catheterization is needed when reliable data cannot be obtained from other diagnostic modalities. Still, diagnostic catheterization should be used selectively because of its associated small risk of neurological complications related to retrograde passage of the catheter through the calcified aortic valve (Omran et al., 2003). Simultaneous pressure tracings are recorded from the left ventricle and the ascending aorta, enabling the measurement of the pressure drop or gradient. Doppler echocardiographic and catheter gradients have good linear agreement, but they measure the pressure drop at different locations. Doppler measures the maximal velocities and gradient at the vena contracta, which is the location of constrained flow just downstream of the anatomic orifice. After the vena contracta region, some of the kinetic energy is reconverted into potential energy, a phenomenon called pressure recovery. Invasively measured AVA is calculated by the Gorlin formula: $AVA = \frac{CO/(SEP\ x\ HR)}{44.3\sqrt{\Delta P_{mean}}}$, where CO is cardiac output, SEP is the systolic ejection period, HR is heart rate and ΔP_{mean} is the mean pressure gradient. The original Gorlin formula was validated in mitral stenosis patients and represents the anatomic valve area rather than the echocardiographic effective orifice area (Gorlin & Gorlin, 1951; Nishimura & Carabello, 2012; Weyman & Scherrer-Crosbie, 2005).

2.1.4.3 Multislice computed tomography

Figure 3 MSCT showing calcified aortic valve.



MSCT has an excellent spatial resolution, making it possible to evaluate cardiac structures in detail. It has an additional role in diagnosing and classifying AS as well as in preprocedural planning of aortic valve intervention.

Similarly to the quantification of calcium in the coronary arteries (Agatston et al., 1990), it is possible to measure the amount of calcification in the stenotic aortic valve by MSCT (Cueff et al., 2011; Messika-Zeitoun et al., 2004) (Fig. 3). In patients with severe AS, the calcium burden of the valve is higher in men than women, and several studies have identified prognostic sex-specific thresholds for severe AS (Aggarwal et al., 2013; Clavel et al., 2013; Pawade et al., 2018). Measuring aortic valve calcium is useful in situations where echocardiographic findings are discordant. A calcium score ≥2000 in men and ≥1200 in women is suggestive of severe AS (Baumgartner et al., 2017b).

2.1.4.4 Grading the severity of aortic stenosis

Current guidelines recommend that AS should be graded with echocardiography as mild, moderate, or severe using the parameters shown in Table 1 (Baumgartner et al., 2017a; Baumgartner et al., 2017b; Nishimura et al., 2014).

Table 1. Recommendations for grading the severity of aortic stenosis

	Mild	Moderate	Severe
Peak velocity (m/s)	2.6-2.9	3.0-4.0	>4.0
Mean gradient (mmHg)	<20	20-40	>40
AVA (cm^2)	>1.5	1.0-1.5	<1.0
AVA, indexed (cm^2/m^2)	>0.85	0.60-0.85	<0.6
Velocity ratio	>0.50	0.25-0.50	<0.25

Modified from Baumgartner et al 2017b. AVA, aortic valve area

However, a common challenge in clinical practice is that in many patients, the aortic valve gradient and area are discordant, leading to difficulties in classifying stenosis severity. In studies by Minners et al., 25-38% of patients with normal left ventricular ejection fraction (LVEF) and AVA <1.0 cm^2 or indexed AVA <0.6 cm^2/m^2 had a mean gradient <40 mmHg measured by echocardiography and cardiac catheterization (Minners et al., 2008, 2010). This suggests that the cut-off values for severe AS recommended by guidelines are highly inconsistent and do not correspond to each other. There are several reasons for inconsistent findings. Importantly, from

a physiological standpoint, a low gradient can result from a low transvalvular flow rate. This is observed in patients with impaired LV systolic function, termed classical low-flow low-gradient AS, and in patients with normal systolic function, termed paradoxical low-flow low-gradient AS. Low-flow, low-gradient aortic stenosis is classically defined as a combination of stroke volume <35 ml/m², mean gradient < 40 mmHg, and AVA <1.0 cm² (Hachicha et al., 2007), but the best prognostic thresholds for reduced stroke volume may be sex-specific, <32 ml/m² for women and <40 ml/m² for men (Guzzetti et al., 2020). Systemic hypertension and reduced arterial compliance correspondingly may affect gradients in normal-flow severe AS (Kadem et al., 2005; Little et al., 2007). Some patients may not have a true severe AS at all if the pressure recovery phenomenon is taken into account and the energy loss index is calculated instead of the indexed AVA (Altes et al., 2020). In the case of a mean gradient <40 mmHg, AVA <1.0 cm² and preserved LVEF, the presence of factors illustrated in Table 2 increases the likelihood of true severe AS.

Table 2. Criteria that increase the likelihood of severe aortic stenosis in patients with discordant echocardiographic findings

Clinical criteria	Physical examination consistent with severe aortic stenosis Typical symptoms without other explanation Elderly patient (>70 years)		
Qualitive imaging criteria	LVH (additional history of hypertension to be considered) Reduced LV longitudinal function without other explanation		
Quantitative imaging criteria	Mean gradient 30–40 mmHg AVA<0.8 cm² Low flow (SV <35 ml/m²) confirmed by other techniques than the standard Doppler technique (LVOT measurement by 3D TEE or MSCT; CMR; invasive data)		
	Calcium score by MSCT		
	Severe AS very likely	men >3000	women >1600
	Severe AS likely	men >2000	women >1200
	Severe AS unlikely	men <1600	women <800

Modified from Baumgartner et al 2017b. AS, aortic stenosis; AVA, aortic valve area, CMR, cardiac magnetic resonance imaging; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MSCT, Multislice computed tomography; SV, stroke volume, TEE, transesophageal echocardiography

2.2 TREATMENT OF AORTIC VALVE STENOSIS

2.2.1 General aspects

Due to the previously described dismal prognosis of symptomatic severe AS, it is important to recognize these individuals and offer proper treatment. Ross and Braunwald concluded in 1968 that the prognosis was rapidly improved after

corrective valve surgery compared to conservative treatment (Ross & Braunwald, 1968).

Before the wide adoption of TAVI, approximately one-third of symptomatic elderly patients with AS did not undergo SAVR because of advanced age, left ventricular dysfunction or high predicted risk for surgery (Bach et al., 2009; Iung et al., 2007). Bach et al. noticed that only a minority of symptomatic patients who were not operated on were offered surgical consultation despite a non-prohibitive calculated operative risk (Bach et al., 2009).

Currently, TAVI and SAVR are methods proven to achieve long-term relief of symptoms and to restore life expectancy to the same level as in the general population (Makkar et al., 2020; Martin et al., 2017a; Viktorsson et al., 2016).

Pharmacological therapies have not been effective in the treatment of calcified aortic valve disease. Despite the known pathophysiological mechanisms, several randomized controlled trials have failed to demonstrate that intensive lipid-lowering therapy reduced disease progression and aortic valve-related adverse outcomes (Chan et al., 2010; Cowell et al., 2005; Rossebø et al., 2008), but a secondary analysis of the SEAS study suggested a potential benefit in a subgroup of patients with mild AS and high low-density lipoprotein levels receiving the simvastatin/ezetimibe combination (Greve et al., 2019). Inhibition of the renin-angiotensin system (RAS) is another potential target for pharmacological treatment in AS. The use of RAS inhibitors may reduce the need for AVR, but data from the few randomized and non-randomized studies are low-quality and insufficient to make firm conclusions (Andersson & Abdulla, 2017). RAS inhibition is associated with better mid-term outcomes after SAVR and TAVI in observational studies, but the results of a randomized controlled study are still pending (Amat-Santos et al., 2018; Chen et al., 2020; Goel et al., 2014; Inohara et al., 2018; Magne et al., 2018; Ochiai et al., 2018; Rodriguez-Gabella et al., 2019).

2.2.2 Surgical aortic valve replacement

The first report of successful subcoronary AVR to treat aortic valve diseases with an artificial heart valve prosthesis was published in 1960. The development of extracorporeal circulation techniques made open-heart procedures possible (Harken et al., 1960). SAVR is conventionally performed via median sternotomy under cardiopulmonary bypass and cardiac arrest. The calcified valve is then excised through aortotomy, and a prosthetic heart valve is sutured to the aortic annulus. Less invasive methods via smaller incisions, including mini-sternotomy and mini-

thoracotomy, have been used, but it is unclear if they are associated with major benefits over full sternotomy (Kirmani et al. 2017). Surgically implanted artificial heart valves are either mechanical or tissue prostheses.

2.2.2.1 Mechanical prostheses

The first mechanical heart valve prosthesis introduced in 1960 was the Starr-Edwards ball-cage valve followed by the Björk-Shiley and Medtronic Hall tilting disc valves. All mechanical prostheses currently implanted are composed of two pivoted leaflets inside the valve housing made of pyrolytic carbon and small amounts of metals in some brand models. The first bi-leaflet mechanical valve by St. Jude Medical (currently Abbott) was introduced in 1977, followed by other bi-leaflet valves (e.g., Carbomedics, Sorin Bicarbon, ATS Open Pivot, On-X) (Grunkemeier et al., 2000).

2.2.2.2 Biological prostheses

Biological heart valve prostheses currently used in the aortic position are made of bovine pericardium with or without a stented frame (e.g., Carpentier-Edwards Perimount Magna Ease, Sorin Mitroflow, Abbott Trifecta), or porcine valves. Stentless porcine bioprostheses as well as human valves (homograft, autograft) are used only in specific situations (Grunkemeier et al., 2000). The Perceval (LivaNova), Intuity (Edwards Lifesciences) and 3F-Enable (Medtronic) sutureless aortic bioprostheses were more recently introduced, and only the first two are currently available. The use of a sutureless prosthesis aims at more rapid deployment than conventional SAVR, which might translate into shorter operation times and better outcomes (Bilkhu et al., 2019). A meta-analysis of two small randomized and several observational studies showed shorter aortic cross-clamp and cardiopulmonary bypass times with sutureless AVR, but there was no difference in postoperative complications or mortality (Sohn et al., 2018). Furthermore, more permanent pacemaker implantation (PPMI) was needed after sutureless SAVR compared to conventional SAVR (Sohn et al., 2018). Preliminary results from randomized, controlled, multicentre trials comparing the sutureless Perceval prosthesis to sutured aortic bioprosthesis were presented in the annual meeting of the American Association of Thoracic Surgery, with promising results regarding safety and effectiveness, but so far, the results have not been published in a peer-reviewed journal.

2.2.2.3 Mechanical versus biological prostheses

In randomized studies comparing SAVR with mechanical valve prostheses and bioprostheses, one trial showed a slight long-term survival benefit with mechanical valves, which was not observed in the two other trials (Hammermeister et al., 2000; Oxenham, 2003; Stassano et al., 2009). Observational studies in patients >65-70 years of age indicate equal or better long-term survival with bioprostheses compared to mechanical valves. In a cohort of >300,000 individuals, the adjusted hazard ratio (HR) for death was 0.97 (95% CI 0.95 to 0.98) with bioprostheses compared to mechanical prostheses (Schelbert et al., 2008), and a more recent study reported an adjusted HR of 1.04 (95% CI 1.01 to 1.07) for death (Brennan et al., 2013). In a Finnish retrospective registry study using propensity score matching of patients, markedly inferior ten-year survival was observed in patients >70 years of age if treated with mechanical valves compared to bioprostheses (HR=1.48; 95% CI 1.21 to 1.80) (Kytö et al., 2019).

2.2.2.4 Selection between a mechanical valve and a bioprosthesis

There has been increasing interest in implanting biological aortic prostheses in younger patients, as was demonstrated in a study by Iribarne showing that the ratio of biological valve implants increased from 20% to 90% of all implants between 1991 and 2015 in a cohort of 50-65-year-old patients (Iribarne et al., 2019). Two systematic reviews and meta-analyses provided conflicting data on long-term outcomes after SAVR with mechanical or biological prostheses in patients <65-70 years of age, but the analysis with less heterogeneity suggested a survival benefit with mechanical valves at 15 years (Diaz et al., 2019; Zhao et al., 2016). Very recent prospective registry data from the United States showed no difference in mortality at 15 years between mechanical and biological prosthesis recipients aged 50 to 65 years (Iribarne et al., 2019), while a retrospective Finnish nationwide registry study found that SAVR with mechanical valves was associated with lower mortality at 10 years in matched patients aged 50 to 70 years (Kytö et al., 2020).

Mechanical valve prostheses require life-long anticoagulation and may therefore expose patients to a higher long-term risk for bleeding compared to bioprostheses (Brennan et al., 2013; Diaz et al., 2019; Hammermeister et al., 2000; Kytö et al., 2019; Oxenham, 2003; Schelbert et al., 2008; Zhao et al., 2016). Weighing the risks of bleeding and reoperation, van Geldorp performed a microsimulation in a large dataset, suggesting that a 60-year-old patient would have higher event-free life expectancy with an aortic bioprosthesis compared to a mechanical prosthesis (van Geldorp et al., 2009).

2.2.3 Transcatheter aortic valve implantation

The basic principle of TAVI is to implant a bioprosthesis inside the calcified native valve via the aorta with a delivery catheter. The native aortic valve is opened and pushed aside by the stent of a bioprosthesis.

The first transluminal subcoronary aortic stent valves were implanted in pigs in 1989 by Henning Rud Andersen (Andersen et al., 1992). After many years of development in animal models, the first-in-man transcatheter aortic valve prosthesis was implanted by Alain Cribier in 2002. The prosthesis consisted of three bovine pericardial leaflets mounted inside a balloon-expandable stent. The prosthesis was crimped on a balloon catheter and implanted antegradely via the femoral vein and a transseptal puncture inside the stenotic bicuspid aortic valve (Cribier et al., 2002). After the first successful implantation, a series of patients who were denied surgery were treated with the Cribier-Edwards prosthesis. This prosthesis was constructed from a stainless-steel stent with an equine pericardial trileaflet valve. It was implanted using either retrograde or antegrade technique, with encouraging haemodynamic and clinical results (Cribier et al., 2004, 2006; Webb et al., 2006). During the same time frame, a self-expanding CoreValve prosthesis was implanted using transfemoral access in 25 inoperable patients, with a high success rate (Grube et al., 2006). Unlike the Cribier valve, the prosthesis was made of a nitinol stent frame and bovine (1st generation) or porcine (2nd generation) pericardial leaflets.

Antegrade transapical implantation via mini-thoracotomy was also developed, and it became the second most used access during the early years of TAVI (Di Mario et al., 2013; Himbert et al., 2009; Walther et al., 2007). However, early and mid-term survival was shown being lower than transfemoral TAVI (Biancari et al., 2016) and the transapical access is currently used only when TAVI through peripheral access sites are not feasible. Due to challenges in accommodating valve delivery systems in different anatomies, alternative access sites have been used: trans-subclavian/-axillary (Asgar et al., 2009), transaortic (Etienne et al., 2011; Latsios et al., 2010), transcarotid (Modine et al., 2010) and transcaval-aortic (Greenbaum et al., 2014).

Technological development has made it possible to further improve the results of TAVI, especially to reduce the incidence of significant paravalvular regurgitation (PVR) and major vascular complications. Several generations of the balloon-expandable Sapien valve (Edwards Lifesciences, CA, USA) (Schymik et al., 2019) and the self-expanding CoreValve/Evolut valve (Medtronic, MN, USA) (Forrest et al., 2020) have been used clinically, and various self-expanding (Kim et al., 2018; Søndergaard et al., 2018; Wenaweser et al., 2016), mechanically expanding (Meredith et al., 2012) and balloon-expandable valves are currently available (Sharma et al.,

2020). In some valve models, the biological part of the valve sits at the level of the native aortic valve (intra-annular), while in others it is above the native annulus (supra-annular).

The encouraging results of extensive research have broadened the indications of TAVI from inoperable patients to high-risk, intermediate-risk and low-risk patients (Leon et al., 2010, 2016; Mack et al., 2019; Popma et al., 2019; Reardon et al., 2017; Smith et al., 2011; Thyregod et al., 2015). The procedural volume of TAVI has surpassed SAVR in the treatment of AS in many countries in 2015-2016 (Culler et al., 2018; Eggebrecht & Mehta, 2019; Mäkikallio et al., 2019).

The remaining challenges in TAVI are optimal treatment of bicuspid AS and degenerated surgical bioprostheses (valve-in-valve) and maintaining access to coronary arteries after TAVI (Barbanti et al., 2019b; Husso et al., 2020).

2.2.4 Perimount and Sapien bioprosthesis technology

Several generations of Carpentier-Edwards Perimount surgical aortic bioprostheses (Edwards Lifesciences, Irvine, CA) have been developed over 40 years for the treatment of aortic valve diseases. The Perimount is a stented bioprosthesis made of a cobalt-chromium alloy frame and silicone rubber sewing ring with polyester clothing. The valve has three bovine pericardial leaflets mounted inside the stent. A patented anti-calcification process (ThermaFix) is utilized to reduce the risk of leaflet degeneration after implantation. Their engineering has strived to optimize valve performance, durability and ease of implantation, and the latest generations, Magna and Magna Ease prosthesis, have supra-annular designs to improve haemodynamic performance. The same tissue engineering and processing are also used in the transcatheter Sapien bioprosthesis (Edwards Lifesciences, Irvine, CA), which has bovine pericardial leaflets sewed inside a cobalt-chromium alloy stent. The latest generations of the Sapien valves have improved sealing cuffs made by polyethylene terephthalate to reduce the risk of paravalvular aortic valve regurgitation.

2.2.5 Transcatheter balloon aortic valvuloplasty

BAV was developed for the treatment of AS in patients with advanced age or high risk for SAVR (Cribier et al., 1986). A decrease in aortic valve gradient, an increase in AVA and symptomatic relief after the procedure are observed, but the clinical improvement lasts for a limited time, usually six months (Kapadia et al., 2015b; Letac et al., 1988).

2.2.5.1 The results of BAV

The inefficiency of BAV at significantly improving longer-term survival can be estimated from the results of the PARTNER 1 trial, which randomized inoperable patients with AS to standard therapy and TAVI. Despite the fact that 84% of the patients in the standard therapy group underwent BAV after randomization, mortality was higher than in the TAVI group (50.7% vs. 30.7% at 1 year, 68.0% vs. 43.3% at 2 years, 93.6% vs. 71.8% at 5 years) (Kapadia et al., 2015b; Leon et al., 2010; Makkar et al., 2012). Several patient series have demonstrated similarly poor long-term survival after BAV, mortality being 50% at one year and 65-80% at two years after the procedure, and cardiac mortality was the major cause of death (Eltchaninoff et al., 2014; Lieberman et al., 1995; Otto et al., 1994b). Associated short-term mortality was 1-9%, the risk of stroke was 1-2% and the major vascular complication rate was 2-10% (Dall'Ara et al., 2020), not significantly different from the results in patients treated with TAVI (Alkhouli et al., 2017).

2.2.5.2 Current use of BAV

In contemporary practice, BAV is usually utilized as a bridge to TAVI or SAVR in patients presenting with cardiogenic shock due to AS or in palliative care (Dall'Ara et al., 2020; Wernly et al., 2020). It is used during TAVI procedures to pre- or post-dilate the aortic valve (Deharo et al., 2018; Hahn et al., 2018), but current evidence does not support the systematic use of valvuloplasty during TAVI (Leclercq et al., 2020; Pagnesi et al., 2020; Toutouzas et al., 2019).

However, in valve-in-valve procedures for the treatment of failed bioprostheses, BAV can be utilized to crack the stent of a failed prosthesis to improve the haemodynamics of the transcatheter prosthesis (Allen et al., 2019; Sathananthan et al., 2020). Some operators use the valvuloplasty in the sizing of the aortic valve annulus to choose the correct transcatheter prosthesis (Xu et al., 2020).

Current European guidelines on valvular heart disease state that BAV may be considered (Class IIb) as a bridge to SAVR or TAVI in haemodynamically unstable patients, in patients with severe symptomatic AS needing urgent noncardiac operation, as a diagnostic procedure in patients with other diseases potentially causing the symptoms, or in patients with potentially reversible severe organ dysfunction (Baumgartner et al., 2017a).

2.3 RISK STRATIFICATION FOR INVASIVE TREATMENT

Patients with AS often have advanced age and significant comorbidities. It is obvious that invasive treatment carries an increased risk for most patients. Here, risk means the probability that a patient undergoing a procedure will experience an adverse event, such as death or a certain complication. A risk factor is an individual feature or an external trigger that increases or decreases the risk.

2.3.1 Risk factors in surgical aortic valve replacement

Risk factors for adverse events in SAVR are related to patient demographics, functional status and associated comorbidities, including age, female sex, obesity, cerebrovascular disease, aortic atherosclerosis, diabetes, CKD, congestive heart failure, low LVEF, acute myocardial infarction, previous cardiac operation, combined procedure, reduced mobility, cachexia, tricuspid regurgitation, pulmonary hypertension, coronary artery disease (CAD), preoperative atrial fibrillation (AF) and anemia (de Arenaza et al., 2010; Hannan et al., 2009; Nashef et al., 2012; Rocha et al., 2019; Thourani et al., 2018).

Age is a major determinant of long-term mortality. The adjusted HR for 30-month mortality after SAVR was 1.6 in patients aged 65 to 74 years compared to patients <65 years of age, and the respective hazards were 2.2 in the 75-84-year and 4.0 in the ≥85-year age groups (Hannan et al., 2009). After surgery, severe CKD was associated with a 3-fold adjusted hazard risk for operative and long-term mortality (Thourani et al., 2011). Cerebrovascular disease, aortic and peripheral vascular disease, chronic obstructive pulmonary disease (COPD), diabetes, immunodeficiency and previous heart surgery are each associated with a HR of ~1.5 for long-term mortality (Hannan et al., 2009).

2.3.2 Risk factors in transcatheter aortic valve implantation

Patients undergoing TAVI are older and have more comorbidities than patients undergoing SAVR (Mäkikallio et al., 2019). Three major risk factors will be herein discussed, CKD, COPD, and frailty, but numerous other risk factors have been identified (e.g., reduced EF, pulmonary hypertension, mitral regurgitation) (Puri et al., 2016).

CKD is usually estimated by plasma creatinine or, more accurately, by estimating the glomerular filtration rate (eGFR). More than half of the patients undergoing TAVI have at least moderately reduced kidney function, i.e., eGFR <60

ml/min/1.73 m² (CKD Stage 3-5). In multivariate analysis of data from the FRANCE-2 registry, 30-day and 1-year mortality were higher with worsening renal function, and eGFR <45 ml/min/1.73 m² was associated with poor 1-year outcome. New York Heart Association (NYHA) class III-IV symptoms, COPD, reduced EF, and elevated pulmonary pressure were also independent predictors for mortality in this study (Oguri et al., 2015). The presence of severe CKD doubled the risk of death one year after the procedure (Bandyopadhyay et al., 2020; Thourani et al., 2016a). In a multicentre study of more than 2,000 patients who underwent TAVI, two-year Kaplan-Meier survival was 48.7% in CKD stage 5, 61.6% in CKD stage 4, 72.4% in CKD stage 3 and 75.2% in CKD stage 1-2 (Allende et al., 2014). A systematic review and meta-analysis of 47 TAVI studies concluded that severe CKD was associated with an unadjusted HR of 2.7 and moderate-to-severe CKD with an adjusted HR of 1.6 for mid-term mortality (Chen et al., 2015). CKD also increased the risk for procedural complications such as stroke, bleeding and acute kidney injury (AKI) (Chen et al., 2015).

The prevalence of COPD in TAVI patient populations varies between 12.5% and 43.4% (Liao et al., 2016). Patients with moderate and severe chronic lung disease (CLD) had reduced survival after TAVI compared to patients without CLD, but most of them still improved their functional class and quality of life from baseline (Crestanello et al., 2017). However, CLD patients less often enjoyed favourable health benefits, which were defined as being alive with an improved quality of life at the 3-year follow-up (Crestanello et al., 2017). Dvir et al. (2014) analysed data from the PARTNER trial showing that high-risk patients with CLD had similar survival in the surgical and transcatheter treatment arms, but overall mortality was higher in patients with CLD than in patients without CLD. Patients with CLD and poor baseline mobility, defined as a 6-minute walk test (6MWT) <50 m, had a 4.9-fold risk for non-cardiovascular mortality during the first year after the procedure compared to those whose 6MWT was >200 m (Dvir et al., 2014). A 6MWT of <150 m was found to predict cumulative mortality in COPD patients after TAVI in another study (Mok et al., 2013). A meta-analysis of 28 studies confirmed the increased risk brought by COPD for short- and longer-term mortality after TAVI (Liao et al., 2016).

The frailty phenotype is typically characterized as a decline in a person's functional, nutritional, or cognitive status, increasing an individual's risk of dependency or death. Many different instruments have been developed to assess frailty (Walston et al., 2018). In a study by Forcillo et al., combined assessment of activities of daily living, walking speed and serum albumin was predictive for worse

30-day composite outcome, and frailty score also had better predictive value for 30-day mortality than the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score in the TAVI patient population (Forcillo et al., 2017). Malnutrition increased the risk for short-term mortality, complications and repeat hospitalizations (Emami et al., 2020), and several frailty indexes (anaemia, serum albumin, handgrip strength, gait speed, and Katz index) were independent predictors of all-cause mortality and poor outcome (death and/or limited improvement in quality of life) in the long term after TAVI (Green et al., 2015; Kiani et al., 2020; Puls et al., 2014). In a comparison of many different frailty assessment tools, a brief 4-item scale covering lower-extremity weakness, cognitive impairment, anaemia, and hypoalbuminaemia had the best predictive value for mortality (Afilalo et al., 2017). Recently, a nationwide study showed that severe frailty significantly improved the predictive ability of the EuroSCORE II in patients undergoing SAVR (Biancari et al., 2020a).

2.3.3 Risk prediction tools

Several risk prediction tools are available to support the clinical decision-making process and patient information before a planned intervention. An optimal risk model should closely estimate the observed mortality (observed-to-expected mortality ratio; O:E ratio), i.e., have a high calibration, but should also have high discrimination for correctly identifying individual risk (Khan et al., 2019).

2.3.3.1 EuroSCORE and EuroSCORE II

In 1995, data from nearly 20,000 patients undergoing cardiac surgery in different European surgical units were collected to derive a practical operative risk calculator, which was later refined with logistic regression into the logistic EuroSCORE (Nashef et al., 1999; Roques et al., 1999; Roques et al., 2003). Observations that EuroSCORE overpredicted the operative risk necessitated updating the risk model. The EuroSCORE II (ES II) was derived in 2010 based on data of more than 22,000 patients undergoing adult cardiac surgery at 154 hospitals from 43 countries (Nashef et al., 2012). The ES II includes ten patient-related, five cardiac-related and three operative factors that can be input into an online calculator to obtain the predicted risk of in-hospital mortality for a given patient.

2.3.3.2 STS – Predicted Risk of Mortality

During past decades, several risk models for cardiac surgery have been created from the databases of The Society of Thoracic Surgeons (STS). The version released in 2008 was based on data from 2002 to 2006 of nearly 1,000,000 patients, including >200,000 patients undergoing isolated valve surgery or combined valve surgery with coronary artery bypass grafting (CABG) (O'Brien et al., 2009; Shahian et al., 2009a, 2009b). The current (2018) models were developed using STS Adult Cardiac Surgery Database records between 2011 and 2014 (670,000 patients) and validated in a patient sample from 2014 to 2016 (Shahian et al., 2018). Sixty-five variables were included in the model. The STS-PROM is defined to include deaths occurring during the hospitalization in which the operation is performed, even if after 30 days, and deaths occurring after discharge from the hospital within 30 days of the procedure. The STS score also provides a risk for other endpoints, such as operative stroke and renal failure.

2.3.4 Other risk prediction tools

Other risk models have been developed from registries, such as the German aortic valve score I and II (Kötting et al., 2013; Schiller et al., 2017), FRANCE-2 score (Iung et al., 2014), OBSERVANT (Capodanno et al., 2014), tAVI2-SCORe (Debonnaire et al., 2015), and STS/ACC TAVR score (Edwards et al., 2016). Many challenges remain, as models are heterogeneous in terms of sample size, endpoint definitions and validation (Arsalan et al., 2018).

2.3.5 Performance of risk scores in predicting operative mortality

Risk models are sensitive to the specific patients populations and time frames when the models are developed, and recalibration is necessary to maintain reliability (Khan et al., 2019; Nashef et al., 2012; O'Brien et al., 2018; Schiller et al., 2017). For example, in a study of patients who underwent SAVR in two time periods (from 2002 to 2006 and from 2007 to 2010), a reduction in actual mortality in intermediate- and high-risk patients was observed, while their predicted risk remained unchanged (Thourani et al., 2015). The ES II and STS-PROM accurately predict operative risk in patients undergoing isolated aortic valve replacement, but in high-risk patients, they tended to underpredict the actual risk (Barili et al., 2013).

The ES II and STS-PROM are based on surgical patient data, so it is controversial whether they reliably predict the risk in TAVI populations. A meta-analysis of ten SAVR and TAVI studies published in 2013 and 2014 showed O:E ratios close to 1

for operative mortality with both ES II and STS-PROM in TAVI and SAVR patients, but they underestimated the risk for mortality in TAVI patients and overestimated the risk in SAVR patients. The overall accuracy of the risk scores was estimated with the pooled area under the receiver operating characteristics curve (AUC) reporting values 0.73 for ES II and 0.75 for STS-PROM in SAVR, and 0.66 for ES II and 0.63 for STS-PROM in TAVR (Biancari et al., 2014). Usually, the larger the AUC, the better is the model.

In a more recent meta-analysis including 24 TAVI studies published from 2011 to 2015, pooled O:E ratios were 0.31 (95% CI 0.25–0.38) for the logistic EuroSCORE, 1.26 (95% CI 1.06–1.51) for ES II and 0.95 (95% CI 0.72–1.27) for STS-PROM. All the scores had similar discriminative ability for operative mortality (C-index 0.62) (Wang T. et al., 2017).

Data from 6676 TAVI patients in the UK TAVI registry showed the smallest absolute difference to observed mortality (shown in parentheses) with STS-PROM (0.3) and STS/ACC TAVR score (0.2), but a greater difference for logistic EuroSCORE (16.5), ES II (2.7), German AV (2.0), OBSERVANT (1.7), and FRANCE-2 (3.8). AUC values varied between 0.57 and 0.64 and were highest for STS/ACC (Martin et al., 2017b).

Henn et al. reported very low O:E ratios for 30-day mortality by STS-PROM: 0.4 for all TAVI patients, <0.5 in all risk categories and 0.8 in the transapical TAVI group (Henn et al., 2019).

The STS/ACC TAVR score was developed and validated in the TAVI population and recently externally validated in two TAVI cohorts. STS/ACC TAVR and STS-PROM showed the best discrimination in both studies, and ES II performed equally well in one of these studies (Arsalan et al., 2018; Codner et al., 2018). In the study by Codner, all the scores predicted higher mortality than was observed (Codner et al., 2018).

One major limitation of the risk scores is that most of them do not capture a major comorbidity burden in low-risk TAVI patients (Bagur et al., 2018). Adding components of frailty assessment to surgical risk score would improve the predictive value of survival and changes in functional status after TAVI (Biancari et al., 2020a; Schoenenberger et al., 2013; Stortecky et al., 2012).

2.4 RESULTS OF SURGICAL AND TRANSCATHETER TREATMENT IN COMPARATIVE STUDIES

The first randomized controlled trials comparing SAVR and TAVI were carried out in inoperable patients and in patients with a high predicted risk for surgery. High risk was assessed by cardiac surgeons and cardiologists and was defined as a >15% chance of dying within 30 days after surgery. A STS-PROM score >10% was used as a guideline for high operative risk (Adams et al., 2014; Smith et al., 2011).

These studies were followed by trials comparing the outcomes of patients in intermediate- and low-risk categories. Intermediate risk was defined as a predicted operative mortality from 4 to 8% (Leon et al., 2016) or from 3 to 15% (Reardon et al., 2017), and low risk was defined as a predicted operative mortality <2% (e.g., STS-PROM <4%) (Mack et al., 2019) or <3% (Popma et al., 2019) by the Heart team.

2.4.1 Short-term outcomes

Peri- and postoperative complications have significant relevance to late mortality and quality of life measures. Major stroke, severe kidney injury, major bleeding and moderate/severe PVR were all associated with worse late outcomes (Arnold et al., 2019; Moriyama et al., 2020; Pibarot et al., 2017). Even mild PVR can be associated with increased late mortality (Kodali et al., 2012; Laakso et al., 2020a). Some studies have found increased risk for mortality and heart failure after new PPMI, but this is still a controversial issue (Arnold et al., 2019; Biancari et al., 2020b; Chamandi et al., 2018; Costa et al., 2019; Fadahunsi et al., 2016).

2.4.1.1 Operative mortality

Thirty-day mortality in the high-risk patient groups was similar after TAVI and SAVR in the PARTNER 1 study (3.4% vs. 6.5%, p=ns) and in the U.S. CoreValve High Risk Study (3.3% vs. 4.5%; p=ns) (Adams et al., 2014; Smith et al., 2011). In intermediate-risk patients, operative mortality was 3.4% after TAVI and 4.0% after SAVR (p=ns) in the PARTNER 2 trial and 2.0% vs 1.3% (p=ns) in the SURTAVI trial (Leon et al., 2016; Reardon et al., 2017). Mainly low-risk patients were randomized in the NOTION trial, and they showed similar 30-day mortality: 2.1% in the TAVI group and 3.7% in the SAVR group (p=ns) (Thyregod et al., 2015). The most recent randomized trials of low-risk patients naturally showed the lowest operative mortality rates, 0.4% in TAVI and 1.1% in SAVR in the PARTNER 3 trial, and 0.5% vs. 0.8% in the Evolut low-risk trial (intention-to-treat) (Mack et al., 2019;

Popma et al., 2019). Lower in-hospital and 30-day mortality were observed after TAVI compared to surgery in the German Aortic Valve Registry (GARY) database of 20,000 patients, particularly in the transvascular cohort (Bekeredjian et al., 2019).

2.4.1.2 Stroke

Higher risk for cerebrovascular events related to TAVI than to SAVR became a concern after the results of the PARTNER 1 trial were published. The combined rate of stroke or transient ischaemic attack (TIA) at 30 days was 5.5% vs. 2.4% (p=0.04) after TAVI vs. after SAVR. However, the rate of stroke was not different (Smith et al., 2011). Other major trials have not found any significant differences in cerebrovascular events. Accordingly, the rates of stroke at 30 days were 4.9% vs. 6.2% in the U.S. CoreValve High Risk Study, 5.6% vs. 5.6% in the PARTNER 2 trial, 2.8% vs. 3.0% in the NOTION trial, and 2.1% vs. 1.9% in the Evolut low-risk trial after TAVI and SAVR, respectively (Adams et al., 2014; Leon et al., 2016; Popma et al., 2019; Thyregod et al., 2015). Moreover, in the PARTNER 3 trial, the risk of stroke was lower in the TAVI cohort than in the SAVR cohort (0.6% vs. 2.4%, p=0.02) (Mack et al., 2019). Registry data on real-life populations have not shown any increased risk for stroke after TAVI compared to SAVR (Rosato et al., 2016; Schaefer et al., 2019).

2.4.1.3 Life-threatening and major bleeding

The rate of bleeding depends on the procedure, patient population, and, importantly, the definitions used for bleeding. In pivotal studies, SAVR was associated with a 2- to 2.5-fold higher risk for major or life-threatening bleeding compared to TAVI (Adams et al., 2014; Smith et al., 2011). The results regarding bleeding were discrepant in intermediate-risk trials, highlighting the importance of the definitions used for bleeding. In PARTNER 2, life-threatening or disabling bleeding occurred in 10.4% of patients in the TAVI group, whereas the rate was 43.4% in the SAVR group (Leon et al., 2016). In contrast, the SURTAVI trial applied very precise definitions for bleeding, leading to more harmonized results between treatment arms, and the estimated rate of life-threatening or major bleeding was 12.2% and 9.3% after TAVI and SAVR, respectively (Reardon et al., 2017). In the NOTION trial, the incidence of bleeding was lower after TAVI than SAVR (11.3% vs. 20.9%, p=0.03) (Thyregod et al., 2015). The most recent low-risk trials used additional criteria to the Valvular Academic Research Consortium 2 (VARC-2) (Kappetein et al., 2012) bleeding definition, demonstrating severe bleeding rates of 1.2% vs. 11.9%

in the PARTNER 3 trial and 2.4% vs. 7.5% in the Evolut Low Risk Trial after TAVI vs. SAVR (Mack et al., 2019; Popma et al., 2019).

2.4.1.4 Major vascular complications

Earlier studies used older-generation TAVI devices mainly in high-risk patients, leading them to have a consistently higher rates of major vascular complications than the SAVR cohorts. Such complications have a major prognostic impact in TAVI patients (Laakso et al., 2020b). The rates of major vascular complications occurred in 6 to 11% of the patients after TAVI but in 1 to 5% of the patients after surgery (Adams et al., 2014; Leon et al., 2016; Reardon et al., 2017; Smith et al., 2011; Thyregod et al., 2015). Recent low-risk trials utilizing improved TAVI devices and delivery systems did not detect statistically significantly higher rates for major vascular complications in TAVI (2.2-3.8%) compared to surgery (1.5-3.2%) (Mack et al., 2019; Popma et al., 2019).

2.4.1.5 Permanent pacemaker implantation

A new conduction disturbance necessitating PPMI is a well-known complication of valvular interventions. After SAVR, the likelihood of needing PPMI has been 4-6% in most randomized studies comparing SAVR and TAVI (Mack et al., 2019; Popma et al., 2019). However, in the respective TAVI cohorts, the risk of PPMI was variable. The lowest PPMI rate, 3.8%, was observed with early-generation balloon-expandable TAVI prostheses (Smith et al., 2011). The use of later versions of balloon-expandable valves was associated with a higher need for PPMI after TAVI (6.6-8.5%) (Leon et al., 2016; Mack et al., 2019).

Contrary to the findings with balloon-expandable TAVI prostheses, a risk for PPMI highly exceeding the respective rates in surgical cohorts is associated with the use of self-expanding TAVI prostheses. The incidence of PPMI with a self-expanding valve was 19.8%, 25.9% and 34.1% in earlier studies (Adams et al., 2014; Reardon et al., 2017; Thyregod et al., 2015) and was 17.4% in the most recent trial (Popma et al., 2019). In registries using both balloon-expandable and self-expanding TAVI prostheses, the risk for PPMI has also been higher after TAVI compared to SAVR (Rosato et al., 2016; Schaefer et al., 2019).

2.4.1.6 Paravalvular regurgitation

The incidence of moderate or severe PVR is <1% after SAVR, 10-15% with first-generation TAVI prostheses, and 3-4% with second-generation TAVI prostheses (Adams et al., 2014; Leon et al., 2016; Popma et al., 2019; Smith et al., 2011; Thyregod et al., 2015). Recent TAVI prostheses with improved technology are associated with a <1% incidence of moderate PVR. However, even with this new-generation prosthesis, the rate of mild PVR is still higher after TAVI than after SAVR (29% vs. 3%) (Mack et al., 2019).

2.4.1.7 Atrial fibrillation

Postoperative AF is common after cardiac surgery. Its pathophysiologic mechanisms include increased oxidative stress and systemic and local inflammation after surgery, and it independently predicts postoperative mortality (Greenberg et al., 2017).

In studies comparing TAVI and SAVR, a higher incidence of postoperative AF is consistently observed after surgery. The rate of new-onset AF was 5.0-7.7% after TAVI and 35.4-39.5% after SAVR in the low-risk trials (Mack et al., 2019; Popma et al., 2019). The incidence was much higher in the NOTION trial combining both worsening and new-onset AF, with rates of 16.9% vs. 57.8% in the TAVI and SAVR cohorts, respectively (Thyregod et al., 2015).

2.4.1.8 Acute kidney injury

SAVR has been associated with a higher risk for postoperative AKI than TAVI, irrespective of the patients' surgical risk level. AKI stage 2-3 was detected in 2-4% of the patients undergoing SAVR and 0.5-2% of the patients undergoing TAVI (Adams et al., 2014; Leon et al., 2016; Popma et al., 2019; Reardon et al., 2017).

2.4.1.9 Postoperative length of stay

The postoperative length of stay has been significantly shorter, usually by 4 days, after TAVI compared to SAVR (Mack et al., 2019; Reardon et al., 2017; Smith et al., 2011).

2.4.2 Long-term mortality and cardiovascular events

2.4.2.1 Patients with increased surgical risk

The PARTNER 1 trial included high-risk patients who were randomized to undergo TAVI (either transfemoral or transapical with a balloon-expandable valve) or SAVR. The primary endpoint of all-cause mortality at 1 year was similar: 24.2% in the TAVI cohort and 26.8% in the SAVR cohort (p=0.44 for noninferiority) (Smith et al., 2011). A similar risk of death from any cause was observed at 2 years, 33.9% vs. 35.0% (p=0.78), and at 5 years, 67.8% vs. 62.4% (p=0.87), for TAVI vs. SAVR (Kodali et al., 2012; Mack et al., 2015). In the U.S. CoreValve High Risk Study, patients randomly underwent TAVI with a self-expanding valve or SAVR. At 1 year, all-cause mortality was lower after TAVI (14.2%) compared to SAVR (19.1%), so TAVI met both noninferiority (p<0.001) and superiority (p=0.04) (Adams et al., 2014). In this study, death from any cause was still lower at 2 years (22.2% vs. 28.6%, p<0.05), but not at 5 years (55.3% vs. 55.4%, p=0.50), in the TAVI cohort compared to the SAVR cohort (Gleason et al., 2018; Reardon et al., 2015).

Later, two randomized trials (PARTNER 2, SURTAVI) included patients in the intermediate-risk category, showing similar primary outcomes (composite of all-cause mortality and disabling stroke) at 1 to 5 years after TAVI and SAVR (Leon et al., 2016; Makkar et al., 2020; Reardon et al., 2017).

The results from observational studies are more conflicting. Analyses of matched populations from the SAPIEN 3 registry and from the PARTNER 2 surgical patient group suggested superior survival and stroke rates after TAVI compared to surgery (Thourani et al., 2016b). In contrast, the results from a French registry study matching high-risk TAVI and SAVR cohorts showed that TAVI was associated with higher mortality at 1 year (16.8% vs. 12.8%; HR 1.33; 95% CI 1.02-1.72) and at 5 years (52.4% vs 37.2%; HR 1.56; 95% CI, 1.33-1.84) compared to SAVR (Armoiry et al., 2018). Similar findings were observed among intermediate-risk patients in the OBSERVANT registry: TAVI was associated with higher mortality than SAVR at 5 years: 44.5% vs. 35.8% (p=0.002) (Barbanti et al., 2019a).

Along with the rate of death, cerebrovascular events are a second major point of interest after intervention. The first results from the PARTNER 1 trial favoured SAVR over TAVI given its lower rates of stroke and TIA at 1 year (8.3% vs. 4.3%, p=0.04) and 2 years (11.2% vs. 6.5%, p=0.05) (Kodali et al., 2012; Smith et al., 2011). No such higher rates of cerebrovascular events were observed after TAVI at 1, 3 and 5 years in the U.S. CoreValve High Risk Study (Adams et al., 2014; Deeb et al., 2016; Gleason et al., 2018). In other randomized studies, the long-term risk for

stroke and myocardial infarction seems to be similar after TAVI and SAVR (Gleason et al., 2018; Makkar et al., 2020; Reardon et al., 2017). Again, in studies of real-life patients, TAVI is associated with a higher incidence of major adverse cardiac and cerebrovascular events (MACCE) at 5 years compared to SAVR (Armoiry et al., 2018; Barbanti et al., 2019a).

2.4.2.2 Patients with low surgical risk

Encouraging results of the randomized studies in high- and intermediate-risk patients inspired trials that compared TAVI and SAVR in low-risk populations. In the STACCATO trial, patients with severe isolated AS aged ≥75 years were randomized to transapical TAVI or SAVR. The predicted risk for operative mortality was ~3%. This study was prematurely terminated after enrolling 70 patients due to the higher event rate in TAVI compared to surgery (Nielsen et al., 2012).

The NOTION trial randomly assigned ≥70-year-old patients (n=280) without severe comorbidities and a need for coronary revascularization to TAVI (transfemoral in 96.5%) or SAVR (Thyregod et al., 2015). Of the randomized patients, 82% had STS-PROM <4% and were thus considered low-risk patients for SAVR. The composite rate of death from any cause, stroke, or myocardial infarction at 1 year was similar in the cohorts, 13.1% for TAVI vs. 16.3% for SAVR (p=0.43 for superiority). The individual components of the primary endpoint were not significantly different, with mortality rates of 4.9% vs. 7.5% and stroke rates of 2.9% vs. 4.6% for TAVI vs. SAVR (Thyregod et al., 2015). Survival was similar in the longer term, and the 5-year all-cause mortality was 27.6% in the TAVI group and 28.9% in the SAVR group (p=0.75) (Thyregod et al., 2019).

In a subanalysis from the SURTAVI trial in patients with STS-PROM <3.0%, TAVI was associated with a significantly lower risk of death or disabling stroke at 1 year (1.5% vs. 6.5%, p=0.04) compared to surgery (Serruys et al., 2018).

The PARTNER 3 and the Evolut Low Risk Trial are thus far the only randomized studies specifically excluding patients at increased risk for surgery. The results of the PARTNER 3 showed superiority of transfemoral TAVI with balloon-expandable valve compared to SAVR in the primary outcome of death from any cause, stroke, or rehospitalization at 1 year, with a hazard ratio of 0.54 (95% CI, 0.37-0.79; p=0.001). At one year, mortality was 1.0% in the TAVI group compared with 2.5% in the SAVR group (HR 0.41; 95% CI, 0.14-1.17), and the respective rates of stroke were 1.2% and 3.1% (HR 0.38; 95% CI, 0.15-1.00) (Mack et al., 2019).

The Evolut Low Risk Trial demonstrated the noninferiority of TAVI with a self-expanding valve compared to SAVR in the estimated incidence of the composite

endpoint (all-cause mortality and disabling stroke) at 2 years using the Bayesian method: the rate was 5.3% rate for TAVI compared to 6.7% for surgery (95% Bayesian credible interval −4.9 to 2.1; probability of noninferiority >0.999) (Popma et al., 2019).

Longer-term outcomes after TAVI and SAVR in low-risk patients have been compared in real-life populations using statistical matching. One analysis of a large GARY database showed similar 1-year mortality (90.0% vs. 91.2%, p=0.158) after TAVI and after SAVR in patients undergoing isolated aortic valve intervention for AS (Bekeredjian et al., 2019). However, the results from two single-centre and one multicentre observational study have indicated that TAVI was associated with poorer survival 2, 3, and 5 years after the procedure compared to SAVR (Rosato et al., 2016; Schaefer et al., 2019; Schymik et al., 2018). In the OBSERVANT study, patients treated with TAVI also had higher rates of MACCE over 3 years (Rosato et al., 2016).

A systematic Cochrane review of randomized low-risk studies suggested that there was little or no mortality difference between TAVI and SAVR (RR 0.70, 95% CI 0.44-1.11) at 1 year (Kolkailah et al., 2020), while in a meta-analysis including a low-risk subgroup from the SURTAVI trial, TAVI was associated with a significantly lower risk of all-cause death (2.1% vs. 3.5%; RR: 0.61; 95% CI: 0.39-0.96; p=0.03) and of cardiovascular death (1.6% vs. 2.9%; RR: 0.55; 95% CI: 0.33-0.90; p=0.02) at 1 year (Kolte et al., 2019).

The results of the key randomized controlled trials are summarized in Table 3.

Table 3. Results of the major randomized trials comparing TAVI and SAVR.

	Smith 2011 Kodali 2012 Mack 2015		Adams 2014 Reardon 2015 Gleason 2018		Leon 2016 Makkar 2020		Reardon 2017		Thyregod 2015, 2019 Søndergaard 2016		Mack 2019		Popma 2019	
	TAVI	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**
Age (years)	83.6	84.5	83.2	83.5	81.5	81.7	79.9	79.7	79.2	79.0	73.3	73.6	74.1	73.6
STS-PROM (%)	11.8	11.7	7.3	7.5	5.8	5.8	4.4	4.5	2.9	3.1	1.9	1.9	1.9	1.9
Operative mortality (%)	3.4	6.5	3.3	4.5	3.9	4.1	2.2	1.7	2.1	3.7	0.4	1.1	0.5	1.3
Stroke/TIA (%)	***5.5***	***2.4***	4.9	6.3	6.4	6.5	4.5	6.5	2.8	3.0	***0.6***	***2.4***	3.4	3.4
MVC (%)	***11.0***	***3.2***	***5.9***	***1.7***	***7.9***	***5.0***	***6.0***	***1.1***	5.6	1.5	2.2	1.5	3.8	3.2
PPMI (%)	3.8	3.6	***19.8***	***7.1***	8.5	6.9	***25.9***	***6.6***	***34.1***	***1.6***	6.5	4.9	***17.4***	***6.1***
Bleeding (%)	***9.3***	***19.5***	***13.6***	***35.0***	***10.4***	***43.4***	12.2	9.3	***11.3***	***20.9***	***1.2***	***11.9***	***2.4***	***7.5***
1-year mortality (%)	24.2	26.8	***14.2***	***19.1***	12.3	12.9	6.7	6.8	4.9	7.5	1.0	2.5	2.4	3.0
2-year mortality (%)	33.9	35.0	**22.2**	**28.6**	16.7	18.0	11.4	11.6	8.0	9.8			4.5	4.5
5-year mortality (%)	67.8	62.4	55.3	55.4	46.0	42.1			27.6	28.9				

Statistically significant differences between TAVI and SAVR are indicated with Bold Italic numbers (p-values <0.05). MVC, major vascular complication; PPMI, permanent pacemaker implantation; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation; TIA, transient ischaemic attack.

2.4.3 Quality of life after TAVI and SAVR

The symptoms and declined functional capacity due to AS easily improved with valve intervention. Recovery was more rapid after TAVI than after SAVR during the first months, but in the long term, the difference in symptomatic and functional status between groups diminished or disappeared (Makkar et al., 2020; Reardon et al., 2017; Smith et al., 2011). However, in low-risk patients, the health status remained better after TAVI than after SAVR at 6 to 12 months after the procedure (Baron et al., 2019).

2.4.4 Durability of aortic bioprostheses

Bioprosthetic valve dysfunction makes patients susceptible to valve-related events such as death and reintervention. The importance of valve durability becomes

especially relevant in younger patients with a longer life expectancy undergoing TAVI and SAVR with bioprosthesis. Variability in definitions, statistical methods, follow-up times, and sample sizes makes the comparison of valve durability between different reports problematic. Reintervention as a categorical event clearly underestimates the incidence of structural valve dysfunction (SVD) for many reasons. Several studies have not used longitudinal core laboratory analysis to measure haemodynamic valve performance. It should also be remembered that death is a competing risk against other time-dependent events, such as SVD (Capodanno et al., 2017; Fatima et al., 2019).

2.4.4.1 Definition of valve dysfunction and failure

The optimal metrics and definitions for valve dysfunction are debated (Akins et al., 2008; Butchart et al., 2020; Capodanno et al., 2017; Capodanno & Søndergaard, 2020; Dvir et al., 2018; Lancellotti et al., 2016). Bioprosthetic valve dysfunction can be categorized as SVD or non-structural valve dysfunction (NSVD). SVD is the irreversible degeneration of leaflets, valve sutures or stent. A valve can also be rendered dysfunctional by thrombosis or infection (Akins et al., 2008; Capodanno et al., 2019). Recently, bioprosthetic valve failure (BVF), defined as valve dysfunction leading to death, valve reintervention, or severe SVD, was suggested to be used as an outcome measure in studies exploring valve durability (Capodanno et al., 2017).

2.4.4.2 Bioprosthesis dysfunction after surgical aortic valve replacement

SVD typically starts occurring 7-8 years after implantation and becomes more evident after 10 years. The cumulative incidence of SVD after SAVR is estimated to be 6.0% at 10 years, 19.3% at 15 years, and 48.0% at 20 years (Foroutan et al., 2016; Wang M. et al., 2017).

Based on a systematic review by Fatima et al., actuarial freedom from SVD at 10 years was 77.9% to 97.6% with the Hancock II, 87.1% to 100% with the Mosaic, 93.1% with the Biocor/Epic, 39.2% to 92.5% with the Mitroflow, and 86% to 98.1% with the Carpentier-Edwards Perimount bioprosthesis (Fatima et al., 2019). A 15% to 20% risk of valve explant due to SVD at 15 to 20 years has been reported (Bourguignon et al., 2015; Iribarne et al., 2019; Johnston et al., 2015).

2.4.4.3 Bioprosthesis dysfunction after transcatheter aortic valve implantation

Data on transcatheter aortic prosthesis durability are limited. The results of studies using current European recommendations for the definition of SVD (Capodanno et al., 2017) were summarized recently, and the weighted incidence of severe SVD was 1.3% (95% CI, 0.8-1.9%) at 5 to 8 years, while the weighted incidence of bioprosthetic valve failure (BVF) was 4.6% (95% CI, 3.0-6.1%) at 6 to 8 years (Capodanno et al., 2019).

2.4.4.4 Durability of bioprostheses in comparative studies

Until a reasonable amount of long-term data is available from direct comparative studies applying uniform definitions of SVD, the durability of TAVI prostheses compared to surgical valves will remain unknown. However, randomized pivotal studies already provide some longer-term data.

The CoreValve High Risk Study and the NOTION study utilizing self-expanding TAVI devices defined SVD according to current European guidelines. SVD by 5-6 years was significantly higher in the SAVR cohorts than the TAVI cohorts in both studies, and the difference was mainly driven by the difference in moderate SVD. Statistically insignificant differences were observed in the incidence of severe SVD, with a 0.7-0.8% rate in TAVI compared with a 1.7-3.0% rate in SAVR at 5 to 6 years. Reintervention was needed in only 3.0% of the high-risk TAVI patients and in 2.2% of the low-risk TAVI patients, compared to a 1% rate of reoperation in the SAVR cohorts (Gleason et al., 2018; Søndergaard et al., 2019a).

In the PARTNER 1 trial, SVD was rare at 5 years, along with <1% reintervention rates in both treatment arms (Mack et al., 2015), and in paired echocardiographic evaluation, the incidence of moderate to severe transvalvular aortic regurgitation increased from 0.8% to 4.1% with TAVI bioprostheses (Douglas et al., 2017). Makkar et al. reported the results from the PARTNER 2 trial at 5 years: There was a 3.2% reintervention rate in patients treated with a 2nd-generation Sapien XT balloon-expandable valve. The reason for the new interventions was mainly progressive stenosis or regurgitation of the prosthesis. Reinterventions were less frequent in the surgical cohort (0.8%) and were performed mostly for endocarditis (Makkar et al., 2020). An extended analysis combining data from the PARTNER 2 trial and the Sapien 3 registry showed higher rates of SVD with the Sapien XT (9.5%) compared to surgical bioprostheses (3.5%) and the Sapien 3 prosthesis (3.9%) at 5 years (Pibarot et al., 2020b).

2.5 ESC/EACTS guidelines for the treatment of severe aortic stenosis

The latest version of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) clinical practice guidelines on valvular heart disease was published in 2017 (Baumgartner et al., 2017a). In the guideline, the strength of the recommendation and the level of evidence were graded as presented in Table 4.

Table 4. Classes of recommendations and levels of evidence

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Modified from Baumgartner et al 2017a.

In AS, the highest class of recommendation for intervention is in symptomatic patients with a high valvular gradient (I B) or low-flow low-gradient with reduced LVEF and evidence of flow reserve (I C). Aortic valve intervention should be considered in patients with symptoms and low-flow low-gradient AS with normal LVEF after additional confirmation of the stenosis severity (IIa C), as well as in patients with symptoms and low-flow low-gradient AS with reduced LVEF without flow reserve (IIa C).

In asymptomatic patients SAVR is indicated in the presence of left ventricular dysfunction due to AS (I C), or if a patient experiences symptoms (I C) or has a significant decrease in blood pressure (IIa C) during exercise testing. In asymptomatic patients, SAVR should be considered if low-risk patients have additional risk factors for adverse events (aortic peak velocity >5.5 m/s; severe valve calcification and peak velocity progression >0.3 m/s per year; markedly elevated [>threefold normal range] neurohormones; systolic pulmonary artery pressure >60 mmHg) (IIa C). Concomitant SAVR during other major cardiac surgeries is indicated

if the stenosis is severe (I C) and should be considered if the stenosis is moderate (IIa C).

The guideline document gives several requirements on the choice of intervention (TAVI or SAVR). The Class I indications for choice of intervention are as follows: 1) interventions should only be performed in centres having on-site cardiology and cardiac surgery departments with a structured heart team (I C); 2) the technical suitability and the individual risk/benefit ratio for treatment should carefully be evaluated while also taking into account available outcome data (I C); 3) SAVR is indicated in low-risk patients without certain risk factors (e.g., porcelain aorta) (I B); 4) TAVI is indicated in inoperable patients (I B); 5) in patients with high surgical risk, the choice between SAVR and TAVI should be evaluated individually by a heart team, favouring TAVI in elderly patients with suitability for transfemoral TAVI (I B).

3 AIMS OF THE STUDY

The nationwide Finnish registry on transcatheter and surgical treatment for aortic stenosis was designed to study the practice of invasive treatment for severe AS during the past ten years in Finland and to provide complementary data on the outcomes after TAVI and SAVR in a large, real-world setting.
The main aims of this thesis were as follows:

I To compare mid- and short-term outcomes in patients at low surgical risk undergoing TAVI or SAVR with or without concomitant coronary revascularization.

II To compare mid- and short-term outcomes in patients at low surgical risk and without concomitant coronary artery disease undergoing TAVI or SAVR.

III To compare the outcomes after TAVI with the Sapien 3 balloon-expandable transcatheter bioprosthesis to the outcomes after SAVR with the Perimount Magna Ease surgical bioprosthesis.

4 MATERIALS AND METHODS

4.1 Study population

4.1.1 The FinnValve registry

All Finnish university hospitals (Helsinki, Kuopio, Oulu, Tampere, Turku) participated to the FinnValve registry, and all consecutive and unselected patients undergoing TAVI and SAVR from January 1, 2008, to November 30, 2017, were included in the registry. Demographic, clinical, operative and follow-up data were retrospectively acquired from the medical records and hospital databases by study group members and trained research nurses in each centre from December 1, 2017 to July 31, 2018. Data on mortality were retrieved from the Finnish Population Register Centre, and data on late cardiovascular events and interventions were retrieved from the registry of the Finnish National Institute for Health and Welfare. A dedicated electronic case report system was used, and the database was administered at the Heart Centre, Turku University Hospital. Using the following inclusion and exclusion criteria, a total of 6463 patients (TAVI, n=2130; SAVR, n=4333) formed the registry.

Inclusion:

- Patients aged >18 years.
- Primary aortic valve procedure with a bioprosthesis for AS with or without associated regurgitation.
- TAVI and SAVR with or without associated coronary revascularization.

Exclusion:

- Patients who underwent any prior procedure on the aortic valve.
- Patients undergoing concomitant procedures on the mitral valve, tricuspid valve, or ascending aorta.
- Patients who underwent surgery for aortic valve endocarditis.
- Patients who underwent surgery for isolated aortic valve regurgitation.

4.1.2 Study I: The low-risk cohort

The definition of low surgical risk was based on not having a high predicted risk of mortality, i.e., a STS-PROM of ≥3.0%, and having none of the following prespecified clinical and procedure-related risk factors: an urgent or emergency procedure, previous cardiac surgery, >85 years of age, chronic dialysis, previous kidney transplant, severe frailty, active malignancy, acute heart failure within 60 days, porcelain aorta, long-term oxygen therapy, LVEF ≤30%, severe mitral valve regurgitation, and non-transfemoral access for TAVI. Data on mortality of these patients were obtained by the end of 2017.

4.1.3 Study II: The low-risk cohort without coronary artery disease

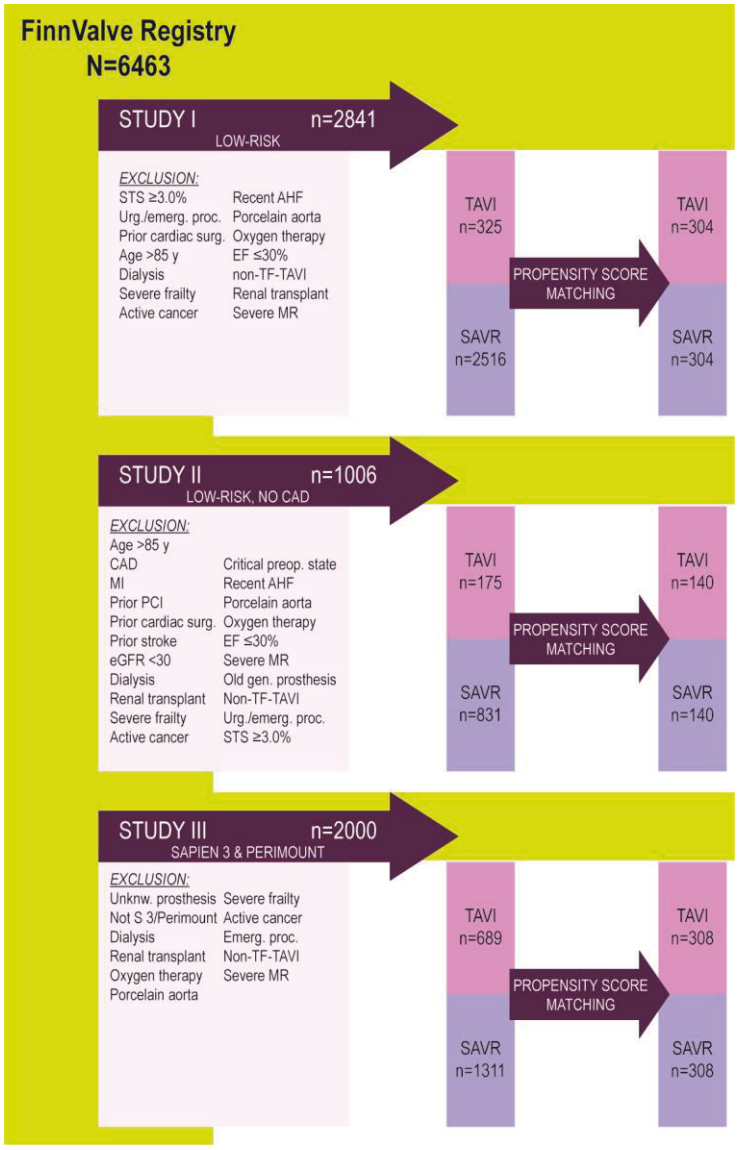
The definition of low surgical risk used in study **I** was applied in study **II**, reinforced further by excluding patients with other comorbidities. Concomitant CAD was hypothesized to be a major confounding factor in the outcome after TAVI and SAVR. Therefore, patients with CAD, previous myocardial infarction and revascularization were excluded. The potential confounding effect of older-generation valves was controlled by excluding other than the Sapien 3, Evolut R, Acurate Neo and Lotus transcatheter, and Perimount Magna Ease and Trifecta surgical prostheses. Additionally, patients with previous stroke, eGRF <30 ml/min/m^2, or critical preoperative state were excluded from the analyses in study **II**. Data on mortality and late events were obtained by the end of 2018.

4.1.4 Study III: Patients treated with the Sapien 3 or Perimount Magna Ease bioprosthesis

Fundamental differences exist in the bioprosthesis technology of both transcatheter and surgical valve prostheses. As reviewed in section 2.2.4, the transcatheter Sapien 3 valve and surgical Perimount Magna Ease valve share some technological features, offering a more unbiased comparison of the longer-term results after TAVI and SAVR. Study **III** included only patients who underwent transfemoral TAVI with the Sapien 3 or SAVR with Perimount Magna Ease prosthesis. Patients who underwent an emergency procedure, were on chronic dialysis, had a previous renal transplant, were on home oxygen therapy, had a porcelain aorta, had severe frailty, had active cancer, or had severe mitral regurgitation were excluded. Data on mortality and late events were obtained by the end of 2018.

The study flow-chart is illustrated in Fig. 4.

Figure 4. Study flow chart.



AHF, acute heart failure; CAD, coronary artery disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; S 3, Sapien 3 bioprosthesis; SAVR, surgical aortic valve replacement: STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TF, transfemoral

4.2 Definitions

4.2.1 Baseline variables

Baseline variables were defined according to EuroSCORE II criteria (Nashef et al., 2012). Extracardiac arteriopathy was defined as claudication, carotid occlusion or >50% stenosis; amputation for arterial disease; or previous or planned intervention on the abdominal aorta, limb, or carotid arteries. CLD was defined as the long-term use of bronchodilators or steroids for lung disease. The critical preoperative state was defined as ventricular tachycardia/fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before the anaesthetic room, preoperative inotropes, intra-aortic balloon pump (IABP), or preoperative acute renal failure. CCS 4 means angina pectoris at rest. Myocardial infarction was recent if it had occurred within 90 days. Pulmonary hypertension was moderate if systolic pulmonary pressure was 31-55 mmHg and severe if systolic pulmonary pressure was >55 mmHg. The procedure was urgent if it was needed during the same hospitalization and emergent if needed before the next working day. New York Heart Association (NYHA) IV class patients are unable to carry out any physical activity without discomfort or symptoms of heart failure at rest. EGFR was calculated by commonly used conventions (Levey et al., 2006, 2009). Severe frailty was defined as Geriatric Status Scale (GSS) 2-3, i.e., at least one of the following: a need of assistance with mobility or activities of daily living, cognitive impairment or diagnosis of dementia (Rockwood et al., 1999). CAD was defined as any narrowing of 50% or more in a main coronary artery. The predicted risk of operative mortality was calculated using the EuroSCORE II and STS-PROM systems (Nashef et al., 2012; O'Brien et al., 2009).

4.2.2 Outcome measures

4.2.2.1 Primary endpoints

The primary endpoints in studies **I** and **II** were 30-day and 3-year all-cause mortality and in study **III** were in-hospital and 4-year all-cause mortality.

4.2.2.2 Secondary endpoints

Several early secondary outcomes were selected. VARC-2 definitions were applied for postoperative stroke, bleeding, PVR, vascular complications, new PPMI, conversion to cardiac surgery, coronary obstruction, and AF (Kappetein et al., 2012). Severe bleeding was also defined according to European Coronary Artery Bypass Grafting (E-CABG) bleeding scores 2-3, i.e., a transfusion of > 4 units of red blood cells and/or reoperation for bleeding (Biancari et al., 2015). AKI was defined according to the KDIGO criteria (Acute Kidney Injury Work Group, 2012). In addition, the rates of blood transfusion, resternotomy for bleeding, and repeated AVR were recorded. Postoperative length of stay was defined as postoperative days in hospital where the procedure was performed. Furthermore, in study **III**, the rates of deep sternal infection, use of postoperative haemodynamic support, and ventricular wall injury were calculated.

Late secondary outcomes were the incidence of prosthetic valve endocarditis and the rates of coronary artery revascularization, PPMI and reintervention for aortic valve prostheses.

4.3 Statistical methods

Statistical and data reporting guidelines for the European Journal of Cardio-Thoracic Surgery and the Interactive CardioVascular and Thoracic Surgery were followed (Hickey et al., 2015). Statistical analyses were performed using the SAS (SAS Institute, USA), SPSS (IBM Corporation, USA) and Stata (StataCorp, USA) statistical packages. Baseline and operative variables were compared with the Mann-Whitney U-test for continuous variables, Fisher's exact test and chi-squared test for categorical variables in the unmatched populations. The matched populations were compared using the paired t-test (continuous variables) or the McNemar or Fleiss-Everitt test (dichotomous variables and standardized differences).

A propensity score was calculated using a non-parsimonious logistic regression. Included covariates in all the studies were age, sex, body mass index, haemoglobin, eGFR, diabetes, pulmonary disease, extracardiac arteriopathy, NYHA class 4 symptoms, left ventricular EF ≤50%, AF, systolic pulmonary artery pressure, mitral valve regurgitation, and previous pacemaker. In study **I**, other covariates were stroke, TIA, recent myocardial infarction, CAD, left main stenosis, and number of diseased coronary arteries. In study **III**, other covariates were stroke, previous cardiac surgery, previous percutaneous coronary intervention (PCI), CAD, number of diseased coronary arteries, recent myocardial infarction, acute heart failure or critical

preoperative state, urgent procedure, frailty, and inactive malignancy. One-to-one propensity matching of the TAVI and SAVR groups was performed. In study **I**, additional propensity score matching was performed in patients >80 years, patients with CAD, and patients with third-generation TAVI prostheses (Sapien 3, Evolut R, Acurate neo, Lotus) along with selected SAVR prostheses (Perimount Magna Ease, Trifecta) to analyse interactions. In all studies, standardized differences <0.10 were defined as an acceptable imbalance between the cohorts. Long-term survival was estimated using the Kaplan-Meier method with the log-rank test. Competing risk analysis with the Fine-Gray test was performed for late cardiac adverse events, and hazard ratios were calculated using Cox models. Statistical significance was set at <0.05, except that <0.10 was used for interaction tests of matched cohorts in study **I**.

4.4 Ethical aspects

The FinnValve study is registered in ClinicalTrials.gov with identifier NCT03385915. It was a retrospective registry study, patients were not contacted during the study, and no exposures to patients were performed. The study protocol was locally approved by the Institutional Review Boards of each study centre and the National Institute of Health and Welfare. The study followed the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (von Elm et al., 2007). Pseudonymized data were used for analyses. The codes of personal data were stored at the Heart Centre of Turku University Hospital, and access to all codes was limited to three study members in the coordinating centre. Each centre was able to access the codes of their own data if necessary.

5 SUMMARY OF THE RESULTS

5.1 Patient characteristics

5.1.1 Study I: Low-risk patients

A total of 2841 patients were the subjects of this study. The mean age was 74.0±6.2 years, and 45.1% of them were female. A total of 325 patients underwent TAVI, and 2516 patients underwent SAVR. The patients in the TAVI cohort were older (78.1±6.0 vs. 73.4±6.0 years, $p<0.001$), more often female (52.9% vs. 44.1%, $p=0.003$), had a higher predicted risk of mortality (ES II 2.6±1.5% vs. 2.1±1.1%, $p<0.001$; STS-PROM 2.1±0.5% vs. 1.8±0.6%, $p<0.001$), and more often had associated comorbidities than the patients in the SAVR cohort.

After propensity score matching, 304 pairs were available for comparative analyses. A total of 86.5% of the TAVI patients received third-generation prostheses. Matching resulted in a good balance of covariates, with standardized differences below 0.1, except for a higher rate of concomitant revascularization for CAD in the SAVR group compared to the TAVI group (16.1% vs. 2.0%, $p<0.001$). The prevalence of CAD was 18.8% in both groups, and no difference was observed in the rate of previous PCI. The mean age of the matched cohorts was 77.9±6.0 and 78.1±4.8 years ($p=0.954$) for TAVI and SAVR, respectively. The mean predicted risk of mortality was 2.6±1.4% vs. 2.5±1.3 ($p=0.646$) by ES II and 2.1±0.9 vs. 2.1±0.5 ($p=0.818$) by STS-PROM for the TAVI and SAVR cohorts.

Detailed characteristics of the patients in the unmatched and propensity score-matched groups are presented in Table 5.

Table 5. Characteristics of the unmatched and propensity score-matched cohorts with low operative risk undergoing TAVI and SAVR.

	Unmatched			Propensity score-matched		
	TAVI N=325	SAVR N=2516	p-value	TAVI N=304	SAVR N=304	p-value
Age, mean (years)	78.1±6.0	73.4±6.0	<0.0001	77.9±6.0	78.1±4.8	0.954
Female, n (%)	172 (52.9)	1109 (44.1)	0.003	161 (53.0)	153 (50.3)	0.570
Body mass index, mean (kg/m^2)	28.6±5.1	28.0±4.7	0.052	28.5±5.1	28.7±4.9	0.330
Haemoglobin, mean (g/L)	130±15	134±13	<0.0001	131±15	130±14	0.602
eGFR, mean (ml/min/1.73 m^2)	76±21	80±20	<0.0001	76±21	76±20	0.954
Diabetes, n (%)	75 (23.1)	555 (22.1)	0.678	68 (22.4)	68 (22.4)	1.000
Stroke, n (%)	29 (8.9)	127 (5.0)	0.004	26 (8.6)	24 (7.9)	0.888
Transient ischaemic attack, n (%)	22 (6.8)	107 (4.3)	0.040	20 (6.6)	19 (6.3)	1.000
Pulmonary disease, n (%)	60 (18.5)	275 (10.9)	<0.0001	54 (17.8)	59 (19.4)	0.675
Extracardiac arteriopathy, n (%)	41 (12.6)	207 (8.2)	0.008	39 (12.8)	42 (13.8)	0.812
Ejection fraction ≤50%, n (%)	47 (14.5)	298 (11.8)	0.175	41 (13.5)	40 (13.2)	1.000
Atrial fibrillation, n (%)	118 (36.3)	457 (18.2)	<0.0001	107 (35.2)	105 (34.5)	0.931
NYHA class IV, n (%)	7 (2.2)	20 (0.8)	0.017	5 (1.6)	8 (2.6)	0.581
SPAP, n (%)			0.105			0.117
31-55 mmHg	109 (33.5)	799 (31.8)		101 (33.2)	95 (31.3)	
>55 mmHg	18 (5.5)	86 (3.4)		15 (4.9)	18 (5.9)	
Moderate mitral regurgitation, n (%)	25 (7.7)	77 (3.1)	<0.0001	20 (6.6)	19 (6.3)	0.798
Recent myocardial infarction, n (%)	4 (1.2)	20 (0.8)	0.419	3 (1.0)	2 (0.7)	1.000
Coronary artery disease, n (%)	60 (18.5)	877 (34.9)	<0.0001	57 (18.8)	57 (18.8)	1.000
Left main coronary stenosis, n (%)	2 (0.6)	76 (3.0)	0.010	2 (0.7)	5 (1.6)	0.453
No. of diseased vessels, mean	0.2±0.5	0.6±0.9	<0.0001	0.2±0.6	0.3±0.6	0.917
Prior PCI, n (%)	65 (20.0)	200 (7.9)	<0.0001	51 (16.8)	49 (16.1)	0.911
Prior permanent pacemaker, n (%)	24 (7.4)	90 (3.6)	0.001	21 (6.9)	15 (4.9)	0.405
Planned revascularization, n (%)	9 (2.8)	812 (32.3)	<0.0001	6 (2.0)	49 (16.1)	<0.0001
EuroSCORE II, mean (%)	2.6±1.5	2.1±1.1	<0.0001	2.6±1.4	2.5±1.3	0.646
STS-PROM, mean (%)	2.1±0.5	1.8±0.6	<0.0001	2.1±0.9	2.1±0.5	0.818

Continuous variables are reported as mean ± standard deviation and categorical variables as counts and percentages. CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; SPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

5.1.2 Study II: Low-risk patients without coronary artery disease

After excluding patients with CAD, stroke, STS-PROM ≥3.0%, and other severe clinical conditions as stated in section 4.1.3, 1006 low-risk patients with most recent generation bioprostheses were identified. TAVI was performed in 175 patients, and SAVR was performed in 831 patients. The mean age of the study population was 73.1±7.0 years, and 532 of them were female (53%). The baseline variables of the unmatched populations are presented in Table 6.

Propensity score matching resulted in 140 pairs. A balloon-expandable valve was implanted in 62%, a self-expanding valve in 21%, and a mechanically expandable valve in 16% of the TAVI patients. The distribution of the implanted prostheses in the surgical cohort was 59% Perimount Magna Ease and 41% Trifecta. The mean age in the TAVI group was 76.5±6.8 years and in the SAVR group 76.9±4.7 years (p=0.458). The predicted risks of mortality for TAVI vs. SAVR were 2.1±0.9 vs. 2.1±1.1 (p=0.398) by ES II and 2.0±0.6 vs. 2.0±0.6 (p=0.845) by STS-PROM. The prevalence of diabetes was 25.0% in the TAVI group and 26.4% in the SAVR group (p=0.883), and the respective rates of any history of AF were 33.6% and 32.9% (p=1.000). All baseline variables were balanced, with standardized differences <0.1. Detailed characteristics of the patients can be found in Table 6.

Table 6. Characteristics of the unmatched and propensity score-matched cohorts with low operative risk without coronary artery disease undergoing TAVI and SAVR.

	Unmatched			Propensity score-matched		
	TAVI n=175	SAVR n=831	p-value	TAVI n=140	SAVR n=140	p-value
Age, mean (years)	77.4±6.4	72.2±6.8	<0.0001	76.5±6.8	76.9±4.7	0.458
Female, n (%)	101 (57.7)	431 (51.9)	0.159	79 (56.4)	75 (53.6)	0.731
Body mass index, mean (kg/m²)	29±5	28±5	0.114	29±5	29±5	0.555
Haemoglobin, mean (g/L)	130±16	135±13	<0.0001	130±16	129±14	0.364
eGFR, mean (ml/min/1.73 m²)	75±21	80±19	0.001	75±21	74±20	0.764
Diabetes, n (%)	46 (26.3)	170 (20.5)	0.088	35 (25.0)	37 (26.4)	0.883
Pulmonary disease, n (%)	30 (17.1)	90 (10.8)	0.019	22 (15.7)	26 (18.6)	0.643
Extracardiac arteriopathy, n (%)	13 (7.4)	46 (5.5)	0.333	11 (7.9)	10 (7.1)	1.000
Ejection fraction ≤50%, n (%)	29 (16.7)	88 (10.6)	0.023	19 (13.6)	21 (15.0)	0.860
Atrial fibrillation, n (%)	63 (36.0)	139 (16.7)	<0.0001	47 (33.6)	46 (32.9)	1.000
NYHA Class IV, n (%)	1 (0.6)	5 (0.6)	1.000	1 (0.7)	2 (1.4)	1.000
SPAP, n (%)			0.519			0.933
31-55 (mmHg)	58 (33.1)	286 (34.4)		45 (32.1)	39 (27.9)	
>55 (mmHg)	9 (5.1)	28 (3.4)		6 (4.3%)	11 (7.9)	
Mitral regurgitation, n (%)			<0.0001			0.944
Mild	54 (33.3)	174 (21.9)		46 (32.9)	43 (30.7)	
Moderate	14 (8.6)	15 (1.9)		7 (5.0)	7 (5.0)	
Prior permanent pacemaker, n (%)	12 (6.9)	30 (3.6)	0.051	7 (5.0)	8 (5.7)	1.000
EuroSCORE II, mean (%)	2.3±1.0	1.6±0.8	<0.0001	2.1±0.9	2.1±1.1	0.398
STS-PROM, mean (%)	2.1±0.6	1.6±0.6	<0.0001	2.0±0.6	2.0±0.6	0.845

Continuous variables are reported as mean ± standard deviation and categorical variables as counts and percentages. eGFR, estimated glomerular filtration; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; SPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

5.1.3 Study III. Patients treated with the Sapien 3 or Perimount Magna Ease bioprosthesis

In study **III**, TAVI was performed in 689 patients with the Sapien 3 prosthesis and SAVR in 1311 patients with the Perimount Magna Ease prosthesis. Of the 2000 patients, 46.1% were female, and the mean age of this cohort was 76.5±7.6 years. In the unmatched cohort, TAVI patients were 9 years older and had a significantly higher associated comorbid burden than the SAVR patients, as shown in Table 7.

A total of 308 matched pairs were formed after propensity score analysis. Relatively smaller proportion of TAVI patients were finally included in the matched group in study **III** compared to studies **I** and **II** due to methodological difference between studies. In studies **I** and **II**, previous cardiac surgery was an exclusion criterion compared to study **III** which did not exclude patients with a history of previous cardiac surgery but used it as a covariate in propensity score matching analysis. The standardized differences in baseline variables were <0.1, except for the rate of planned coronary revascularization, which was higher in the SAVR group than the TAVI group (27.3% vs. 4.5%, p<0.001). No significant differences were observed in the prevalence of CAD or in the number of previous PCIs between the groups. The predicted risk of operative mortality was slightly high in both cohorts based on ES II (5.0±5.2 and 4.9±5.9, p=0.752) and STS-PROM (3.5±2.2 and 3.5±2.8, p=0.918) (Table 7).

Table 7. Characteristics of the unmatched and matched patient cohorts undergoing TAVI with the Sapien 3 and SAVR with the Perimount Magna Ease bioprosthesis.

	Unmatched			Propensity score-matched		
	Sapien 3 n=689	Perimount n=1311	p-value	Sapien 3 n=308	Perimount n=308	p-value
Age, mean (years)	81.3±6.4	74.0±6.9	<0.0001	78.8±6.9	79.0±5.3	0.697
Female, n (%)	365 (53.0)	556 (42.4)	<0.0001	160 (51.9)	165 (53.6)	0.674
Body mass index, mean (kg/m^2)	27.4±4.9	28.0±4.8	0.012	28.1±5.2	28.0±5.0	0.848
Diabetes, n (%)	207 (30.0)	353 (26.9)	0.140	93 (30.2)	87 (28.2)	0.578
Atrial fibrillation, n (%)	293 (42.5)	255 (19.5)	<0.0001	102 (33.1)	99 (32.1)	0.782
Extracardiac arteriopathy, n (%)	117 (17.0)	137 (10.5)	<0.0001	49 (15.9)	41 (13.3)	0.383
Pulmonary disease, n (%)	149 (21.6)	172 (13.1)	<0.0001	65 (21.1)	62 (20.1)	0.761
Haemoglobin, mean (g/l)	125.7±15.2	133.6±15.1	<0.0001	128.7±15.2	127.8±15.3	0.421
eGFR, mean (ml/m^2/min)	62.0±18.5	72.6±16.7	<0.0001	65.6±18.1	66.4±16.1	0.550
Stroke, n (%)	70 (10.2)	70 (5.3)	0.0001	27 (8.8)	29 (9.4)	0.782
Prior permanent pacemaker, n (%)	65 (9.4)	50 (3.8)	<0.0001	20 (6.5)	19 (6.2)	0.862
Previous cardiac surgery, n (%)	110 (16.0)	24 (1.8)	<0.0001	17 (5.5)	18 (5.8)	0.847
Prior PCI, n (%)	140 (20.3)	130 (9.9)	<0.0001	47 (15.3)	40 (13.0)	0.370
Coronary artery disease, n (%)	181 (26.3)	563 (42.9)	<0.0001	102 (33.1)	97 (31.5)	0.665
Number of diseased vessels, mean	0.36±0.7	0.78±1.1	<0.0001	0.47±0.8	0.46±0.8	0.836
Planned revascularization, n (%)	29 (4.2)	511 (39.0)	<0.0001	14 (4.5)	84 (27.3)	<0.0001
Recent MI	17 (2.5)	72 (5.5)	0.0018	9 (2.9)	9 (2.9)	1.000
NYHA class IV	82 (11.9)	94 (7.2)	0.0004	31 (10.1)	34 (11.0)	0.696
AHF or critical preoperative state[y], n (%)	75 (10.9)	101 (7.7)	0.017	33 (10.7)	33 (10.7)	1.000
Urgent procedure, n (%)	55 (8.0)	148 (11.3)	0.020	28 (9.1)	33 (10.7)	0.508
Ejection fraction, n (%)			<0.0001			0.699
>50%	499 (72.4)	1069 (81.5)		230 (74.7)	239 (77.6)	
31-50%	158 (22.9)	220 (16.8)		68 (22.1)	60 (19.5)	
21-30%	31 (4.5)	22 (1.7)		10 (3.2)	9 (2.9)	
SPAP, n (%)			<0.0001			<0.0001
31-55 mmHg	245 (35.6)	524 (40.0)		131 (42.5)	121 (39.3)	
>55 mmHg	75 (10.9)	92 (7.0)		34 (11.0)	39 (12.7)	
Mitral regurgitation, n (%)			<0.0001			0.652
Mild	255 (37.0)	278 (21.2)		116 (37.7)	107 (34.7)	
Moderate	80 (11.6)	39 (3.0)		23 (7.5)	21 (6.8)	
EuroSCORE II, mean (%)	6.5±7.1	3.4±4.2	<0.0001	5.0±5.2	4.9±5.9	0.752
STS-PROM, mean (%)	4.3±2.9	2.6±2.1	<0.0001	3.5±2.2	3.5±2.8	0.918

Continuous variables are reported as mean ± standard deviation and categorical variables as counts and percentages. AHF, acute heart failure within 60 days before procedure; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MI, myocardial infarction within 90 days before procedure; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; SPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation; [y]critical preoperative state based on the EuroSCORE II criteria.

5.2 Short-term outcomes

5.2.1 Mortality

Operative death was similar after TAVI (1.2-2.1%) compared to SAVR (1.6-3.6%) in all studies, with no statistical significance, as indicated in Table 8. The O:E mortality ratios (by STS-PROM) in low-risk studies **I** and **II** were 0.6-0.8 for TAVI and 1.0 for SAVR. The respective O:E ratios were 0.3 and 0.8 in study **III**.

Table 8. Operative mortality in the unmatched and propensity score-matched cohorts.

		TAVI	SAVR	p-value
Study I*	Low-risk Unmatched, n (%)	4 (1.2)	50 (2.0)	0.52
	Low-risk Matched, n (%)	4 (1.3)	11 (3.6)	0.12
Study II*	Low-risk, no CAD Unmatched, n (%)	3 (1.7)	13 (1.6)	0.885
	Low-risk, no CAD Matched, n (%)	3 (2.1)	2 (2.1)	1.000
Study III¥	Sapien 3 vs. Perimount Unmatched, n (%)	8 (1.2)	26 (2.0)	0.177
	Sapien 3 vs. Perimount Matched, n (%)	4 (1.3)	11 (3.6)	0.092

*, 30-day; ¥, In-hospital mortality; CAD, coronary artery disease.

5.2.2 Stroke

TAVI and SAVR were associated with similar rates of stroke in studies **I** and **II** in the unmatched cohorts: 1.8% vs. 3.0% (p=0.23 in **I**) and 2.3% vs. 2.4% (p=1.00 in **II**). The result was similar in the matched TAVI and SAVR groups: 2.0% vs. 5.3% (p=0.12 in **I**) and 2.1% vs. 2.1% (p=1.00 in **II**). In contrast, in study **III**, TAVI was associated with a lower incidence of stroke, 1.3% vs. 3.7% (p=0.003) in the unmatched cohort and 0.3% vs. 3.6% (p=0.006) in the matched cohort, compared to surgery (Fig. 5A).

5.2.3 Vascular complications

Vascular complications occurred more frequently in TAVI than in SAVR throughout studies **I**-**III**. In the matched series, the rates of major vascular complications were 8.9% vs. 2.3% (p=0.001) (**I**), 7.9% vs. 0.7% (p=0.006) (**II**), and 9.4% vs. 0.6% (p<0.0001) (**III**) in TAVI and SAVR, respectively (Fig. 5B). Transfemoral TAVI with Sapien 3 was also correlated with a 2.6% rate of minor vascular complications. The risk for annular rupture was 0.3% with the Sapien 3 balloon-expandable valve, and the rate of aortic dissection or rupture was ≤0.8% in both treatment groups.

5.2.4 Bleeding

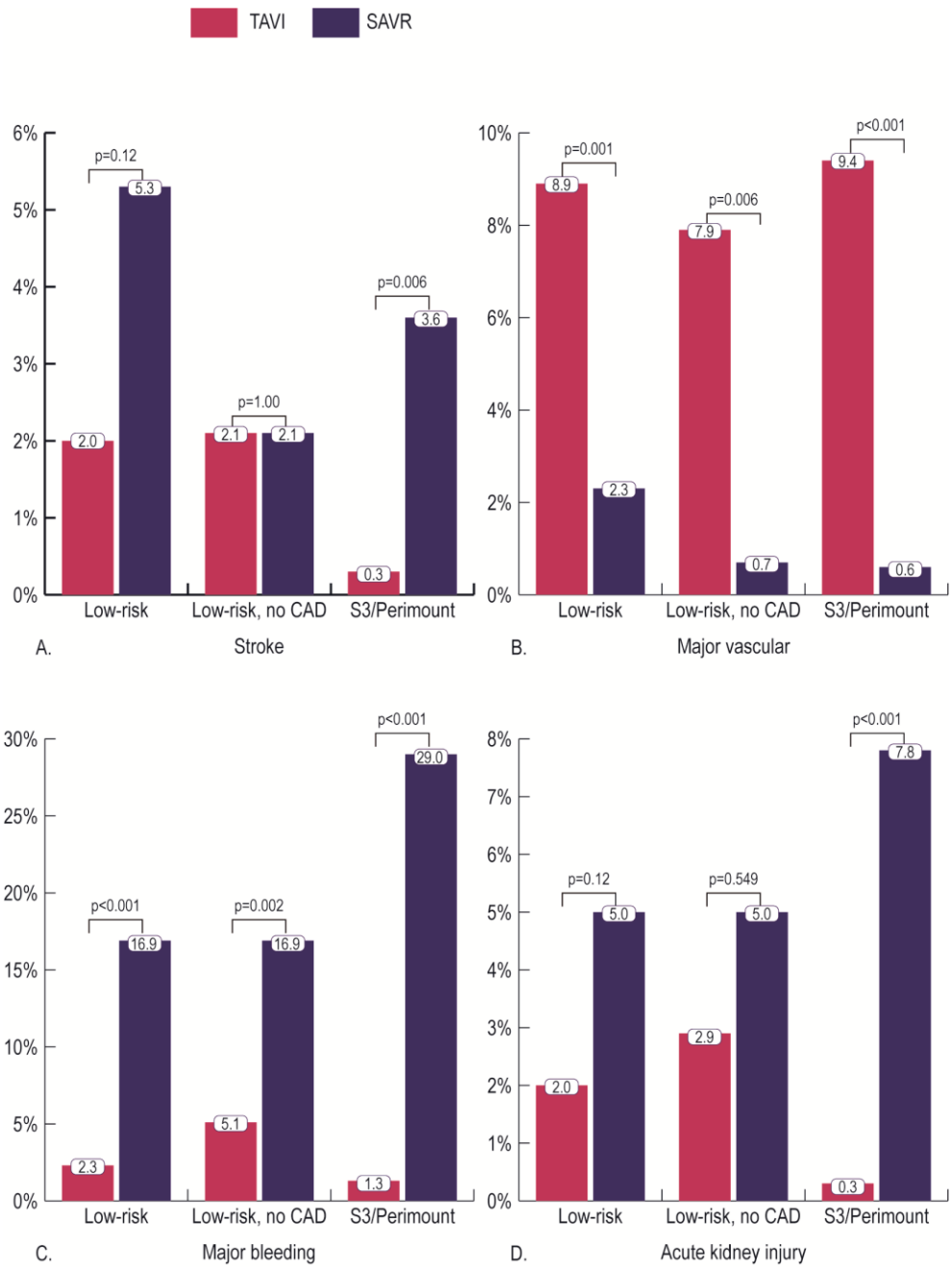
Compared to TAVI, SAVR was associated with higher rates of bleeding in the unmatched and propensity score-matched cohorts irrespective of the definition used for bleeding. Herein, the bleeding rates in the matched cohorts are presented. In study **I**, severe bleeding by E-CABG occurred in 2.3% of the TAVI patients and in 16.9% of the SAVR patients (p<0.001). In study **II**, the respective rates were 5.1% vs. 16.9% (p=0.002) for TAVI and SAVR. The incidence of VARC-2 major and life-threatening or disabling bleeding events in study **II** was 24.7% in TAVI and 90.7% in SAVR (p<0.0001). The E-CABG bleeding rates in study **III** were 1.3% vs. 29.0% (p<0.0001) in the TAVI and SAVR groups, respectively. Fig. 5C. Resternotomy or thoracotomy to control bleeding was needed more often in SAVR in the low-risk studies (**I**, **II**). For example, in study **I**, 1 patient (0.3%) undergoing TAVI and 18 patients (5.9%) undergoing SAVR underwent reoperation (sternotomy) for bleeding (p<0.001). Reoperation for bleeding was also more common in study **III**, with an incidence of 2.3% after TAVI compared with 10.7% after SAVR (p<0.001). The need for peri- or postoperative red blood cell (RBC) transfusion was more common during the surgical treatment period; for example, in study **II**, 69.1% of the patients

treated with SAVR received RBCs compared to 9.6% in the TAVI cohort ($p<0.0001$).

5.2.5 Acute kidney injury

In the propensity score-matched low-risk studies (**I**-**II**), 2.0% and 2.9% of the patients in the TAVI groups experienced AKI. The risk was 5.0% in the SAVR groups, and no statistically significant differences were observed between the treatment cohorts. In study **III**, however, only 1 patient (0.3%) in the matched TAVI group suffered from AKI, compared to 24 patients (7.8%) in the matched surgical cohort ($p<0.001$). Fig. 5D. The need for postoperative dialysis was also higher after surgery, 0% vs. 2.3% ($p=0.015$).

Figure 5. Short-term outcomes in the propensity score-matched cohorts. A. Stroke; B. Major vascular complication; C. Major bleeding complication (E-CABG); D. Acute kidney injury Stage 2-3.



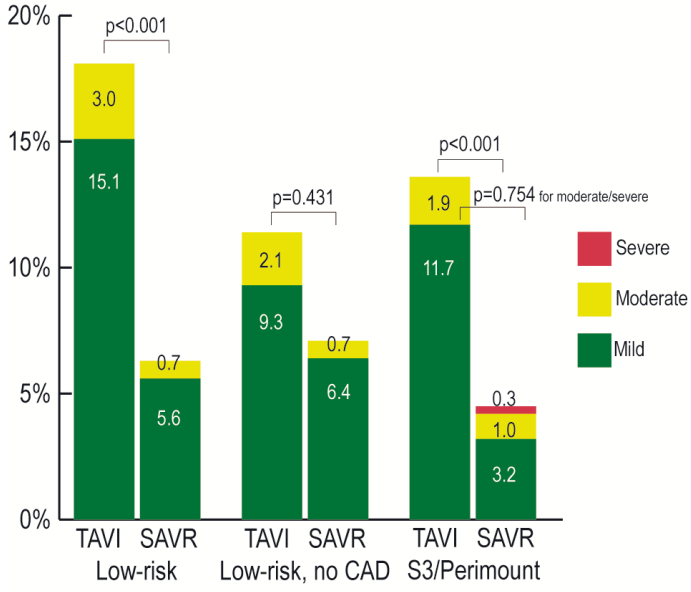
5.2.6 Permanent pacemaker implantation

Postoperative new PPMI rates in the unmatched cohorts were 7.5-10.9% with TAVI vs. 3.6-3.9% with SAVR ($p \leq 0.001$ for all comparisons between TAVI and SAVR). In the matched cohorts, the rates were 9.5% vs. 4.6% ($p=0.03$) in study **I**, 9.8% vs. 6.1% ($p=0.481$) in study **II**, and 9.1% vs. 5.2% ($p=0.064$) in study **III**.

5.2.7 Paravalvular regurgitation

TAVI was associated with a statistically higher incidence of mild, moderate, or severe PVR compared to SAVR in the total cohort. After propensity score matching, the difference in PVR remained statistically significant, except in study **II**. This is demonstrated in Fig. 6. The difference between TAVI and SAVR was more evident in the incidences of mild PVR. Analysing only the rates of moderate/severe PVR associated with Sapien 3 and Perimount Magna Ease (**III**), there were no significant differences in the unmatched cohort (TAVI: 1.2%; SAVR: 0.8%; $p=0.370$) or in the matched cohort (TAVI: 1.9%; SAVR: 1.3%; $p=0.754$) (Fig. 6).

Figure 6. Paravalvular regurgitation in the propensity matched cohorts.



5.2.8 Atrial fibrillation

AF was two-fold more likely in the surgical patients than the TAVI patients during the postoperative period. The rates in the matched cohorts were 30.3% vs. 63.4% ($p<0.001$) (**I**), 30.7% vs. 58.6% ($p<0.0001$) (**II**) and 33.1% vs. 64.9% ($p<0.0001$) (**III**).

5.2.9 Duration of the hospital stay

Patients who underwent SAVR had a 3- to 4-day longer hospital stay than those who underwent TAVI. The respective mean lengths were as follows in studies **I**-**III**: 4.1±3.3 vs. 7.9±5.2 ($p<0.001$), 3.7±3.2 vs. 7.5±3.4 ($p<0.0001$), and 4.1±3.7 vs. 8.4±6.8 (<0.0001) days for TAVI vs. SAVR.

5.3 Long-term outcomes

5.3.1 Mortality

In the unmatched cohorts of low-risk patients (**I**), TAVI was associated with 85.5% survival at 3 years compared to 92.0% survival in the surgical group, a statistically insignificant difference ($p=0.20$). Correspondingly, in patients with low surgical risk and without CAD (**II**) survival was 83.4% in the TAVI group and 93.2% in the SAVR group ($p=0.003$) at three years.

After propensity score matching, mid-term survival at 3 to 4 years was similar after TAVI compared to SAVR in all studies. In study **I**, an 85.7% survival rate for TAVI and 87.7% for SAVR was observed ($p=0.45$) at three years (Fig. 7). Interaction tests suggested inferior three-year survival in patients with CAD undergoing SAVR ($p=0.078$ for interaction). The interaction tested showed similar survival after TAVI and SAVR in patients aged <80 or ≥80 years and in patients who received selected bioprostheses compared to the patients who did not (see section 4.3). In study **II**, matching resulted in equal 3-year survival, 83.0% vs. 85.4% ($p=0.805$) for TAVI vs. SAVR. The corresponding Kaplan-Meier estimate for mid-term mortality is presented in Fig. 8.

Figure 7. Kaplan-Meier estimate of survival in the propensity score-matched pairs of low-risk patients with aortic stenosis who underwent TAVI or SAVR.

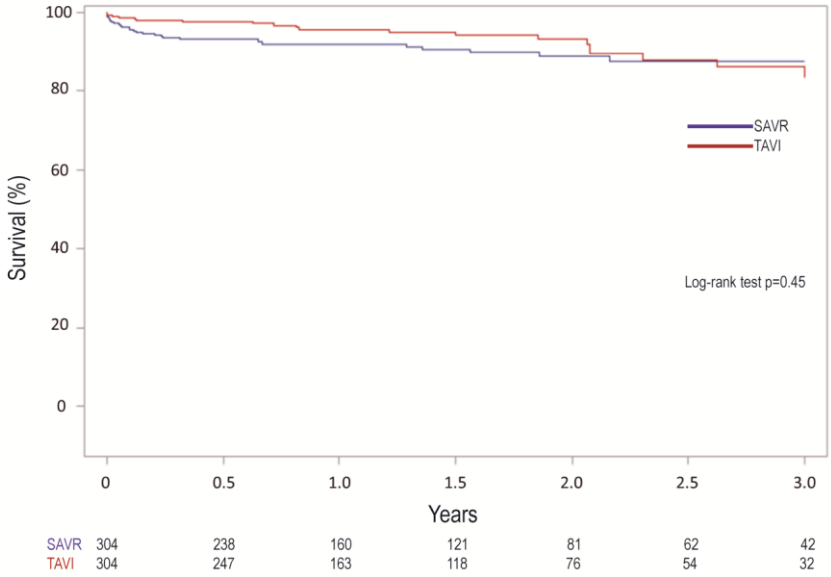
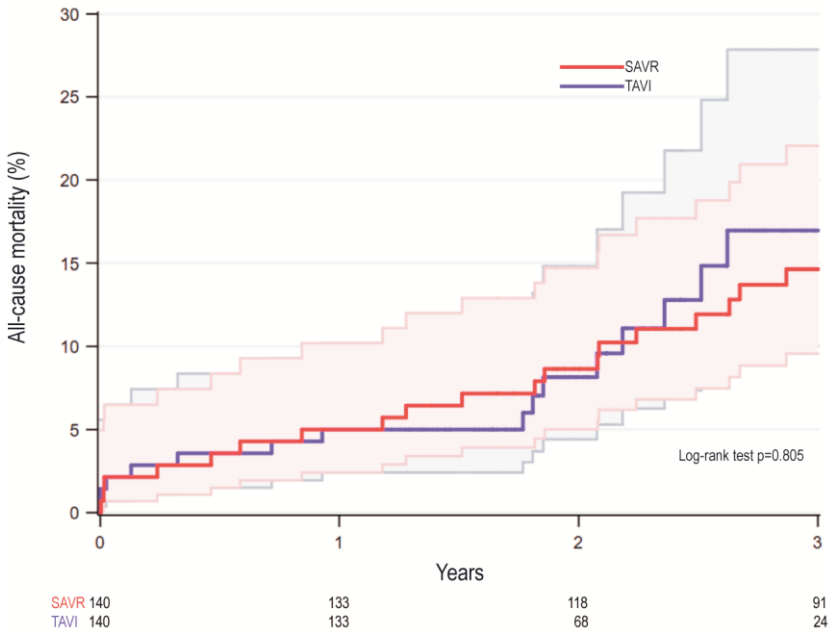


Figure 8. Kaplan-Meier estimate of all-cause mortality in the propensity score-matched pairs of low-risk patients with aortic stenosis without coronary artery disease who underwent TAVI or SAVR.



In study **III**, survival analysis at 4 years demonstrated similar outcomes, with a 74.1% survival rate in the Sapien 3 cohort compared with a 79.4% survival rate in the Perimount Magna Ease cohort (p=0.910). The Kaplan-Meier mortality curves are presented in Fig. 9.

Cumulative mortality at 1 year, 2 years, 3 years, and 4 years in the low-risk study without CAD patients (**II**) and in the Sapien 3 vs. Perimount study (**III**) is summarized in Table 9.

Figure 9. Kaplan-Meier estimate of all-cause mortality in the propensity score-matched pairs of patients with aortic stenosis who underwent TAVI with Sapien 3 or SAVR with Perimount Magna Ease.

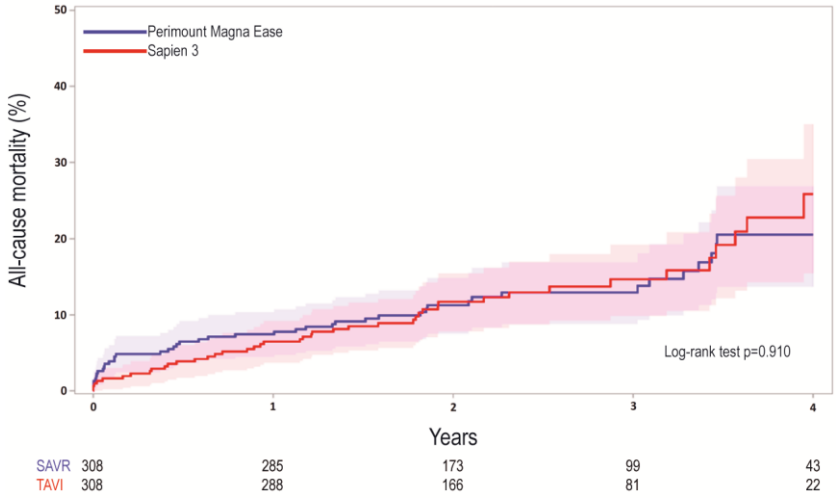


Table 9. Cumulative estimate of mortality in the propensity score-matched cohort of patients with low risk and without CAD and the cohort of patients treated with Sapien 3 or Perimount Magna Ease.

	Low-risk patients without CAD			Patients treated with Sapien 3 or Perimount Magna Ease		
	TAVI n=140	SAVR n=140		Sapien 3 n=308	Perimount n=308	
1-year	5.0%	5.0%		6.5%	7.5%	
2-year	8.2%	8.7%	Log-rank p=0.805	11.7%	11.3%	HR 0.96; 95% CI 0.63-1.46
3-year	17.0%	14.6%		14.7%	12.9%	Log-rank p=0.910
4-year				25.9%	20.6%	

CAD, coronary artery disease; CI, Confidence interval; HR, hazard ratio; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

5.3.2 Aortic valve reintervention

None of the TAVI patients underwent repeat aortic valve intervention during the three-year follow-up in study **II**, compared to the 0.8% estimated incidence of reoperation in the SAVR cohort. In the unmatched groups of study **III**, reintervention at 4 years for SVD was performed in 2 patients with the Sapien 3 valve: one was treated with TAVI, and the other was treated with SAVR. In the Perimount Magna Ease group, reintervention was performed in 8 patients. Of them, six patients underwent a new surgery due to PVR, 1 patient with SVD was treated with valve-in-valve TAVI, and 1 patient received SAVR for prosthetic valve endocarditis. Additionally, one patient operated on for PVR underwent a second redo surgery for prosthetic valve endocarditis. In the propensity score-matched groups, the cumulative incidence for reintervention was 0.4% for both groups (p=0.989; HR 1.02, 95% CI 0.06-16.14) (**III**).

5.3.3 Permanent pacemaker implantation

The cumulative incidence of new PPMI at 3 years was higher for TAVI (15.4%) than SAVR (6.0%) in the unmatched low-risk patients without CAD (**II**) (p<0001), but the difference was not statistically significant in the matched groups (TAVI: 14.6%; SAVR: 9.3%; p=0.082). The 4-year incidence of PPMI was 13.9% with Sapien 3 compared to 6.9% with Perimount Magna Ease (p=0.004, HR 2.16; 95% CI 1.27-3.68) (**III**).

5.3.4 Prosthetic valve endocarditis

No cases of prosthetic valve endocarditis were observed in study **II**. In study **III**, the cumulative incidence was 0.6% after TAVI and 0.5% after SAVR in the matched populations (p=0.991, HR 1.01; 95% CI 0.06-16.10). In the total cohort, nine patients were treated with antibiotics, and two patients in the SAVR group underwent surgical treatment.

5.3.5 Coronary artery revascularization

In patients at low risk for surgery and without concomitant CAD at the time of primary valve intervention, TAVI was associated with a similar rate of coronary revascularization compared to SAVR (2.6% vs. 1.5%, p=0.858) during the three-year follow-up. The difference was not significant in the matched cohorts, either (3.6% vs. 1.7%, p=0.679) (**II**). No significant difference in the rate of revascularization at

4 years was observed in the propensity score-matched groups of Sapien 3 (1.5%) and Perimount Magna Ease patients (1.4%) (p=0.721, HR 0.76; 95% CI 0.17-3.43) (**III**). PCI was utilized in all patients in the Sapien 3 and Perimount cohorts needing revascularization.

6 DISCUSSION

6.1 General considerations

This thesis is based on the nationwide FinnValve registry carried out in all Finnish university hospitals. It included all consecutive, unselected patients who underwent TAVI or SAVR for severe AS during a 10-year period. The registry included a total of 6463 patients (33% TAVI, 67% SAVR), enabling us to explore the national practice and results of invasive aortic valve treatment. We showed previously that in Finland, the number of TAVI procedures exceeded the number of SAVRs performed for AS in 2016. Improved short-term and two-year outcomes were associated with both treatment modalities during the study period (Mäkikallio et al., 2019).

TAVI was first introduced for the treatment of inoperable, extremely high-surgical-risk patients with AS, and soon it was adopted for the treatment of intermediate- and low-risk patients. This paradigm shift was supported only recently by randomized controlled trials in low-risk patient groups (Mack et al., 2019; Popma et al., 2019). However, the few comparative studies from real-life practice in such patient groups suggested better long-term outcomes with SAVR compared to TAVI (Rosato et al., 2016). Our studies add important short- and long-term outcome data observed in real-life populations treated for severe AS. In the studies included in this thesis, we selected only patients whose surgical risk was not significantly increased and who were treated mainly with the most recent bioprostheses, since technological improvements may result in better outcomes. This is the patient group whose treatment options are most often debated in current practice. Another important aspect of this thesis was to describe the results of TAVI and SAVR in Finland because no such data had been previously collected and published systematically. This material reliably represents the national practice of invasive treatment of AS between 2008 and 2017, although a small number of TAVI and SAVR procedures were performed in central hospitals during the study period. It should be noted that benchmarking of different university hospitals was not the aim of this registry, and inter-institutional comparisons were not allowed.

The definition of low surgical risk in our study was based on a similar type of algorithm used in recent randomized trials. We excluded patients whose clinical

condition could introduce a significant bias to the comparisons made on the outcomes (for example, active cancer, severe frailty, long-term oxygen therapy). We also excluded non-transfemoral TAVI patients from the present study. The proportion of non-transfemoral routes has decreased dramatically to less than 5% of all TAVI procedures in Finland. We must also realize that in this study, the low-risk patients treated were not selected for transcatheter treatment because of their risk level but merely by the discretion of the local heart team and occasionally by the patient's preference.

The strength of this registry is the large database of patients treated over a long period of time. Additionally, nationwide and centrally stored data provide comprehensive data for the analysis of late events. Data were robustly checked and completed before analyses. Even so, several general limitations must be acknowledged. First, data were retrospectively collected, so all relevant individual characteristics and findings might not have been properly captured. For example, defining a procedural bleeding complication uniformly from retrospective data can be challenging when there is limited information available in the case records. Furthermore, data on symptomatic status and bioprosthetic function after the procedure were incomplete, prohibiting important, clinically relevant analyses. Second, although the data underwent robust checking, external monitoring of the data was not performed. Third, much of the work of this thesis is limited to very specific patient groups whose risk for surgery was deemed low based on the absence of comorbidities and a high score by risk calculators. It is possible that some patients were misclassified and included or excluded incorrectly. Fourth, the comparative analyses were based on statistical matching (propensity score) of the TAVI and SAVR cohorts. Some important variables might not have been recognized and included in our analyses. Additionally, statistical matching of very selected patient groups yielded relatively small groups in study **II**.

6.2 Patients

Despite the abovementioned limitations, we succeeded in including patients at low risk for surgery. This is evidenced by several indicators. The characteristics of the patients were typical compared to other studies of low- and intermediate-risk patients, including the mean age of 78-80 years. Only the most recent low-risk trials included younger patients with a mean age of 71-74 years (Popma et al., 2019; Waksman et al., 2018). In our study, the prevalence of comorbidities (diabetes in 20-25%, pulmonary disease and extracardiac arteriopathy in 15-20%) did not differ

significantly from those in other studies. However, one-third of patients had AF, which was more common than in other studies (Mack et al., 2019). The predicted risk for operative death by ES II and STS-PROM (2%) in studies **I**-**II** was comparable to those in other low-risk studies, and in study **III**, the risk level (STS-PROM 3.5%) resembled the respective numbers in low-to-intermediate-risk studies (Barbanti et al., 2019a; Bekeredjian et al., 2019; Mack et al., 2019; Popma et al., 2019; Søndergaard et al., 2019a; Waksman et al., 2018).

In summary, our study populations represented typical low- and intermediate-risk patients included in previously published studies in terms of age and associated comorbidities.

6.3 Concomitant coronary artery disease and revascularization

Some deeper inspection is required on the practice of associated revascularization in our study. The patients with AS and concomitant CAD were less frequently revascularized in the TAVI cohorts compared to the surgery cohorts, although after propensity score matching the prevalence of CAD, number of diseased coronary arteries, rate of recent myocardial infarctions and number of previous PCIs were similar between the TAVI and SAVR patient groups.

In the low-risk study (**I**), 19% of the patients in the matched population had CAD, but the associated revascularization rate was only 2% in TAVI compared to 16% in SAVR ($p<0.0001$). The same was apparent in the Sapien 3 versus Perimount study (**III**), in which 32% of the patients had CAD, but only 5% of the TAVI patients underwent revascularization compared to 27% in the SAVR cohort ($p<0.0001$). Therefore, taking studies **I** and **III** together, only 12% of the patients with CAD in the TAVI cohort compared to 86% of the patients with CAD in the SAVR cohort were revascularized at the time of valve intervention. Interestingly, different practices of revascularization did not lead to differences in long-term mortality or in the rate of late coronary revascularization. Unfortunately, we did not have data on late myocardial infarctions. The reasons for the different outlooks on revascularization during TAVI cannot be deduced from our results. The possible reasons are that some patients might not have had very severe (i.e., >70-80%) coronary stenosis, some of the stenoses might have been studied by haemodynamic evaluation and been considered non-severe, or the treating physician may have opted to treat the CAD later, if the patient remained symptomatic. This latter approach may be easier to implement in TAVI patients due to the minimal risk of myocardial ischaemia during the procedure compared to SAVR patients, who are at increased

risk of myocardial damage and dysfunction during the perioperative phase of cardiopulmonary bypass surgery.

Concomitant CABG in patients with CAD undergoing SAVR for AS is recommended to reduce myocardial infarction and mortality (Nishimura et al., 2014; Thalji et al., 2015). The prognostic importance of CAD and revascularization has not been firmly established in the TAVI era. Several studies suggest that severe CAD and incomplete revascularization are associated with worse prognosis among TAVI patients (Khawaja et al., 2015; Michail et al., 2020; Stefanini et al., 2014; Witberg et al., 2017), but opposite findings have also been reported (Elbaz et al., 2020; López Otero et al., 2019; Paradis et al., 2017; Saia et al., 2020b). A recent meta-analysis suggested increased mortality in patients with severe CAD (Syntax score >22) undergoing TAVI and lower one-year mortality in patients who had a low residual Syntax score (<8) after PCI (D'Ascenzo et al., 2018). Thus, our use of the cut-off of 50% stenosis as the only criterion of CAD and the lack of data on the completeness of revascularization are clear limitations of our study.

Many pivotal trials excluded patients with CAD requiring revascularization (Adams et al., 2014; Smith et al., 2011; Thyregod et al., 2015), but the PARTNER 2 & 3, SURTAVI and Evolut Low-Risk trials included patients with non-complex CAD (prevalence: 65% in the intermediate-risk trials and 30% in the low-risk trials). Associated revascularization was performed more rarely with TAVI than with SAVR in those trials (Leon et al., 2016; Popma et al., 2019; Reardon et al., 2017).

The rates of associated revascularizations in comparative observational studies are not always reported, or patients with combined procedures are excluded from the analyses (Armoiry et al., 2018; Bekeredjian et al., 2019; Latib et al., 2012; Schaefer et al., 2019).

Based on the subanalysis of the SURTAVI trial, combined TAVI and PCI might be a reasonable option for SAVR and CABG (Søndergaard et al., 2019b).

In summary, we observed that one-fifth of the low-risk patients and one-third of the intermediate-risk patients undergoing valve intervention for AS had concomitant CAD. The rate of associated coronary revascularization was lower among TAVI patients with CAD than patients treated with open-heart surgery, but despite different practices, we did not observe a higher rate of late revascularization or worse late outcome in the TAVI cohorts.

6.4 Procedural safety

Recognizing and weighing the risks of invasive procedures against the assumed benefits of the treatment is essential for every practitioner and patient. Severe procedural complications, especially major stroke, AKI, severe bleeding and moderate to severe PVR, increase the risk of longer-term mortality. Severe stroke and AKI are associated with a 2-5-fold and severe bleeding with a 1.5-2.5-fold higher adjusted hazard for 1-year mortality. Interestingly, major vascular damage is not always associated with increased late mortality (Arnold et al., 2019; Généreux et al., 2014). Although a very low rate of procedural complications can be achieved in low-risk patient populations, they still occur (Thourani et al., 2015; Waksman et al., 2018).

6.4.1 Risk of death

We observed a numerically lower but statistically non-significant difference in operative mortality related to TAVI (1-2%) compared to SAVR (2-3.6%), a result that is in line with numbers in other low-risk studies of similar populations, which have reported a 1.5-2.5% death rate with TAVI and 2.5-3% with SAVR (Bekeredjian et al., 2019; Rosato et al., 2016; Thyregod et al., 2015). Our and other results indicate that elderly low-risk patients with AS, in the absence of a heavy comorbidity burden, have a quite low and acceptable risk for mortality in transfemoral TAVI and SAVR procedures (**I**-**II**). The patients in study **III** had a slightly higher risk profile than the patients in our other studies. In-hospital mortality in the TAVI cohort was only 1.3% and was almost three times higher in the SAVR cohort ($p=0.092$).

In summary, the results of the FinnValve study show that TAVI and SAVR were safely performed in terms of operative mortality, a result that is in line with reports from other countries and practices. No significant differences in operative mortality were observed between treatment modalities.

6.4.2 Stroke and acute kidney injury

Stroke can be a devastating complication that is not fully understood on an individual level, and despite the growing body of experience and research, temporal improvements in neurologic events after TAVI have not been observed (Huded et al., 2019). Similar rates of postoperative stroke (2% vs. 2-5%) were observed after TAVI vs. after SAVR in the low-risk studies (**I**-**II**). One randomized low-risk trial and one study with inverse probability-weighed low-risk cohorts reported even lower rates of neurological events: 0-0.6% in patients treated with transfemoral TAVI and

0.6-2.4% in patients who underwent SAVR (Mack et al., 2019; Waksman et al., 2018). However, the patients in these studies were 5-7 years younger than our cohorts. Furthermore, many other low-risk studies observed a 1-3% stroke rate, closer to the numbers in our studies (Popma et al., 2019; Rosato et al., 2016; Thourani et al., 2015; Thyregod et al., 2015).

In the SAVR cohorts (**I**, **II**), twice as many patients had AKI following surgery as in the TAVI cohorts (5% vs. 2-3%), but the difference was not statistically significant. The increased risk of stage 2-3 AKI with SAVR has been demonstrated in randomized trials. In these trials, the frequency of AKI after TAVI was less than 1%, compared to the rate of 2-6.7% after surgery, and thus was lower after TAVI than the rate observed in our study (Mack et al., 2019; Popma et al., 2019; Thyregod et al., 2015). However, their younger patient populations may explain the different AKI outcomes.

Stroke and AKI in the Sapien 3 vs. Perimount Magna Ease study (**III**) need to be discussed together. Patients in the Perimount cohort experienced stroke (3.6% vs. 0.3%, $p=0.006$) and AKI (7.8% vs. 0.3%, $p<0.0001$) more often than their counterparts in the Sapien 3 group and more often than the patients in our low-risk studies. One probable explanation for this is the higher occurrence of severe bleeding and the higher rate of RBC transfusions in SAVR, which are known to increase the risk for mortality, stroke and AKI (Brascia et al., 2017; Généreux et al., 2014; Maaranen et al., 2019; Nuis et al., 2012; Tchetche et al., 2012).

In summary, the rates of stroke and AKI were low and similar in the TAVI and SAVR groups, except in study **III**, where TAVI was associated with favourable safety in terms of risk for operative stroke and AKI. Higher rates of significant complications in the Perimount cohort might have had an influence on operative mortality.

6.4.3 Major vascular complications and bleeding

It is easy to see that vascular complications are inevitably related to TAVI procedures since transvascular routes are utilized in valve delivery. An expected and highly significant difference in the occurrence of major vascular complications was seen in all our studies, favouring SAVR over TAVI. Historically, during the early phase of TAVI, the rate of major vascular complications was >10%, which then decreased to 4-7% and most recently to 2-2.5%, which was not different from the rate observed in surgery (Ludman et al., 2015; Mack et al., 2019; Rosato et al., 2016; Saia et al., 2020a; Smith et al., 2011; Thyregod et al., 2015; Waksman et al., 2018; Walther et al.,

2015). Decreases were possible because of improved delivery systems and increased operator experience. Compared to the rates in other studies, the major vascular complication rate in our low-risk series was slightly higher in the TAVI cohort (7.9-9.4%) and lower in the SAVR cohort (0.6-2.3%), which would be expected. Especially in the Sapien 3 cohort, the rates of 8.4% in the unmatched and 9.4% in the matched groups appear high, considering that Sapien 3 utilizes a more advanced delivery system and was mainly used later in the study period (after 2013), when decent operator experience was already achieved. In comparison, in the prospective SOURCE 3 registry on post-market implantations with the Sapien 3 bioprosthesis, the major vascular complication (VARC-2) rate was 4.3% in the transfemoral group and 3.2% in the non-transfemoral group, half of that observed in our series (Wendler et al., 2017).

Annular rupture is a unique vascular complication related mainly to balloon-expandable valves in TAVI, and it is a significant predictor for death, with an odds ratio of 7.1 (Walther et al., 2015). In our Sapien 3 cohort, the incidence was 0.3%, which was as low as in previous reports (Pasic et al., 2015; Wendler et al., 2017).

Major vascular complications in TAVI and low baseline haemoglobin in SAVR patients are predictors of bleeding. The majority of bleedings are intraprocedural in both TAVI and SAVR, and one-third of the major bleedings in transfemoral TAVI are related to ilio-femoral artery injuries, while early post-procedural bleeding is more common in SAVR (Généreux et al., 2014). TAVI appeared to be a safer option compared to SAVR in terms of bleeding and a need for blood transfusion across all our studies. Other studies have almost uniformly found the same (Généreux et al., 2014; Popma et al., 2019; Thourani et al., 2016b). Bleeding is partly inherent to SAVR due to the nature of open-heart surgery. Blood products are also sometimes needed for haemodilution during cardiopulmonary bypass. In study **III**, 29% of the SAVR patients compared with 1.3% of the TAVI patients ($p<0.0001$) had a severe bleeding event. The surgical patients also had a higher rate of reoperation to control bleeding (11% vs. 2%, $p<0.0001$) and received more RBCs (3.5 vs. 1.0 units, $p<0.0001$). These were potentially associated with other adverse events in the Perimount SAVR cohort, as touched on above. The correlates of these complications were beyond the scope of the study. Slightly less profound but highly significant differences between treatment groups were also observed in studies **I** and **II**, favouring TAVI.

Comparison and interpretation of bleeding events between different studies must be done cautiously since commonly accepted definitions might have been modified and frequencies of events are presented differently. We mostly used the E-CABG bleeding score 2-3 (transfusion >4 units of red blood cells and/or reoperation for

bleeding) for severe bleeding for its simplicity. We also reported VARC-2 bleeding in study **II**, with a highly significant difference favouring TAVI. However, it was challenging to reliably apply the VARC-2 criteria to these retrospectively collected data. For that reason, the VARC-2 bleeding rate must be taken with caution.

In summary, we observed that SAVR is associated with lower rates of significant vascular complications and that TAVI is associated with a lower rate of severe bleeding, which are both explained by the inherent nature of each procedure. Efforts to reduce the rates of these complications should be made.

6.4.4 Paravalvular regurgitation

PVR was more common in TAVI than in SAVR, mainly due to the increased incidence of mild PVR. The incidence of moderate and severe PVR was not higher with the most recent TAVI prostheses compared to the surgically implanted prostheses. Relatively low rates of moderate PVR (2-3%) with TAVI were probably achieved by the use of MSCT-based valve sizing (Jilaihawi et al., 2012) and new bioprosthesis technology with improved sealing properties (Forrest et al., 2020; Schymik et al., 2019). In the surgical cohorts, the rate of moderate-severe PVR was 0.7-1.3%, somewhat higher than the incidence (0-0.2%) in recent low-risk trials (Mack et al., 2019; Popma et al., 2019). At the same time, it must be recognized that echocardiographic grading of PVR is usually a difficult task (Lancellotti et al., 2016). Our results must be taken with caution due to the nature of the study design, in which all echocardiographies were performed, interpreted, and reported by on-site cardiologists without core laboratory analysis. The rate of 1.9% of moderate PVR with Sapien 3 is, however, in line with the core laboratory-judged incidence of 0.8-3.5% in the PARTNER studies (Pibarot et al., 2017, 2020a). Nevertheless, the low rate of significant PVR in our study potentially favourably affected the outcomes, since moderate to severe PVR is a predictor of increased late mortality after TAVI (Arnold et al., 2019; Tamburino et al., 2011) and SAVR (Sponga et al., 2012). We should aim to further improve the incidence of PVR because some studies have shown that even mild PVR predicted late mortality (Kodali et al., 2015).

In summary, TAVI and SAVR were associated with similar rates of moderate and severe PVR when third-generation TAVI prostheses were compared to surgical prostheses. Overall, significant PVR was uncommon, but mild PVR was seen in 10-15% of TAVI prosthesis recipients.

6.4.5 Permanent pacemaker implantation

The importance of PPMI after TAVI as a risk factor for heart failure and one-year all-cause mortality is recognized (Faroux et al., 2020), but the effect on survival beyond 1 year remains debatable (Chamandi et al., 2018; Costa et al., 2019). The risk for a new conduction abnormality necessitating PPMI is increased after TAVI and depends on the type of prosthesis used, as well as on patient-related factors such as preoperative right bundle branch block. The incidence of PPMI is ~10-15% with the balloon-expandable Sapien 3, ~15-25% with the self-expanding Evolut, ~10% with the self-expanding Acurate, and 30-35% with the mechanically expandable Lotus valve (van Rosendael et al., 2018).

In our low-risk TAVI cohorts, who received a mixed proportion of different types of third-generation valves, the pacemaker rates were 7-10%. With the Sapien 3 prosthesis, 7.5-9.1% of the patients needed a new permanent pacemaker. The numbers were lower in the surgical cohorts (3.5-4%) with similar rates to those observed with SAVR in recent randomized trials. Pacemakers might be needed less frequently in the future if the implantation technique of TAVI prostheses is optimized (Husser et al., 2016; Jilaihawi et al., 2019).

In summary, PPMI was needed in nearly one of ten patients after TAVI, which was higher than the rate associated with SAVR.

6.4.6 Atrial fibrillation

One-third of the propensity score-matched patients had pre-existing paroxysmal, persistent, or long-standing persistent AF. Postoperatively, 30% of patients in the TAVI cohorts and 60% of the patients in the SAVR cohorts had any type of AF, highlighting the importance of increased inflammation and oxidative stress triggered by surgical trauma (Greenberg et al., 2017). The reported incidence of postoperative AF in our study was based on simple stratification ("no", "paroxysmal" or "persistent"). More specific criteria, for example, on the duration of atrial tachycardia to define AF, could not be applied. The lower occurrence of new-onset AF after TAVI compared to SAVR is widely recognized in previous reports, which have shown AF rates of 10% and 30-60% after TAVI and SAVR, respectively (Kalra et al., 2019; Tanawuttiwat et al., 2014; Vora et al., 2018).

In summary, TAVI was associated with significantly lower rates of postoperative AF than SAVR.

6.4.7 Hospital stay

Hospital stay was four days shorter in the TAVI cohorts, possibly due to the less invasive nature and more rapid functional recovery after TAVI compared to surgery (Baron et al., 2019). The true length of hospitalization before returning home could not be determined from our registry because length of hospital stay was counted as days in hospital where the procedure was done. Inevitably, some patients needed rehabilitation and care in other institutions after TAVI and SAVR.

In summary, the length of stay in hospital after the procedure seemed shorter after TAVI, but the real difference between the treatment cohorts is unknown due to shortcomings in data collection.

6.5 Late mortality

Survival analysis was performed in well-balanced propensity score matched TAVI and SAVR cohorts in all studies. We observed similar survival at 3 to 4 years after transfemoral TAVI compared to SAVR in patients with severe AS and 1) who were at low risk for surgery, 2) who were at low risk for surgery and did not have concomitant CAD, or 3) who were at low to intermediate risk for surgery and were treated with the transfemoral Sapien 3 bioprosthesis or with conventional SAVR using the Perimount Magna Ease bioprosthesis.

Our study demonstrates very low all-cause one-year mortality in real-life low-risk patients treated with either TAVI or SAVR. The one-year mortality rates of 5% (**II**) and 6.5-7.5% (**III**) are comparable to the results from the GARY registry study (mean STS-PROM 2.7%, no associated revascularization), which reported similar 1-year survival between the TAVI and SAVR cohorts (90.0% vs. 91.2%, p=0.158) (Bekeredjian et al., 2019).

We observed a similar risk for death from any cause at three years, 14.3% in the TAVI cohort compared to 12.3% in the surgical cohort (p=0.45) (**I**). Accordingly, the groups without concomitant CAD had an estimated all-cause 3-year mortality of 17.0% after TAVI and 14.6% after SAVR (p=0.805) (**II**). Any comparisons of mortality rates between these low-risk studies with or without CAD are not meaningful because of overlapping patients and the low number of subjects in study **II**. Study **III** was designed to minimize the potential bias related to the different types of bioprostheses used and thus to allow more precise analysis of late outcomes after TAVI and SAVR that were performed with prostheses that share some structural properties and manufacturing processes. The main result was that all-cause mortality at 4 years was similar if AS was treated with transfemoral TAVI using

Sapien 3 or with SAVR using Perimount Magna Ease. The estimated death rates were 25.9% and 20.6% (HR 0.96; 95% CI 0.63–1.46; p=0.910) for TAVI and SAVR, respectively. The patients in this study had a higher overall risk profile than the patients in studies **I** and **II** but still had similarly good survival at 3 years. It is purely speculative whether the favourable outcome was related to the prosthesis technology.

Interestingly, previous observational studies have observed different results from ours. For example, in a large multicentre OBSERVANT study, TAVI was associated with inferior 3-year survival to SAVR, 72% vs. 83% (p=0.0015) (Rosato et al., 2016). Similar findings were reported by a single-centre study, with 75% survival after TAVI compared to 90% survival after SAVR at 3 years (p=0.013) (Schaefer et al., 2019). Schymik showed inferior survival at 2 years after TAVI compared to SAVR (adjusted OR 0.31, 95% CI 0.16-0.61) (Schymik et al., 2018). Interestingly, the 3-year survival of the SAVR cohorts in these studies was almost identical to the survival of our SAVR cohorts (85-88%). However, the survival of TAVI cohorts in other studies was much lower than ours (83-86%). One possible reason for the conflicting results between our and other studies is the different use of various transcatheter prostheses. The OBSERVANT trial collected patients from 2010 to 2012, and only older-generation TAVI prostheses were available at that time. Schaefer et al. included patients from 2008 to 2016, and some proportion of the prostheses used were likely previous models. The rate of moderate-severe PVR was 7-10% in those studies, a problem that is often associated with older-generation TAVI valves and, importantly, with worse outcomes.

The results of our studies confirm that similar survival at 3 to 4 years after TAVI compared to SAVR can be achieved in real-life populations, a result that is observed only in randomized studies that typically include highly selected patient populations. The NOTION trial randomized mainly low-risk patients (without needing associated revascularization) to TAVI or SAVR. No significant difference in all-cause mortality was observed up to six years. In the NOTION trial, mortality at 1 year was 4.9% vs. 7.5%, at 2 years was 8.0% vs. 9.8%, at 5 years was 27.6% vs. 28.9%, and at 6 years was 42.5% vs. 37.7% for TAVI vs. SAVR (Søndergaard et al., 2016; Søndergaard et al., 2019a; Thyregod et al., 2015, 2019). TAVI was superior to SAVR in the PARTNER 3 trial using a composite of death, stroke and rehospitalization at 1 year as a primary endpoint, and the individual component of mortality was similar (1.0% vs. 2.5% for TAVI vs. SAVR; HR 0.41, 95% CI, 0.14-1.17) (Mack et al., 2019). Noninferiority of TAVI with a self-expanding valve compared to SAVR was also

demonstrated in the Evolut Low Risk Trial using Bayesian analysis of the composite endpoint of death and disabling stroke at 2 years (Popma et al., 2019).

Finally, the survival curves of the TAVI and SAVR cohorts seemed to cross each other after 2-2.5 years in all our studies. Whether this is indicative of different survival of the cohorts beyond 3 to 4 years remains speculative. The relatively small sized matched cohorts, different lengths of follow-up after TAVI and SAVR, and unrecognized imbalances in the variables might have influenced the analyses. Further studies with longer-term follow-up periods are needed. A prospective national registry including all patients undergoing invasive treatment for AS would be an important task to undertake.

In summary, our findings indicate that similar mid-term survival can be achieved in patients with severe AS who are at low- or intermediate-risk for surgery and who are treated either with transfemoral TAVI or with SAVR with recent prosthesis technologies. This finding is different from the results from previous observational studies.

6.6 Late cardiac events

Data on late events after valve intervention were available in studies **II** and **III**. All time-to-event analyses were performed by competing risk analysis to minimize the effect of death on the estimates of the incidences of these events.

Reinterventions for aortic valves were rare, and only single patients (<1%) underwent repeat operations at 3 and 4 years. In the unmatched cohorts (**III**), most reoperations were performed for PVR. Other studies observed that reinterventions were performed in 2-3% of patients after TAVI (mainly for SVD with Sapien XT) and in 1% of patients after SAVR (mainly for endocarditis) at 5-6 years (Makkar et al., 2020; Søndergaard et al., 2019a). The incidence of SVD in our study cannot be estimated based on the incidence of reoperation, as many patients might not have been candidates for a second operation. Unfortunately, the limited follow-up data on valve performance did not allow us to assess the incidence of SVD in our studies. The incidence of prosthetic valve endocarditis was <1% at 4 years, while others reported a 5% cumulative risk at five years (Butt et al., 2019).

As discussed above, the short-term risk for pacemakers is dependent on the TAVI prosthesis used. However, longer-term pacemaker rates were quite similar in **II** and **III** using mixed-selection and third-generation balloon-expandable TAVI prostheses. Compared to SAVR, TAVI was associated with a 1.5-2-fold risk of PPMI at mid-term follow-up, which is not surprising. While the PARTNER 2 study did

not find excess risk for pacemakers with second-generation balloon-expandable valves, the OBSERVANT study reported a 2.7-fold increased risk with older generation balloon-expandable and self-expanding valves in the long term (Barbanti et al., 2019a; Makkar et al., 2020).

The cumulative risk estimate for coronary revascularization at 3 years was 3.6% after TAVI and 1.7% after SAVR (p=0.679) in patients who were free of CAD at the time of the index valve procedure (**II**). The rates of revascularization in study **III**, including patients with CAD, were similar in the Sapien 3 cohort (1.5%) compared to the Perimount Magna Ease cohort (1.4%) at 4 years, with a hazard ratio of 0.76 (p=0.721). These events were very uncommon considering the fact that one-third of patients in the matched population were diagnosed with CAD in preoperative examination and the fact that a minority of these patients in the TAVI group and the majority of these patients in the SAVR group were revascularized along with valve implantation. A similar 1.5-2.5% risk for late revascularization was estimated by other investigators (Barbanti et al., 2019a). It is plausible that most patients in our series with CAD were adequately medicated, were mildly symptomatic at most, and did not have severe ischaemic cardiomyopathy that would meet an indication for revascularization (Knuuti et al., 2019).

In summary, repeated aortic valve intervention and late coronary revascularization are rarely needed after 3-4 years of TAVI or SAVR. TAVI seems to carry a higher risk for PPMI several years after the procedure than surgical AVR.

7 SUMMARY AND CONCLUSIONS

A patient with severe AS needs to be recognized early and treated when symptoms or ventricular dysfunction occurs because otherwise, the prognosis is dismal. Conventional AVR has offered the possibility to treat this valve disease for more than a half decade but has been limitedly performed in patients with high surgical risk. TAVI has been developed as an alternative method for the treatment of severe AS and is proven to be a valid option for surgery in patients whose risk for surgery is increased. More recently, positive results were also achieved with transcatheter treatment in patients with low surgical risk, but scientific data and follow-up data of these cohorts are limited, and comparable results are not often observed in real-life populations. Additionally, technological advances in the field of TAVI have improved the treatment options.

In this study, we collected all patients with severe AS undergoing surgical or transcatheter implantation of aortic valve bioprostheses during a 10-year period in Finland. The study was carried out in all Finnish university hospitals. The work of this thesis is focused on the comparison of transcatheter and surgical aortic valve intervention mainly in patients with low surgical risk.

The main findings are as follows:

1. Comparable mid-term survival can be achieved with TAVI compared to SAVR in patients with severe AS who are at low risk for surgery.
2. The risk of prosthetic valve endocarditis and aortic valve reintervention 3-4 years after the procedure is low and similar after TAVI and SAVR.
3. The need for coronary revascularization 3-4 years after valve intervention is rare, even in unrevascularized patients who have CAD at the time of TAVI.
4. TAVI with a balloon-expandable valve is associated with a higher incidence of new PPMI at 4 years compared to SAVR.
5. TAVI is associated with higher short-term incidences of PVR and major vascular complications compared to SAVR.
6. SAVR is associated with a higher short-term incidence of bleeding complications compared to TAVI.
7. The incidence of postoperative stroke and AKI is similar after TAVI and SAVR among low-risk patients.

8. The incidences of postoperative stroke and AKI are higher after SAVR with Perimount Magna Ease than TAVI with Sapien 3 in patients with low to intermediate surgical risk.
9. Postoperative AF occurred less frequently after TAVI than after SAVR.
10. In Finland, 11.4% of the low-risk patients with severe AS who underwent valve intervention from 2008 to 2017 were treated with TAVI.

Conclusions: Based on the findings of this study, TAVI can be offered as an alternative to SAVR in patients who need bioprosthesis implantation for the treatment of severe aortic stenosis and whose risk for surgery is low. However, the choice between TAVI and SAVR should be individualized and based on several components. Patient preference, coexisting medical conditions, individual anatomical and procedure-specific factors are considered during clinical decision-making. Importantly, lack of long-term (>10 years) data on TAVI durability impedes its current use in patients who have longer life expectancy. More randomized studies in younger patients are needed.

8 REFERENCES

Acute Kidney Injury Work Group. (2012). Section 2: AKI Definition. *Kidney International Supplements*, *2*(1), 19–36. https://doi.org/10.1038/kisup.2011.32

Adams, D. H., Popma, J. J., Reardon, M. J., Yakubov, S. J., Coselli, J. S., Deeb, G. M., … Oh, J. K. (2014). Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis. *New England Journal of Medicine*, *370*(19), 1790–1798. https://doi.org/10.1056/NEJMoa1400590

Afilalo, J., Lauck, S., Kim, D. H., Lefèvre, T., Piazza, N., Lachapelle, K., … Perrault, L. P. (2017). Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. *Journal of the American College of Cardiology*, *70*(6), 689–700. https://doi.org/10.1016/j.jacc.2017.06.024

Agatston, A. S., Janowitz, W. R., Hildner, F. J., Zusmer, N. R., Viamonte, M., & Detrano, R. (1990). Quantification of coronary artery calcium using ultrafast computed tomography. *Journal of the American College of Cardiology*, *15*(4), 827–832. https://doi.org/10.1016/0735-1097(90)90282-T

Aggarwal, S. R., Clavel, M.-A., Messika-Zeitoun, D., Cueff, C., Malouf, J., Araoz, P. A., … Enriquez-Sarano, M. (2013). Sex Differences in Aortic Valve Calcification Measured by Multidetector Computed Tomography in Aortic Stenosis. *Circulation: Cardiovascular Imaging*, *6*(1), 40–47. https://doi.org/10.1161/CIRCIMAGING.112.980052

Aikawa, E., & Schoen, F. J. (2014). *Cellular and Molecular Pathobiology of Cardiovascular Disease*. (M. Willis, J. W. Homeister, & J. R. Stone, Eds.). San Diego, UNITED STATES: Elsevier Science & Technology. Retrieved from http://ebookcentral.proquest.com/lib/tampere/detail.action?docID=1584552

Akins, C. W., Miller, D. C., Turina, M. I., Kouchoukos, N. T., Blackstone, E. H., Grunkemeier, G. L., … Lytle, B. W. (2008). Guidelines for reporting mortality and morbidity after cardiac valve interventions. *The Journal of Thoracic and Cardiovascular Surgery*, *135*(4), 732–738. https://doi.org/10.1016/j.jtcvs.2007.12.002

Alkhouli, M., Zack, C. J., Sarraf, M., Bashir, R., Nishimura, R. A., Eleid, M. F., … Rihal, C. S. (2017). Morbidity and Mortality Associated With Balloon Aortic Valvuloplasty. *Circulation: Cardiovascular Interventions*, *10*(5), 1–9. https://doi.org/10.1161/CIRCINTERVENTIONS.116.004481

Allen, K. B., Chhatriwalla, A. K., Saxon, J. T., Cohen, D. J., Nguyen, T. C., Webb, J., … Yeung, A. (2019). Bioprosthetic valve fracture: Technical insights from a multicenter study. *The Journal of Thoracic and Cardiovascular Surgery*, *158*(5), 1317-1328.e1. https://doi.org/10.1016/j.jtcvs.2019.01.073

Allende, R., Webb, J. G., Munoz-Garcia, A. J., de Jaegere, P., Tamburino, C., Dager, A. E., … Rodés-Cabau, J. (2014). Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. *European Heart Journal*, *35*(38), 2685–2696. https://doi.org/10.1093/eurheartj/ehu175

Altes, A., Ringle, A., Bohbot, Y., Bouchot, O., Appert, L., Guerbaai, R. A., … Maréchaux, S. (2020). Clinical significance of energy loss index in patients with low-gradient severe aortic

stenosis and preserved ejection fraction. *European Heart Journal - Cardiovascular Imaging*, *33*, 1–8. https://doi.org/10.1093/ehjci/jeaa010

Amat-Santos, I. J., Catalá, P., Diez del Hoyo, F., Fernandez-Diaz, J. A., Alonso-Briales, J. H., Del Trigo, M., … San Roman, J. A. (2018). Impact of renin-angiotensin system inhibitors on clinical outcomes and ventricular remodelling after transcatheter aortic valve implantation: rationale and design of the RASTAVI randomised multicentre study. *BMJ Open*, *8*(2), e020255. https://doi.org/10.1136/bmjopen-2017-020255

Andell, P., Li, X., Martinsson, A., Andersson, C., Stagmo, M., Zöller, B., … Smith, J. G. (2017). Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. *Heart*, *103*(21), 1696–1703. https://doi.org/10.1136/heartjnl-2016-310894

Andersen, H. R., Knudsen, L. L., & Hasenkam, J. M. (1992). Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs. *European Heart Journal*, *13*(5), 704–708. https://doi.org/10.1093/oxfordjournals.eurheartj.a060238

Andersson, C., & Abdulla, J. (2017). Is the use of renin–angiotensin system inhibitors in patients with aortic valve stenosis safe and of prognostic benefit? A systematic review and meta-analysis. *European Heart Journal - Cardiovascular Pharmacotherapy*, *3*(1), 21–27. https://doi.org/10.1093/ehjcvp/pvw027

Armoiry, X., Obadia, J. F., Pascal, L., Polazzi, S., & Duclos, A. (2018). Comparison of transcatheter versus surgical aortic valve implantation in high-risk patients: A nationwide study in France. *Journal of Thoracic and Cardiovascular Surgery*, *156*(3), 1017-1025.e4. https://doi.org/10.1016/j.jtcvs.2018.02.092

Armstrong, W. F., & Ryan, T. (2010). *Feigenbaum's Echocardiography*. (W. F. Armstrong & T. Ryan, Eds.) (7th Editio). Lippincott Williams and Wilkins.

Arnold, S. V., Zhang, Y., Baron, S. J., McAndrew, T. C., Alu, M. C., Kodali, S. K., … Cohen, D. J. (2019). Impact of Short-Term Complications on Mortality and Quality of Life After Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *12*(4), 362–369. https://doi.org/10.1016/j.jcin.2018.11.008

Arsalan, M., Maren, W., Hecker, F., Filardo, G., Kim, W.-K., Pollock, B., … Walther, T. (2018). TAVI risk scoring using established versus new scoring systems: role of the new STS/ACC model. *EuroIntervention*, *13*(13), 1520–1526. https://doi.org/10.4244/EIJ-D-17-00421

Asgar, A. W., Mullen, M. J., Delahunty, N., Davies, S. W., Dalby, M., Petrou, M., … Moat, N. (2009). Transcatheter aortic valve intervention through the axillary artery for the treatment of severe aortic stenosis. *The Journal of Thoracic and Cardiovascular Surgery*, *137*(3), 773–775. https://doi.org/10.1016/j.jtcvs.2007.12.084

Azevedo, C. F., Nigri, M., Higuchi, M. L., Pomerantzeff, P. M., Spina, G. S., Sampaio, R. O., … Rochitte, C. E. (2010). Prognostic Significance of Myocardial Fibrosis Quantification by Histopathology and Magnetic Resonance Imaging in Patients With Severe Aortic Valve Disease. *Journal of the American College of Cardiology*, *56*(4), 278–287. https://doi.org/10.1016/j.jacc.2009.12.074

Bach, D. S., Siao, D., Girard, S. E., Duvernoy, C., McCallister, B. D., & Gualano, S. K. (2009). Evaluation of Patients With Severe Symptomatic Aortic Stenosis Who Do Not Undergo Aortic Valve Replacement. *Circulation: Cardiovascular Quality and Outcomes*, *2*(6), 533–539. https://doi.org/10.1161/CIRCOUTCOMES.109.848259

Bagur, R., Martin, G. P., Nombela-Franco, L., Doshi, S. N., George, S., Toggweiler, S., … Mamas, M. A. (2018). Association of comorbid burden with clinical outcomes after transcatheter aortic valve implantation. *Heart*, *104*(24), 2058–2066. https://doi.org/10.1136/heartjnl-2018-313356

Bandyopadhyay, D., Sartori, S., Baber, U., Cao, D., Chandiramani, R., Tchétché, D., … Mehran, R. (2020). The impact of chronic kidney disease in women undergoing transcatheter aortic valve replacement: Analysis from the Women's INternational Transcatheter Aortic Valve Implantation (WIN-TAVI) registry. *Catheterization and Cardiovascular Interventions*, *96*(1), 198–207. https://doi.org/10.1002/ccd.28752

Barbanti, M., Tamburino, C., D'Errigo, P., Biancari, F., Ranucci, M., Rosato, S., … OBSERVANT Research Group. (2019a). Five-Year Outcomes of Transfemoral Transcatheter Aortic Valve Replacement or Surgical Aortic Valve Replacement in a Real World Population. *Circulation. Cardiovascular Interventions*, *12*(7), e007825. https://doi.org/10.1161/CIRCINTERVENTIONS.119.007825

Barbanti, M., Webb, J. G., Dvir, D., & Prendergast, B. D. (2019b). Residual challenges in TAVI: moving forward. *EuroIntervention*, *15*(10), 857–866. https://doi.org/10.4244/EIJ-D-19-00788

Barili, F., Pacini, D., Capo, A., Ardemagni, E., Pellicciari, G., Zanobini, M., … Parolari, A. (2013). Reliability of new scores in predicting perioperative mortality after isolated aortic valve surgery: A comparison with the society of thoracic surgeons score and logistic EuroSCORE. *Annals of Thoracic Surgery*, *95*(5), 1539–1544. https://doi.org/10.1016/j.athoracsur.2013.01.058

Baron, S. J., Magnuson, E. A., Lu, M., Wang, K., Chinnakondepalli, K., Mack, M., … Cohen, D. J. (2019). Health Status After Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients With Aortic Stenosis. *Journal of the American College of Cardiology*, *74*(23), 2833–2842. https://doi.org/10.1016/j.jacc.2019.09.007

Baumgartner, H., Falk, V., Bax, J. J., De Bonis, M., Hamm, C., Holm, P. J., … Brecker, S. J. D. (2017a). 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *European Heart Journal*, *38*(36), 2739–2791. https://doi.org/10.1093/eurheartj/ehx391

Baumgartner, H., Hung, J., Bermejo, J., Chambers, J. B., Edvardsen, T., Goldstein, S., … Otto, C. M. (2017b). Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *European Heart Journal - Cardiovascular Imaging*, *18*(3), 254–275. https://doi.org/10.1093/ehjci/jew335

Bekeredjian, R., Szabo, G., Balaban, Ü., Bleiziffer, S., Bauer, T., Ensminger, S., … Walther, T. (2019). Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results from the German Aortic Valve Registry (GARY). *European Heart Journal*, *40*(17), 1323–1330. https://doi.org/10.1093/eurheartj/ehy699

Beppu, S., Suzuki, S., Matsuda, H., Ohmori, F., Nagata, S., & Miyatake, K. (1993). Rapidity of progression of aortic stenosis in patients with congenital bicuspid aortic valves. *The American Journal of Cardiology*, *71*(4), 322–327. https://doi.org/10.1016/0002-9149(93)90799-I

Biancari, F., Juvonen, T., Onorati, F., Faggian, G., Heikkinen, J., Airaksinen, J., & Mariscalco, G. (2014). Meta-analysis on the performance of the EuroSCORE II and the society of thoracic surgeons scores in patients undergoing aortic valve replacement. *Journal of Cardiothoracic and Vascular Anesthesia*, *28*(6), 1533–1539. https://doi.org/10.1053/j.jvca.2014.03.014

Biancari, F., Ruggieri, V. G., Perrotti, A., Svenarud, P., Dalén, M., Onorati, F., … Juvonen, T. (2015). European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG registry): Study Protocol for a Prospective Clinical Registry and Proposal of Classification of Postoperative Complications. *Journal of Cardiothoracic Surgery*, *10*(1), 90. https://doi.org/10.1186/s13019-015-0292-z

Biancari, F., Rosato, S., D'Errigo, P., Ranucci, M., Onorati, F., Barbanti, M., … Seccareccia, F. (2016). Immediate and Intermediate Outcome After Transapical Versus Transfemoral Transcatheter Aortic Valve Replacement. *The American Journal of Cardiology*, *117*(2), 245–251. https://doi.org/10.1016/j.amjcard.2015.10.036

Biancari, F., Rosato, S., Costa, G., Barbanti, M., D'Errigo, P., Tamburino, C., … Seccareccia, F. (2020a). A Novel, comprehensive tool for predicting 30-day mortality after surgical aortic valve replacement: the OBS AVR Score. *European Journal of Cardio-Thoracic Surgery*, in press.

Biancari, F., Pykäri, J., Savontaus, M., Laine, M., Husso, A., Virtanen, M., … Airaksinen, J. (2020b). Early and late pace-maker implantation after transcatheter and surgical aortic valve replacement. *Catheterization and Cardiovascular Interventions*, ccd.29177. https://doi.org/10.1002/ccd.29177

Bilkhu, R., Borger, M. A., Briffa, N. P., & Jahangiri, M. (2019). Sutureless aortic valve prostheses. *Heart*, *105*(Suppl 2), s16–s20. https://doi.org/10.1136/heartjnl-2018-313513

Bourguignon, T., Bouquiaux-Stablo, A.-L., Candolfi, P., Mirza, A., Loardi, C., May, M.-A., … Aupart, M. (2015). Very Long-Term Outcomes of the Carpentier-Edwards Perimount Valve in Aortic Position. *The Annals of Thoracic Surgery*, *99*(3), 831–837. https://doi.org/10.1016/j.athoracsur.2014.09.030

Brascia, D., Garcia-Medina, N., Kinnunen, E.-M., Tauriainen, T., Airaksinen, J., & Biancari, F. (2017). Impact of transfusion on stroke after cardiovascular interventions: Meta-analysis of comparative studies. *Journal of Critical Care*, *38*, 157–163. https://doi.org/10.1016/j.jcrc.2016.11.004

Brennan, J. M., Edwards, F. H., Zhao, Y., O'Brien, S., Booth, M. E., Dokholyan, R. S., … Peterson, E. D. (2013). Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: Results from the society of thoracic surgeons adult cardiac surgery national database. *Circulation*, *127*(16), 1647–1655. https://doi.org/10.1161/CIRCULATIONAHA.113.002003

Butchart, E. G., Chambers, J., Borer, J. S., Grunkemeier, G., & Yoganathan, A. (2020). Long-Term Durability of Transcatheter Valves. *JACC: Cardiovascular Interventions*, *13*(2), 253–256. https://doi.org/10.1016/j.jcin.2019.10.003

Butt, J. H., Ihlemann, N., De Backer, O., Søndergaard, L., Havers-Borgersen, E., Gislason, G. H., … Fosbøl, E. L. (2019). Long-Term Risk of Infective Endocarditis After Transcatheter Aortic Valve Replacement. *Journal of the American College of Cardiology*, *73*(13), 1646–1655. https://doi.org/10.1016/j.jacc.2018.12.078

Capodanno, D., Barbanti, M., Tamburino, C., D'Errigo, P., Ranucci, M., Santoro, G., … Seccareccia, F. (2014). A simple risk tool (the OBSERVANT score) for prediction of 30-day mortality after transcatheter aortic valve replacement. *American Journal of Cardiology*, *113*(11), 1851–1858. https://doi.org/10.1016/j.amjcard.2014.03.014

Capodanno, D., Petronio, A. S., Prendergast, B., Eltchaninoff, H., Vahanian, A., Modine, T., … Haude, M. (2017). Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interven. *European Heart Journal*, *38*(45), 3382–3390. https://doi.org/10.1093/eurheartj/ehx303

Capodanno, D., Søndergaard, L., & Tamburino, C. (2019). Durability of transcatheter bioprosthetic aortic valves: the story so far. *EuroIntervention*, *15*(10), 846–849. https://doi.org/10.4244/EIJV15I10A160

Capodanno, D., & Søndergaard, L. (2020). How to Define Durability of Transcatheter and Surgical Bioprosthetic Aortic Valves: Facts and Misconceptions. *JACC: Cardiovascular Interventions*, *13*(2), 257–260. https://doi.org/10.1016/j.jcin.2019.11.025

Capoulade, R., Clavel, M.-A., Dumesnil, J. G., Chan, K. L., Teo, K. K., Tam, J. W., … Pibarot, P. (2012). Impact of Metabolic Syndrome on Progression of Aortic Stenosis. *Journal of the American College of Cardiology*, *60*(3), 216–223. https://doi.org/10.1016/j.jacc.2012.03.052

Carabello, B. A., & Paulus, W. J. (2009). Aortic stenosis. *The Lancet*, *373*(9667), 956–966. https://doi.org/10.1016/S0140-6736(09)60211-7

Chamandi, C., Barbanti, M., Munoz-Garcia, A., Latib, A., Nombela-Franco, L., Gutiérrez-Ibanez, E., … Rodés-Cabau, J. (2018). Long-Term Outcomes in Patients With New Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *11*(3), 301–310. https://doi.org/10.1016/j.jcin.2017.10.032

Chan, K. L., Teo, K., Dumesnil, J. G., Ni, A., & Tam, J. (2010). Effect of Lipid Lowering With Rosuvastatin on Progression of Aortic Stenosis. *Circulation*, *121*(2), 306–314. https://doi.org/10.1161/CIRCULATIONAHA.109.900027

Chen, C., Zhao, Z.-G., Liao, Y.-B., Peng, Y., Meng, Q.-T., Chai, H., … Huang, D.-J. (2015). Impact of Renal Dysfunction on Mid-Term Outcome after Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-Analysis. *PLOS ONE*, *10*(3), e0119817. https://doi.org/10.1371/journal.pone.0119817

Chen, S., Redfors, B., Nazif, T., Kirtane, A., Crowley, A., Ben-Yehuda, O., … Leon, M. B. (2020). Impact of renin–angiotensin system inhibitors on clinical outcomes in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement: an analysis of from the PARTNER 2 trial and registries. *European Heart Journal*, *41*(8), 943–954. https://doi.org/10.1093/eurheartj/ehz769

Chin, C. W. L., Everett, R. J., Kwiecinski, J., Vesey, A. T., Yeung, E., Esson, G., … Dweck, M. R. (2017). Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. *JACC: Cardiovascular Imaging*, *10*(11), 1320–1333. https://doi.org/10.1016/j.jcmg.2016.10.007

Cioffi, G., Faggiano, P., Vizzardi, E., Tarantini, L., Cramariuc, D., Gerdts, E., & de Simone, G. (2011). Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart*, *97*(4), 301–307. https://doi.org/10.1136/hrt.2010.192997

Clavel, M.-A., Messika-Zeitoun, D., Pibarot, P., Aggarwal, S. R., Malouf, J., Araoz, P. A., … Enriquez-Sarano, M. (2013). The Complex Nature of Discordant Severe Calcified Aortic Valve Disease Grading. *Journal of the American College of Cardiology*, *62*(24), 2329–2338. https://doi.org/10.1016/j.jacc.2013.08.1621

Clavel, M.-A., Malouf, J., Messika-Zeitoun, D., Araoz, P. A., Michelena, H. I., & Enriquez-Sarano, M. (2015). Aortic Valve Area Calculation in Aortic Stenosis by CT and Doppler Echocardiography. *JACC: Cardiovascular Imaging*, *8*(3), 248–257. https://doi.org/10.1016/j.jcmg.2015.01.009

Codner, P., Malick, W., Kouz, R., Patel, A., Chen, C.-H., Terre, J., … Kodali, S. (2018). Mortality risk after transcatheter aortic valve implantation: analysis of the predictive accuracy of the Transcatheter Valve Therapy registry risk assessment model. *EuroIntervention*, *14*(4), e405–e412. https://doi.org/10.4244/EIJ-D-18-00032

Costa, G., Zappulla, P., Barbanti, M., Cirasa, A., Todaro, D., Rapisarda, G., … Calvi, V. (2019). Pacemaker dependency after transcatheter aortic valve implantation: incidence, predictors and long-term outcomes. *EuroIntervention*, *15*(10), 875–883. https://doi.org/10.4244/EIJ-D-18-01060

Cowell, S. J., Newby, D. E., Prescott, R. J., Bloomfield, P., Reid, J., Northridge, D. B., & Boon, N. A. (2005). A Randomized Trial of Intensive Lipid-Lowering Therapy in Calcific Aortic Stenosis. *New England Journal of Medicine*, *352*(23), 2389–2397. https://doi.org/10.1056/NEJMoa043876

Crestanello, J. A., Popma, J. J., Adams, D. H., Deeb, G. M., Mumtaz, M., George, B., … Reardon, M. J. (2017). Long-Term Health Benefit of Transcatheter Aortic Valve Replacement in

Patients With Chronic Lung Disease. *JACC: Cardiovascular Interventions*, *10*(22), 2283–2293. https://doi.org/10.1016/j.jcin.2017.07.025

Cribier, A., Saoudi, N., Berland, J., Savin, T., Rocha, P., & Letac, B. (1986). PERCUTANEOUS TRANSLUMINAL VALVULOPLASTY OF ACQUIRED AORTIC STENOSIS IN ELDERLY PATIENTS: AN ALTERNATIVE TO VALVE REPLACEMENT? *The Lancet*, *327*(8472), 63–67. https://doi.org/10.1016/S0140-6736(86)90716-6

Cribier, A., Eltchaninoff, H., Bash, A., Borenstein, N., Tron, C., Bauer, F., … Leon, M. B. (2002). Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: First human case description. *Circulation*, *106*(24), 3006–3008. https://doi.org/10.1161/01.CIR.0000047200.36165.B8

Cribier, A., Eltchaninoff, H., Tron, C., Bauer, F., Agatiello, C., Sebagh, L., … Leon, M. B. (2004). Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. *Journal of the American College of Cardiology*, *43*(4), 698–703. https://doi.org/10.1016/j.jacc.2003.11.026

Cribier, A., Eltchaninoff, H., Tron, C., Bauer, F., Agatiello, C., Nercolini, D., … Babaliaros, V. (2006). Treatment of calcific aortic stenosis with the percutaneous heart valve: Mid-term follow-up from the initial feasibility studies: The French experience. *Journal of the American College of Cardiology*, *47*(6), 1214–1223. https://doi.org/10.1016/j.jacc.2006.01.049

Cueff, C., Serfaty, J.-M., Cimadevilla, C., Laissy, J.-P., Himbert, D., Tubach, F., … Messika-Zeitoun, D. (2011). Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. *Heart*, *97*(9), 721–726. https://doi.org/10.1136/hrt.2010.198853

Culler, S. D., Cohen, D. J., Brown, P. P., Kugelmass, A. D., Reynolds, M. R., Ambrose, K., … Katz, M. R. (2018). Trends in Aortic Valve Replacement Procedures Between 2009 and 2015: Has Transcatheter Aortic Valve Replacement Made a Difference? *Annals of Thoracic Surgery*, *105*(4), 1137–1143. https://doi.org/10.1016/j.athoracsur.2017.10.057

d'Arcy, J. L., Coffey, S., Loudon, M. A., Kennedy, A., Pearson-Stuttard, J., Birks, J., … Prendergast, B. D. (2016). Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *European Heart Journal*, *37*(47), 3515–3522. https://doi.org/10.1093/eurheartj/ehw229

D'Ascenzo, F., Verardi, R., Visconti, M., Conrotto, F., Scacciatella, P., Dziewierz, A., … Salizzoni, S. (2018). Independent impact of extent of coronary artery disease and percutaneous revascularisation on 30-day and one-year mortality after TAVI: a meta-analysis of adjusted observational results. *EuroIntervention*, *14*(11), e1169–e1177. https://doi.org/10.4244/EIJ-D-18-00098

Dahl, J. S., Eleid, M. F., Michelena, H. I., Scott, C. G., Suri, R. M., Schaff, H. V., & Pellikka, P. A. (2015). Effect of Left Ventricular Ejection Fraction on Postoperative Outcome in Patients With Severe Aortic Stenosis Undergoing Aortic Valve Replacement. *Circulation: Cardiovascular Imaging*, *8*(4), 1–8. https://doi.org/10.1161/CIRCIMAGING.114.002917

Dall'Ara, G., Tumscitz, C., Grotti, S., Santarelli, A., Balducelli, M., Tarantino, F., & Saia, F. (2020). Contemporary balloon aortic valvuloplasty: Changing indications and refined technique. *Catheterization and Cardiovascular Interventions*, 1–10. https://doi.org/10.1002/ccd.28807

Danielsen, R., Aspelund, T., Harris, T. B., & Gudnason, V. (2014). The prevalence of aortic stenosis in the elderly in Iceland and predictions for the coming decades: The AGES–Reykjavík study. *International Journal of Cardiology*, *176*(3), 916–922. https://doi.org/10.1016/j.ijcard.2014.08.053

de Arenaza, D. P., Pepper, J., Lees, B., Rubinstein, F., Nugara, F., Roughton, M., … Flather, M. (2010). Preoperative 6-minute walk test adds prognostic information to Euroscore in patients undergoing aortic valve replacement. *Heart*, *96*(2), 113–117. https://doi.org/10.1136/hrt.2008.161174

de Monchy, C. C., Lepage, L., Boutron, I., Leye, M., Detaint, D., Hyafil, F., … Messika-Zeitoun, D. (2009). Usefulness of the right parasternal view and non-imaging continuous-wave Doppler transducer for the evaluation of the severity of aortic stenosis in the modern area. *European Journal of Echocardiography*, *10*(3), 420–424. https://doi.org/10.1093/ejechocard/jen301

Debonnaire, P., Fusini, L., Wolterbeek, R., Kamperidis, V., Van Rosendael, P., Van Der Kley, F., … Delgado, V. (2015). Value of the "tAVI2-SCORe" versus surgical risk scores for prediction of one year mortality in 511 patients who underwent transcatheter aortic valve implantation. *American Journal of Cardiology*, *115*(2), 234–242. https://doi.org/10.1016/j.amjcard.2014.10.029

Deeb, G. M., Reardon, M. J., Chetcuti, S., Patel, H. J., Grossman, P. M., Yakubov, S. J., … Popma, J. J. (2016). 3-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. *Journal of the American College of Cardiology*, *67*(22), 2565–2574. https://doi.org/10.1016/J.JACC.2016.03.506

Deharo, P., Jaussaud, N., Grisoli, D., Camus, O., Resseguier, N., Le Breton, H., … Cuisset, T. (2018). Impact of Direct Transcatheter Aortic Valve Replacement Without Balloon Aortic Valvuloplasty on Procedural and Clinical Outcomes. *JACC: Cardiovascular Interventions*, *11*(19), 1956–1965. https://doi.org/10.1016/j.jcin.2018.06.023

Di Mario, C., Eltchaninoff, H., Moat, N., Goicolea, J., Ussia, G. P., Kala, P., … Tavazzi, L. (2013). The 2011-12 pilot European Sentinel Registry of Transcatheter Aortic Valve Implantation: In-hospital results in 4,571 patients. *EuroIntervention*, *8*(12), 1362–1371. https://doi.org/10.4244/EIJV8I12A209

Diaz, R., Hernandez-Vaquero, D., Alvarez-Cabo, R., Avanzas, P., Silva, J., Moris, C., & Pascual, I. (2019). Long-term outcomes of mechanical versus biological aortic valve prosthesis: Systematic review and meta-analysis. *The Journal of Thoracic and Cardiovascular Surgery*, *158*(3), 706-714.e18. https://doi.org/10.1016/j.jtcvs.2018.10.146

Doris, M. K., Jenkins, W., Robson, P., Pawade, T., Andrews, J. P., Bing, R., … Dweck, M. R. (2020). Computed tomography aortic valve calcium scoring for the assessment of aortic stenosis progression. *Heart*, heartjnl-2020-317125. https://doi.org/10.1136/heartjnl-2020-317125

Douglas, P. S., Leon, M. B., Mack, M. J., Svensson, L. G., Webb, J. G., Hahn, R. T., … Blackstone, E. H. (2017). Longitudinal hemodynamics of transcatheter and surgical aortic valves in the PARTNER Trial. *JAMA Cardiology*, *2*(11), 1197–1206. https://doi.org/10.1001/jamacardio.2017.3306

Dvir, D., Waksman, R., Barbash, I. M., Kodali, S. K., Svensson, L. G., Tuzcu, E. M., … Pichard, A. D. (2014). Outcomes of Patients With Chronic Lung Disease and Severe Aortic Stenosis Treated With Transcatheter Versus Surgical Aortic Valve Replacement or Standard Therapy. *Journal of the American College of Cardiology*, *63*(3), 269–279. https://doi.org/10.1016/j.jacc.2013.09.024

Dvir, D., Bourguignon, T., Otto, C. M., Hahn, R. T., Rosenhek, R., Webb, J. G., … Leon, M. B. (2018). Standardized Definition of Structural Valve Degeneration for Surgical and Transcatheter Bioprosthetic Aortic Valves. *Circulation*, *137*(4), 388–399. https://doi.org/10.1161/CIRCULATIONAHA.117.030729

Dweck, M. R., Joshi, S., Murigu, T., Alpendurada, F., Jabbour, A., Melina, G., … Prasad, S. K. (2011). Midwall Fibrosis Is an Independent Predictor of Mortality in Patients With Aortic

Stenosis. *Journal of the American College of Cardiology*, *58*(12), 1271–1279. https://doi.org/10.1016/j.jacc.2011.03.064

Edwards, F. H., Cohen, D. J., O'Brien, S. M., Peterson, E. D., Mack, M. J., Shahian, D. M., … Holmes, D. R. (2016). Development and Validation of a Risk Prediction Model for In-Hospital Mortality After Transcatheter Aortic Valve Replacement. *JAMA Cardiology*, *1*(1), 46. https://doi.org/10.1001/jamacardio.2015.0326

Eggebrecht, H., & Mehta, R. H. (2019). Transcatheter aortic valve implantation (TAVI) in Germany: more than 100,000 procedures and now the standard of care for the elderly. *EuroIntervention*, *14*(15), e1549–e1552. https://doi.org/10.4244/EIJ-D-18-01010

Elbaz, G. G., Henning, K. A., Qiu, F., Fremes, S. E., Austin, P. C., Komatsu, I., … Wijeysundera, H. C. (2020). Impact of Coronary Artery Severity and Revascularization Prior to Transcatheter Aortic Valve Implantation. *The American Journal of Cardiology*, *125*(6), 924–930. https://doi.org/10.1016/j.amjcard.2019.12.021

Eltchaninoff, H., Durand, E., Borz, B., Furuta, A., Bejar, K., Canville, A., … Cribier, A. (2014). Balloon aortic valvuloplasty in the era of transcatheter aortic valve replacement: Acute and long-term outcomes. *American Heart Journal*, *167*(2), 235–240. https://doi.org/10.1016/j.ahj.2013.10.019

Emami, S., Rudasill, S., Bellamkonda, N., Sanaiha, Y., Cale, M., Madrigal, J., … Benharash, P. (2020). Impact of Malnutrition on Outcomes Following Transcatheter Aortic Valve Implantation (from a National Cohort). *American Journal of Cardiology*, *125*(7), 1096–1101. https://doi.org/10.1016/j.amjcard.2019.12.038

Etienne, P.-Y., Papadatos, S., El Khoury, E., Pieters, D., Price, J., & Glineur, D. (2011). Transaortic Transcatheter Aortic Valve Implantation With the Edwards Sapien Valve: Feasibility, Technical Considerations, and Clinical Advantages. *The Annals of Thoracic Surgery*, *92*(2), 746–748. https://doi.org/10.1016/j.athoracsur.2011.03.014

Eveborn, G. W., Schirmer, H., Heggelund, G., Lunde, P., & Rasmussen, K. (2013). The evolving epidemiology of valvular aortic stenosis. The Tromsø Study. *Heart*, *99*(6), 396–400. https://doi.org/10.1136/heartjnl-2012-302265

Everett, R. J., Treibel, T. A., Fukui, M., Lee, H., Rigolli, M., Singh, A., … Dweck, M. R. (2020). Extracellular Myocardial Volume in Patients With Aortic Stenosis. *Journal of the American College of Cardiology*, *75*(3), 304–316. https://doi.org/10.1016/j.jacc.2019.11.032

Fadahunsi, O. O., Olowoyeye, A., Ukaigwe, A., Li, Z., Vora, A. N., Vemulapalli, S., … Donato, A. (2016). Incidence, Predictors, and Outcomes of Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *9*(21), 2189–2199. https://doi.org/10.1016/j.jcin.2016.07.026

Faroux, L., Chen, S., Muntané-Carol, G., Regueiro, A., Philippon, F., Sondergaard, L., … Rodés-Cabau, J. (2020). Clinical impact of conduction disturbances in transcatheter aortic valve replacement recipients: a systematic review and meta-analysis. *European Heart Journal*, *41*(29), 2771–2781. https://doi.org/10.1093/eurheartj/ehz924

Fatima, B., Mohananey, D., Khan, F. W., Jobanputra, Y., Tummala, R., Banerjee, K., … Kapadia, S. (2019). Durability Data for Bioprosthetic Surgical Aortic Valve. *JAMA Cardiology*, *4*(1), 71–80. https://doi.org/10.1001/jamacardio.2018.4045

Forcillo, J., Condado, J. F., Ko, Y.-A., Yuan, M., Binongo, J. N., Ndubisi, N. M., … Thourani, V. H. (2017). Assessment of Commonly Used Frailty Markers for High- and Extreme-Risk Patients Undergoing Transcatheter Aortic Valve Replacement. *The Annals of Thoracic Surgery*, *104*(6), 1939–1946. https://doi.org/10.1016/j.athoracsur.2017.05.067

Foroutan, F., Guyatt, G. H., O'Brien, K., Bain, E., Stein, M., Bhagra, S., … Vandvik, P. O. (2016). Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. *BMJ*, *354*, i5065. https://doi.org/10.1136/bmj.i5065

Forrest, J. K., Kaple, R. K., Tang, G. H. L., Yakubov, S. J., Nazif, T. M., Williams, M. R., … Reardon, M. J. (2020). Three Generations of Self-Expanding Transcatheter Aortic Valves: A Report From the STS/ACC TVT Registry. *JACC: Cardiovascular Interventions*, *13*(2), 170–179. https://doi.org/10.1016/j.jcin.2019.08.035

Gahl, B., Çelik, M., Head, S. J., Vanoverschelde, J.-L., Pibarot, P., Reardon, M. J., … da Costa, B. R. (2020). Natural History of Asymptomatic Severe Aortic Stenosis and the Association of Early Intervention With Outcomes. *JAMA Cardiology*. https://doi.org/10.1001/jamacardio.2020.2497

Garcia, D., Pibarot, P., Kadem, L., & Durand, L.-G. (2007). Respective impacts of aortic stenosis and systemic hypertension on left ventricular hypertrophy. *Journal of Biomechanics*, *40*(5), 972–980. https://doi.org/https://doi.org/10.1016/j.jbiomech.2006.03.020

Gaspar, T., Adawi, S., Sachner, R., Asmer, I., Ganaeem, M., Rubinshtein, R., & Shiran, A. (2012). Three-Dimensional Imaging of the Left Ventricular Outflow Tract: Impact on Aortic Valve Area Estimation by the Continuity Equation. *Journal of the American Society of Echocardiography*, *25*(7), 749–757. https://doi.org/10.1016/j.echo.2012.05.001

Généreux, P., Cohen, D. J., Williams, M. R., Mack, M., Kodali, S. K., Svensson, L. G., … Leon, M. B. (2014). Bleeding Complications After Surgical Aortic Valve Replacement Compared With Transcatheter Aortic Valve Replacement: Insights From the PARTNER I Trial (Placement of Aortic Transcatheter Valve). *Journal of the American College of Cardiology*, *63*(11), 1100–1109. https://doi.org/https://doi.org/10.1016/j.jacc.2013.10.058

Généreux, P., Pibarot, P., Redfors, B., Mack, M. J., Makkar, R. R., Jaber, W. A., … Leon, M. B. (2017). Staging classification of aortic stenosis based on the extent of cardiac damage. *European Heart Journal*, *38*(45), 3351–3358. https://doi.org/10.1093/eurheartj/ehx381

Gleason, T. G., Reardon, M. J., Popma, J. J., Deeb, G. M., Yakubov, S. J., Lee, J. S., … Adams, D. H. (2018). 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. *Journal of the American College of Cardiology*, *72*(22), 2687–2696. https://doi.org/10.1016/j.jacc.2018.08.2146

Goel, S. S., Aksoy, O., Gupta, S., Houghtaling, P. L., Tuzcu, E. M., Marwick, T., … Kapadia, S. R. (2014). Renin-angiotensin system blockade therapy after surgical aortic valve replacement for severe aortic stenosis: a cohort study. *Annals of Internal Medicine*, *161*(10), 699–710. https://doi.org/10.7326/M13-1505

Gorlin, R., & Gorlin, S. G. (1951). Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. I. *American Heart Journal*, *41*(1), 1–29. https://doi.org/10.1016/0002-8703(51)90002-6

Green, P., Arnold, S. V., Cohen, D. J., Kirtane, A. J., Kodali, S. K., Brown, D. L., … Mack, M. J. (2015). Relation of Frailty to Outcomes After Transcatheter Aortic Valve Replacement (from the PARTNER Trial). *The American Journal of Cardiology*, *116*(2), 264–269. https://doi.org/10.1016/j.amjcard.2015.03.061

Greenbaum, A. B., O'Neill, W. W., Paone, G., Guerrero, M. E., Wyman, J. F., Cooper, R. L., & Lederman, R. J. (2014). Caval-aortic access to allow transcatheter aortic valve replacement in otherwise ineligible patients: initial human experience. *Journal of the American College of Cardiology*, *63*(25 Pt A), 2795–2804. https://doi.org/10.1016/j.jacc.2014.04.015

Greenberg, J. W., Lancaster, T. S., Schuessler, R. B., & Melby, S. J. (2017). Postoperative atrial fibrillation following cardiac surgery: a persistent complication. *European Journal of Cardio-Thoracic Surgery*, *52*(4), 665–672. https://doi.org/10.1093/ejcts/ezx039

Greve, A. M., Bang, C. N., Boman, K., Egstrup, K., Kesäniemi, Y. A., Ray, S., … Wachtell, K. (2019). Relation of Lipid-Lowering Therapy to Need for Aortic Valve Replacement in Patients With Asymptomatic Mild to Moderate Aortic Stenosis. *The American Journal of Cardiology*, *124*(11), 1736–1740. https://doi.org/10.1016/j.amjcard.2019.08.037

Grube, E., Laborde, J. C., Gerckens, U., Felderhoff, T., Sauren, B., Buellesfeld, L., … Stone, G. W. (2006). Percutaneous Implantation of the CoreValve Self-Expanding Valve Prosthesis in High-Risk Patients With Aortic Valve Disease. *Circulation*, *114*(15), 1616–1624. https://doi.org/10.1161/CIRCULATIONAHA.106.639450

Grunkemeier, G. L., Li, H.-H., Naftel, D. C., Starr, A., & Rahimtoola, S. H. (2000). Long-term performance of heart valve prostheses. *Current Problems in Cardiology*, *25*(2), 78–154. https://doi.org/10.1053/cd.2000.v25.a103682

Guzzetti, E., Poulin, A., Annabi, M.-S., Zhang, B., Kalavrouziotis, D., Couture, C., … Clavel, M.-A. (2020). Transvalvular Flow, Sex, and Survival After Valve Replacement Surgery in Patients With Severe Aortic Stenosis. *Journal of the American College of Cardiology*, *75*(16), 1897–1909. https://doi.org/https://doi.org/10.1016/j.jacc.2020.02.065

Hachicha, Z., Dumesnil, J. G., Bogaty, P., & Pibarot, P. (2007). Paradoxical Low-Flow, Low-Gradient Severe Aortic Stenosis Despite Preserved Ejection Fraction Is Associated With Higher Afterload and Reduced Survival. *Circulation*, *115*(22), 2856–2864. https://doi.org/10.1161/CIRCULATIONAHA.106.668681

Hahn, R. T., & Pibarot, P. (2017). Accurate Measurement of Left Ventricular Outflow Tract Diameter: Comment on the Updated Recommendations for the Echocardiographic Assessment of Aortic Valve Stenosis. *Journal of the American Society of Echocardiography*, *30*(10), 1038–1041. https://doi.org/10.1016/j.echo.2017.06.002

Hahn, R. T., Pibarot, P., Leipsic, J., Blanke, P., Douglas, P. S., Weissman, N. J., … Kodali, S. (2018). The Effect of Post-Dilatation on Outcomes in the PARTNER 2 SAPIEN 3 Registry. *JACC: Cardiovascular Interventions*, *11*(17), 1710–1718. https://doi.org/10.1016/j.jcin.2018.05.035

Hammermeister, K., Sethi, G. K., Henderson, W. G., Grover, F. L., Oprian, C., & Rahimtoola, S. H. (2000). Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *Journal of the American College of Cardiology*, *36*(4), 1152–1158. https://doi.org/10.1016/S0735-1097(00)00834-2

Hannan, E. L., Samadashvili, Z., Lahey, S. J., Smith, C. R., Culliford, A. T., Higgins, R. S. D., … Jones, R. H. (2009). Aortic Valve Replacement for Patients With Severe Aortic Stenosis: Risk Factors and Their Impact on 30-Month Mortality. *Annals of Thoracic Surgery*, *87*(6), 1741–1749. https://doi.org/10.1016/j.athoracsur.2009.02.058

Harken, D. E., Soroff, H. S., Taylor, W. J., Lefemine, A. A., Gupta, S. K., & Lunzer, S. (1960). PARTIAL AND COMPLETE PROSTHESES IN AORTIC INSUFFICIENCY. *The Journal of Thoracic and Cardiovascular Surgery*, *40*(6), 744–762. https://doi.org/10.1016/S0022-5223(19)32572-3

Helske, S., Kupari, M., Lindstedt, K. A., & Kovanen, P. T. (2007). Aortic valve stenosis: an active atheroinflammatory process. *Current Opinion in Lipidology*, *18*(5), 483–491. https://doi.org/10.1097/MOL.0b013e3282a66099

Henn, M. C., Zajarias, A., Quader, N., Sintek, M., Lasala, J. M., Koogler, K., … Maniar, H. S. (2019). Observed to expected 30-day mortality as a benchmark for transcatheter aortic valve replacement. *The Journal of Thoracic and Cardiovascular Surgery*, *157*(3), 874-882.e8. https://doi.org/10.1016/j.jtcvs.2018.06.097

Hickey, G. L., Dunning, J., Seifert, B., Sodeck, G., Carr, M. J., Burger, H. U., … Committees, on behalf of the E. and I. E. (2015). Statistical and data reporting guidelines for the European Journal of Cardio-Thoracic Surgery and the Interactive CardioVascular and Thoracic Surgery. *European Journal of Cardio-Thoracic Surgery*, *48*(2), 180–193. https://doi.org/10.1093/ejcts/ezv168

Himbert, D., Descoutures, F., Al-Attar, N., Iung, B., Ducrocq, G., Detaint, D., … Vahanian, A. (2009). Results of transfemoral or transapical aortic valve implantation following a

uniform assessment in high-risk patients with aortic stenosis. *Journal of the American College of Cardiology*, *54*(4), 303–311. https://doi.org/10.1016/j.jacc.2009.04.032

Horstkotte, D., & Loogen, F. (1988). The natural history of aortic valve stenosis. *European Heart Journal*, *9 Suppl E*, 57–64. https://doi.org/10.1093/eurheartj/9.suppl_E.57

Huded, C. P., Tuzcu, E. M., Krishnaswamy, A., Mick, S. L., Kleiman, N. S., Svensson, L. G., … Kapadia, S. R. (2019). Association between Transcatheter Aortic Valve Replacement and Early Postprocedural Stroke. *JAMA - Journal of the American Medical Association*, *321*(23), 2306–2315. https://doi.org/10.1001/jama.2019.7525

Husser, O., Pellegrini, C., Kessler, T., Burgdorf, C., Thaller, H., Mayr, N. P., … Hengstenberg, C. (2016). Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve. *JACC: Cardiovascular Interventions*, *9*(3), 244–254. https://doi.org/10.1016/j.jcin.2015.09.036

Husso, A., Airaksinen, J., Juvonen, T., Laine, M., Dahlbacka, S., Virtanen, M., … Biancari, F. (2020). Transcatheter and surgical aortic valve replacement in patients with bicuspid aortic valve. *Clinical Research in Cardiology*. https://doi.org/10.1007/s00392-020-01761-3

Inohara, T., Manandhar, P., Kosinski, A. S., Matsouaka, R. A., Kohsaka, S., Mentz, R. J., … Vemulapalli, S. (2018). Association of Renin-Angiotensin Inhibitor Treatment With Mortality and Heart Failure Readmission in Patients With Transcatheter Aortic Valve Replacement. *JAMA*, *320*(21), 2231. https://doi.org/10.1001/jama.2018.18077

Iribarne, A., Leavitt, B. J., Robich, M. P., Sardella, G. L., Gelb, D. J., Baribeau, Y. R., … DiScipio, A. W. (2019). Tissue versus mechanical aortic valve replacement in younger patients: A multicenter analysis. *The Journal of Thoracic and Cardiovascular Surgery*, *158*(6), 1529-1538.e2. https://doi.org/10.1016/j.jtcvs.2019.02.076

Ito, S., Miranda, W. R., Nkomo, V. T., Connolly, H. M., Pislaru, S. V., Greason, K. L., … Oh, J. K. (2018). Reduced Left Ventricular Ejection Fraction in Patients With Aortic Stenosis. *Journal of the American College of Cardiology*, *71*(12), 1313–1321. https://doi.org/10.1016/j.jacc.2018.01.045

Iung, B., Baron, G., Butchart, E. G., Delahaye, F., Gohlke-Bärwolf, C., Levang, O. W., … Vahanian, A. (2003). A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *European Heart Journal*, *24*(13), 1231–1243. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12831818

Iung, B., Baron, G., Tornos, P., Gohlke-Bärwolf, C., Butchart, E. G., & Vahanian, A. (2007). Valvular Heart Disease in the Community: A European Experience. *Current Problems in Cardiology*, *32*(11), 609–661. https://doi.org/10.1016/j.cpcardiol.2007.07.002

Iung, B., Laouénan, C., Himbert, D., Eltchaninoff, H., Chevreul, K., Donzeau-Gouge, P., … Gilard, M. (2014). Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. *Heart*, *100*(13), 1016–1023. https://doi.org/10.1136/heartjnl-2013-305314

Iung, B., Delgado, V., Rosenhek, R., Price, S., Prendergast, B., Wendler, O., … Rahman-Haley, S. (2019). Contemporary Presentation and Management of Valvular Heart Disease. *Circulation*, *140*(14), 1156–1169. https://doi.org/10.1161/CIRCULATIONAHA.119.041080

Jilaihawi, H., Kashif, M., Fontana, G., Furugen, A., Shiota, T., Friede, G., … Makkar, R. R. (2012). Cross-Sectional Computed Tomographic Assessment Improves Accuracy of Aortic Annular Sizing for Transcatheter Aortic Valve Replacement and Reduces the Incidence of Paravalvular Aortic Regurgitation. *Journal of the American College of Cardiology*, *59*(14), 1275–1286. https://doi.org/10.1016/j.jacc.2011.11.045

Jilaihawi, H., Zhao, Z., Du, R., Staniloae, C., Saric, M., Neuburger, P. J., … Williams, M. (2019). Minimizing Permanent Pacemaker Following Repositionable Self-Expanding

Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *12*(18), 1796–1807. https://doi.org/https://doi.org/10.1016/j.jcin.2019.05.056

Johnston, D. R., Soltesz, E. G., Vakil, N., Rajeswaran, J., Roselli, E. E., Sabik, J. F., … Blackstone, E. H. (2015). Long-Term Durability of Bioprosthetic Aortic Valves: Implications From 12,569 Implants. *The Annals of Thoracic Surgery*, *99*(4), 1239–1247. https://doi.org/10.1016/j.athoracsur.2014.10.070

Kadem, L. (2005). Impact of systemic hypertension on the assessment of aortic stenosis. *Heart*, *91*(3), 354–361. https://doi.org/10.1136/hrt.2003.030601

Kalra, R., Patel, N., Doshi, R., Arora, G., & Arora, P. (2019). Evaluation of the Incidence of New-Onset Atrial Fibrillation After Aortic Valve Replacement. *JAMA Internal Medicine*, *179*(8), 1122–1130. https://doi.org/10.1001/jamainternmed.2019.0205

Kaltoft, M., Langsted, A., & Nordestgaard, B. G. (2020a). Obesity as a Causal Risk Factor for Aortic Valve Stenosis. *Journal of the American College of Cardiology*, *75*(2), 163–176. https://doi.org/10.1016/j.jacc.2019.10.050

Kaltoft, M., Langsted, A., & Nordestgaard, B. G. (2020b). Triglycerides and remnant cholesterol associated with risk of aortic valve stenosis: Mendelian randomization in the Copenhagen General Population Study. *European Heart Journal*, *41*(24), 2288–2299. https://doi.org/10.1093/eurheartj/ehaa172

Kampaktsis, P. N., Kokkinidis, D. G., Wong, S.-C., Vavuranakis, M., Skubas, N. J., & Devereux, R. B. (2017). The role and clinical implications of diastolic dysfunction in aortic stenosis. *Heart*, *103*(19), 1481–1487. https://doi.org/10.1136/heartjnl-2017-311506

Kapadia, S., Leon, M. B., Makkar, R. R., Tuzcu, E. M., Svensson, L. G., Kodali, S., … Davidson, M. J. (2015a). 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *The Lancet*, *385*(9986), 2485–2491. https://doi.org/10.1016/S0140-6736(15)60290-2

Kapadia, S., Stewart, W. J., Anderson, W. N., Babaliaros, V., Feldman, T., Cohen, D. J., … Tuzcu, E. M. (2015b). Outcomes of Inoperable Symptomatic Aortic Stenosis Patients Not Undergoing Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *8*(2), 324–333. https://doi.org/10.1016/j.jcin.2014.08.015

Kappetein, A. P., Head, S. J., Généreux, P., Piazza, N., van Mieghem, N. M., Blackstone, E. H., … Leon, M. B. (2012). Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *European Heart Journal*, *33*(19), 2403–2418. https://doi.org/10.1093/eurheartj/ehs255

Katz, R., Budoff, M. J., Takasu, J., Shavelle, D. M., Bertoni, A., Blumenthal, R. S., … O'Brien, K. D. (2009). Relationship of Metabolic Syndrome With Incident Aortic Valve Calcium and Aortic Valve Calcium Progression: The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes*, *58*(4), 813–819. https://doi.org/10.2337/db08-1515

Khan, A. A., Murtaza, G., Khalid, M. F., & Khattak, F. (2019). Risk Stratification for Transcatheter Aortic Valve Replacement. *Cardiology Research*, *10*(6), 323–330. https://doi.org/10.14740/cr966

Khawaja, M. Z., Asrress, K. N., Haran, H., Arri, S., Nadra, I., Bolter, K., … Redwood, S. (2015). The effect of coronary artery disease defined by quantitative coronary angiography and SYNTAX score upon outcome after transcatheter aortic valve implantation (TAVI) using the Edwards bioprosthesis. *EuroIntervention*, *11*(4), 450–455. https://doi.org/10.4244/EIJY14M05_09

Kiani, S., Stebbins, A., Thourani, V. H., Forcillo, J., Vemulapalli, S., Kosinski, A. S., … Devireddy, C. (2020). The Effect and Relationship of Frailty Indices on Survival After Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *13*(2), 219–231. https://doi.org/10.1016/j.jcin.2019.08.015

Kim, W.-K., Hengstenberg, C., Hilker, M., Kerber, S., Schafer, U., Rudolph, T., … Mollmann, H. (2018). The SAVI-TF Registry: 1-Year Outcomes of the European Post-Market Registry Using the ACURATE neo Transcatheter Heart Valve Under Real-World Conditions in 1,000 Patients. *JACC. Cardiovascular Interventions*, *11*(14), 1368–1374. https://doi.org/10.1016/j.jcin.2018.03.023

Kirmani, B. H., Jones, S. G., Malaisrie, S. C., Chung, D. A., & Williams, R. J. (2017). Limited versus full sternotomy for aortic valve replacement (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. *Cochrane Database of Systematic Reviews*, *4*(4), CD011793. https://doi.org/10.1002/14651858.CD011793.pub2.www.cochranelibrary.com

Knuuti, J., Wijns, W., Saraste, A., Capodanno, D., Barbato, E., Funck-Brentano, C., … Group, E. S. C. S. D. (2019). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *European Heart Journal*, *41*(3), 407–477. https://doi.org/10.1093/eurheartj/ehz425

Kodali, S. K., Williams, M. R., Smith, C. R., Svensson, L. G., Webb, J. G., Makkar, R. R., … Leon, M. B. (2012). Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement. *New England Journal of Medicine*, *366*(18), 1686–1695. https://doi.org/10.1056/NEJMoa1200384

Kodali, S., Pibarot, P., Douglas, P. S., Williams, M., Xu, K., Thourani, V., … Hahn, R. T. (2015). Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. *European Heart Journal*, *36*(7), 449–456. https://doi.org/10.1093/eurheartj/ehu384

Kolkailah, A. A., Doukky, R., Pelletier, M. P., Volgman, A. S., Kaneko, T., & Nabhan, A. F. (2020). Cochrane corner: transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis in people with low surgical risk. *Heart*, *106*(14), 1043–1045. https://doi.org/10.1136/heartjnl-2020-316661

Kolte, D., Vlahakes, G. J., Palacios, I. F., Sakhuja, R., Passeri, J. J., Inglessis, I., & Elmariah, S. (2019). Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients. *Journal of the American College of Cardiology*, *74*(12), 1532–1540. https://doi.org/10.1016/j.jacc.2019.06.076

Kötting, J., Schiller, W., Beckmann, A., Schäfer, E., Döbler, K., Hamm, C., … Welz, A. (2013). German aortic valve score: A new scoring system for prediction of mortality related to aortic valve procedures in adults. *European Journal of Cardio-Thoracic Surgery*, *43*(5), 971–977. https://doi.org/10.1093/ejcts/ezt114

Kytö, V., Myllykangas, M. E., Sipilä, J., Niiranen, T. J., Rautava, P., & Gunn, J. (2019). Long-term Outcomes of Mechanical Vs Biologic Aortic Valve Prosthesis in Patients Older Than 70 Years. *The Annals of Thoracic Surgery*, *108*(5), 1354–1360. https://doi.org/10.1016/j.athoracsur.2019.04.012

Kytö, V., Sipilä, J., Ahtela, E., Rautava, P., & Gunn, J. (2020). Mechanical Versus Biologic Prostheses for Surgical Aortic Valve Replacement in Patients Aged 50 to 70. *The Annals of Thoracic Surgery*, *110*(1), 102–110. https://doi.org/10.1016/j.athoracsur.2019.10.027

Laakso, T., Laine, M., Moriyama, N., Dahlbacka, S., Airaksinen, J., Virtanen, M., … Raivio, P. (2020a). Impact of paravalvular regurgitation on the mid-term outcome after transcatheter and surgical aortic valve replacement. *European Journal of Cardio-Thoracic Surgery*. https://doi.org/10.1093/ejcts/ezaa254

Laakso, T., Moriyama, N., Raivio, P., Dahlbacka, S., Kinnunen, E.-M., Juvonen, T., … Laine, M. (2020b). Impact of Major Vascular Complication Access Site Status on Mortality After Transfemoral Transcatheter Aortic Valve Replacement — Results From the FinnValve

Registry —. *Circulation Reports*, *2*(3), 182–191. https://doi.org/10.1253/circrep.CR-20-0007

Lancellotti, P., Pibarot, P., Chambers, J., Edvardsen, T., Delgado, V., Dulgheru, R., … Habib, G. (2016). Recommendations for the imaging assessment of prosthetic heart valves: A report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian . *European Heart Journal Cardiovascular Imaging*, *17*(6), 589–590. https://doi.org/10.1093/ehjci/jew025

Larson, E. W., & Edwards, W. D. (1984). Risk factors for aortic dissection: A necropsy study of 161 cases. *The American Journal of Cardiology*, *53*(6), 849–855. https://doi.org/10.1016/0002-9149(84)90418-1

Latib, A., Maisano, F., Bertoldi, L., Giacomini, A., Shannon, J., Cioni, M., … Colombo, A. (2012). Transcatheter vs surgical aortic valve replacement in intermediate-surgical-risk patients with aortic stenosis: A propensity score–matched case-control study. *American Heart Journal*, *164*(6), 910–917. https://doi.org/10.1016/j.ahj.2012.09.005

Latsios, G., Gerckens, U., & Grube, E. (2010). Transaortic transcatheter aortic valve implantation: A novel approach for the truly "no-access option" patients. *Catheterization and Cardiovascular Interventions*, *75*(7), 1129–1136. https://doi.org/10.1002/ccd.22378

Leclercq, F., Robert, P., Akodad, M., Macia, J.-C., Gandet, T., Delseny, D., … Cayla, G. (2020). Prior Balloon Valvuloplasty Versus Direct Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *13*(5), 594–602. https://doi.org/10.1016/j.jcin.2019.12.006

Leon, M. B., Smith, C. R., Mack, M., Miller, D. C., Moses, J. W., Svensson, L. G., … Pocock, S. (2010). Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. *New England Journal of Medicine*, *363*(17), 1597–1607. https://doi.org/10.1056/NEJMoa1008232

Leon, M. B., Smith, C. R., Mack, M. J., Makkar, R. R., Svensson, L. G., Kodali, S. K., … Webb, J. G. (2016). Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *New England Journal of Medicine*, *374*(17), 1609–1620. https://doi.org/10.1056/NEJMoa1514616

Letac, B., Cribier, A., Koning, R., & Bellefleur, J.-P. (1988). Results of percutaneous transluminal valvuloplasty in 218 adults with valvular aortic stenosis. *The American Journal of Cardiology*, *62*(9), 598–605. https://doi.org/10.1016/0002-9149(88)90663-7

Levey, A. S., Coresh, J., Greene, T., Stevens, L. A., Zhang, Y. L., Hendriksen, S., … Van Lente, F. (2006). Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate. *Annals of Internal Medicine*, *145*(4), 247. https://doi.org/10.7326/0003-4819-145-4-200608150-00004

Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., Feldman, H. I., … Coresh, J. (2009). A New Equation to Estimate Glomerular Filtration Rate. *Annals of Internal Medicine*, *150*(9), 604. https://doi.org/10.7326/0003-4819-150-9-200905050-00006

Liao, Y.-B., He, Z.-X., Zhao, Z.-G., Wei, X., Zuo, Z., Li, Y.-J., … Chen, M. (2016). The relationship between chronic obstructive pulmonary disease and transcatheter aortic valve implantation-A systematic review and meta-analysis. *Catheterization and Cardiovascular Interventions*, *87*(S1), 570–578. https://doi.org/10.1002/ccd.26443

Lieberman, E. B., Bashore, T. M., Hermiller, J. B., Wilson, J. S., Pieper, K. S., Keeler, G. P., … Davidson, C. J. (1995). Balloon aortic valvuloplasty in adults: Failure of procedure to improve long-term survival. *Journal of the American College of Cardiology*, *26*(6), 1522–1528. https://doi.org/10.1016/0735-1097(95)00363-0

Lindroos, M., Kupari, M., Heikkilä, J., & Tilvis, R. (1993). Prevalence of aortic valve abnormalities in the elderly: An echocardiographic study of a random population sample. *Journal of the*

American College of Cardiology, *21*(5), 1220–1225. https://doi.org/10.1016/0735-1097(93)90249-Z

Linefsky, J. P., O'Brien, K. D., Katz, R., de Boer, I. H., Barasch, E., Jenny, N. S., … Kestenbaum, B. (2011). Association of Serum Phosphate Levels With Aortic Valve Sclerosis and Annular Calcification. *Journal of the American College of Cardiology*, *58*(3), 291–297. https://doi.org/10.1016/j.jacc.2010.11.073

Little, S. H., Chan, K.-L., & Burwash, I. G. (2007). Impact of blood pressure on the Doppler echocardiographic assessment of severity of aortic stenosis. *Heart*, *93*(7), 848–855. https://doi.org/10.1136/hrt.2006.098392

López Otero, D., Ávila-Carrillo, A., González Ferreiro, R., Cid Menéndez, A., Iglesias Álvarez, D., Álvarez Rodríguez, L., … González-Juanatey, J. R. (2019). Impact of Coronary Revascularization in Patients Who Underwent Transcatheter Aortic Valve Implantation. *The American Journal of Cardiology*, *123*(6), 948–955. https://doi.org/10.1016/j.amjcard.2018.12.007

Ludman, P. F., Moat, N., de Belder, M. A., Blackman, D. J., Duncan, A., Banya, W., … Gray, H. (2015). Transcatheter Aortic Valve Implantation in the United Kingdom. *Circulation*, *131*(13), 1181–1190. https://doi.org/10.1161/CIRCULATIONAHA.114.013947

Maaranen, P., Husso, A., Tauriainen, T., Lahtinen, A., Valtola, A., Ahvenvaara, T., … Biancari, F. (2019). Blood Transfusion and Outcome After Transfemoral Transcatheter Aortic Valve Replacement. *Journal of Cardiothoracic and Vascular Anesthesia*, *33*(11), 2949–2959. https://doi.org/10.1053/j.jvca.2019.06.038

Mack, M. J., Leon, M. B., Smith, C. R., Miller, D. C., Moses, J. W., Tuzcu, E. M., … Akin, J. (2015). 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *The Lancet*, *385*(9986), 2477–2484. https://doi.org/10.1016/S0140-6736(15)60308-7

Mack, M. J., Leon, M. B., Thourani, V. H., Makkar, R., Kodali, S. K., Russo, M., … Smith, C. R. (2019). Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *New England Journal of Medicine*, *380*(18), 1695–1705. https://doi.org/10.1056/NEJMoa1814052

Magne, J., Guinot, B., Le Guyader, A., Begot, E., Marsaud, J.-P., Mohty, D., & Aboyans, V. (2018). Relation Between Renin-Angiotensin System Blockers and Survival Following Isolated Aortic Valve Replacement for Aortic Stenosis. *The American Journal of Cardiology*, *121*(4), 455–460. https://doi.org/10.1016/j.amjcard.2017.11.013

Mäkikallio, T., Jalava, M. P., Husso, A., Virtanen, M., Laakso, T., Ahvenvaara, T., … Biancari, F. (2019). Ten-year experience with transcatheter and surgical aortic valve replacement in Finland. *Annals of Medicine*, *51*(3–4), 270–279. https://doi.org/10.1080/07853890.2019.1614657

Makkar, R. R., Fontana, G. P., Jilaihawi, H., Kapadia, S., Pichard, A. D., Douglas, P. S., … Leon, M. B. (2012). Transcatheter Aortic-Valve Replacement for Inoperable Severe Aortic Stenosis. *New England Journal of Medicine*, *366*(18), 1696–1704. https://doi.org/10.1056/NEJMoa1202277

Makkar, R. R., Thourani, V. H., Mack, M. J., Kodali, S. K., Kapadia, S., Webb, J. G., … Leon, M. B. (2020). Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. *New England Journal of Medicine*, *382*(9), 799–809. https://doi.org/10.1056/NEJMoa1910555

Martin, G. P., Sperrin, M., Hulme, W., Ludman, P. F., de Belder, M. A., Toff, W. D., … Mamas, M. A. (2017a). Relative survival after transcatheter aortic valve implantation: How do patients undergoing transcatheter aortic valve implantation fare relative to the general

population? *Journal of the American Heart Association*, *6*(10), 1–13. https://doi.org/10.1161/JAHA.117.007229

Martin, G. P., Sperrin, M., Ludman, P. F., de Belder, M. A., Gale, C. P., Toff, W. D., … Mamas, M. A. (2017b). Inadequacy of existing clinical prediction models for predicting mortality after transcatheter aortic valve implantation. *American Heart Journal*, *184*, 97–105. https://doi.org/10.1016/j.ahj.2016.10.020

Martinsson, A., Li, X., Andersson, C., Nilsson, J., Smith, J. G., & Sundquist, K. (2015). Temporal Trends in the Incidence and Prognosis of Aortic Stenosis. *Circulation*, *131*(11), 988–994. https://doi.org/10.1161/CIRCULATIONAHA.114.012906

Matsumura, T., Ohtaki, E., Misu, K., Tohbaru, T., Asano, R., Nagayama, M., … Hosoda, S. (2002). Etiology of aortic valve disease and recent changes in Japan:a study of 600 valve replacement cases. *International Journal of Cardiology*, *86*(2–3), 217–223. https://doi.org/10.1016/S0167-5273(02)00199-7

Meredith, I., Hood, K., Haratani, N., Allocco, D., & Dawkins, K. (2012). Boston Scientific Lotus valve. *EuroIntervention*, *8*(Q), Q70–Q74. https://doi.org/10.4244/EIJV8SQA12

Merryman, W. D., & Schoen, F. J. (2013). Mechanisms of Calcification in Aortic Valve Disease: Role of Mechanokinetics and Mechanodynamics. *Current Cardiology Reports*, *15*(5), 355. https://doi.org/10.1007/s11886-013-0355-5

Messika-Zeitoun, D., Aubry, M.-C., Detaint, D., Bielak, L. F., Peyser, P. A., Sheedy, P. F., … Enriquez-Sarano, M. (2004). Evaluation and Clinical Implications of Aortic Valve Calcification Measured by Electron-Beam Computed Tomography. *Circulation*, *110*(3), 356–362. https://doi.org/10.1161/01.CIR.0000135469.82545.D0

Michail, M., Thakur, U., Comella, A., Lim, R. Y., Gupta, V., Tan, S., … Brown, A. J. (2020). Angiographic functional scoring of coronary artery disease predicts mortality in patients with severe aortic stenosis undergoing TAVR. *Cardiovascular Revascularization Medicine*. https://doi.org/10.1016/j.carrev.2020.04.024

Milano, A. D., Faggian, G., Dodonov, M., Golia, G., Tomezzoli, A., Bortolotti, U., & Mazzucco, A. (2012). Prognostic value of myocardial fibrosis in patients with severe aortic valve stenosis. *The Journal of Thoracic and Cardiovascular Surgery*, *144*(4), 830–837. https://doi.org/10.1016/j.jtcvs.2011.11.024

Minners, J., Allgeier, M., Gohlke-Baerwolf, C., Kienzle, R.-P., Neumann, F.-J., & Jander, N. (2008). Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *European Heart Journal*, *29*(8), 1043–1048. https://doi.org/10.1093/eurheartj/ehm543

Minners, J., Allgeier, M., Gohlke-Baerwolf, C., Kienzle, R.-P., Neumann, F.-J., & Jander, N. (2010). Inconsistent grading of aortic valve stenosis by current guidelines: haemodynamic studies in patients with apparently normal left ventricular function. *Heart*, *96*(18), 1463–1468. https://doi.org/10.1136/hrt.2009.181982

Minners, J., Rossebo, A., Chambers, J. B., Gohlke-Baerwolf, C., Neumann, F.-J., Wachtell, K., & Jander, N. (2020). Sudden cardiac death in asymptomatic patients with aortic stenosis. *Heart*, *106*(21), 1646–1650. https://doi.org/10.1136/heartjnl-2019-316493

Modine, T., Lemesle, G., Azzaoui, R., & Sudre, A. (2010). Aortic valve implantation with the CoreValve ReValving System via left carotid artery access: first case report. *The Journal of Thoracic and Cardiovascular Surgery*, *140*(4), 928–929. https://doi.org/10.1016/j.jtcvs.2010.03.001

Mok, M., Nombela-Franco, L., Dumont, E., Urena, M., Delarochellière, R., Doyle, D., … Rodés-Cabau, J. (2013). Chronic obstructive pulmonary disease in patients undergoing transcatheter aortic valve implantation: Insights on clinical outcomes, prognostic markers, and functional status changes. *JACC: Cardiovascular Interventions*, *6*(10), 1072–1084. https://doi.org/10.1016/j.jcin.2013.06.008

Moriyama N., Laakso T., Raivio P., Dahlbacka S., Kinnunen EM., Juvonen T., Valtola A., Husso A., Jalava MP., Ahvenvaara T., … Laine M. (2020). Acute Kidney Injury Following Aortic Valve Replacement in Patients Without Chronic Kidney Disease. *Can J Cardiol*. S0828-282X(20)30270-1. doi: 10.1016/j.cjca.2020.03.015

Musa, T. A., Treibel, T. A., Vassiliou, V. S., Captur, G., Singh, A., Chin, C., … Greenwood, J. P. (2018). Myocardial Scar and Mortality in Severe Aortic Stenosis. *Circulation*, *138*(18), 1935–1947. https://doi.org/10.1161/CIRCULATIONAHA.117.032839

Nashef, S A M, Roques, F., Michel, P., Gauducheau, E., Lemeshow, S., Salamon, R., & group, the E. study. (1999). European system for cardiac operative risk evaluation (EuroSCORE). *European Journal of Cardio-Thoracic Surgery*, *16*(1), 9–13. https://doi.org/10.1016/S1010-7940(99)00134-7

Nashef, Samer A M, Roques, F., Sharples, L. D., Nilsson, J., Smith, C., Goldstone, A. R., & Lockowandt, U. (2012). EuroSCORE II. *European Journal of Cardio-Thoracic Surgery*, *41*(4), 734–745. https://doi.org/10.1093/ejcts/ezs043

Nielsen, H., Klaaborg, K.-E., Nissen, H., Terp, K., Mortensen, P., Kjeldsen, B., … Hjortdal, V. (2012). A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. *EuroIntervention*, *8*(3), 383–389. https://doi.org/10.4244/EIJV8I3A58

Nishimura, R. A., & Carabello, B. A. (2012). Hemodynamics in the Cardiac Catheterization Laboratory of the 21st Century. *Circulation*, *125*(17), 2138–2150. https://doi.org/10.1161/CIRCULATIONAHA.111.060319

Nishimura, R. A., Otto, C. M., Bonow, R. O., Carabello, B. A., Erwin, J. P., Guyton, R. A., … Thomas, J. D. (2014). 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. *Circulation*, *129*(23), 521–643. https://doi.org/10.1161/CIR.0000000000000031

Nistri, S., Faggiano, P., Olivotto, I., Papesso, B., Bordonali, T., Vescovo, G., … Bonow, R. O. (2012). Hemodynamic Progression and Outcome of Asymptomatic Aortic Stenosis in Primary Care. *The American Journal of Cardiology*, *109*(5), 718–723. https://doi.org/10.1016/j.amjcard.2011.10.035

Nkomo, V. T., Gardin, J. M., Skelton, T. N., Gottdiener, J. S., Scott, C. G., & Enriquez-Sarano, M. (2006). Burden of valvular heart diseases: a population-based study. *The Lancet*, *368*(9540), 1005–1011. https://doi.org/10.1016/S0140-6736(06)69208-8

Nuis, R.-J., Rodés-Cabau, J., Sinning, J.-M., van Garsse, L., Kefer, J., Bosmans, J., … de Jaegere, P. P. (2012). Blood Transfusion and the Risk of Acute Kidney Injury After Transcatheter Aortic Valve Implantation. *Circulation: Cardiovascular Interventions*, *5*(5), 680–688. https://doi.org/10.1161/CIRCINTERVENTIONS.112.971291

O'Brien, S. M., Shahian, D. M., Filardo, G., Ferraris, V. A., Haan, C. K., Rich, J. B., … Anderson, R. P. (2009). The Society of Thoracic Surgeons 2008 Cardiac Surgery Risk Models: Part 2—Isolated Valve Surgery. *The Annals of Thoracic Surgery*, *88*(1, Supplement), S23–S42. https://doi.org/https://doi.org/10.1016/j.athoracsur.2009.05.056

O'Brien, S. M., Feng, L., He, X., Xian, Y., Jacobs, J. P., Badhwar, V., … Shahian, D. M. (2018). The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 2—Statistical Methods and Results. *Annals of Thoracic Surgery*, *105*(5), 1419–1428. https://doi.org/10.1016/j.athoracsur.2018.03.003

Ochiai, T., Saito, S., Yamanaka, F., Shishido, K., Tanaka, Y., Yamabe, T., … Hayashida, K. (2018). Renin–angiotensin system blockade therapy after transcatheter aortic valve implantation. *Heart*, *104*(8), 644–651. https://doi.org/10.1136/heartjnl-2017-311738

Oguri, A., Yamamoto, M., Mouillet, G., Gilard, M., Laskar, M., Eltchaninoff, H., … Teiger, E. (2015). Impact of chronic kidney disease on the outcomes of transcatheter aortic valve

implantation: Results from the FRANCE 2 registry. *EuroIntervention*, *10*(9), e1–e9. https://doi.org/10.4244/EIJV10I9A183

Omran, H., Schmidt, H., Hackenbroch, M., Illien, S., Bernhardt, P., von der Recke, G., … Sommer, T. (2003). Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. *The Lancet*, *361*(9365), 1241–1246. https://doi.org/10.1016/S0140-6736(03)12978-9

Otto, C. M., Kuusisto, J., Reichenbach, D. D., Gown, A. M., & O'Brien, K. D. (1994a). Characterization of the early lesion of "degenerative" valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation*, *90*(2), 844–853. https://doi.org/10.1161/01.cir.90.2.844

Otto, C. M., Mickel, M. C., Kennedy, J. W., Alderman, E. L., Bashore, T. M., Block, P. C., … Holmes, D. R. (1994b). Three-year outcome after balloon aortic valvuloplasty. Insights into prognosis of valvular aortic stenosis. *Circulation*, *89*(2), 642–650. https://doi.org/10.1161/01.CIR.89.2.642

Owens, D. S., Katz, R., Takasu, J., Kronmal, R., Budoff, M. J., & O'Brien, K. D. (2010). Incidence and Progression of Aortic Valve Calcium in the Multi-Ethnic Study of Atherosclerosis (MESA). *American Journal of Cardiology*, *105*(5), 701–708. https://doi.org/10.1016/j.amjcard.2009.10.071

Oxenham, H. (2003). Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *Heart*, *89*(7), 715–721. https://doi.org/10.1136/heart.89.7.715

Pagnesi, M., Kim, W.-K., Conradi, L., Barbanti, M., Stefanini, G. G., Schofer, J., … Latib, A. (2020). Impact of Predilatation Prior to Transcatheter Aortic Valve Implantation With the Self-Expanding Acurate neo Device (from the Multicenter NEOPRO Registry). *The American Journal of Cardiology*, *125*(9), 1369–1377. https://doi.org/10.1016/j.amjcard.2020.02.003

Paradis, J.-M., White, J. M., Généreux, P., Urena, M., Doshi, D., Nazif, T., … Kodali, S. (2017). Impact of Coronary Artery Disease Severity Assessed With the SYNTAX Score on Outcomes Following Transcatheter Aortic Valve Replacement. *Journal of the American Heart Association*, *6*(2). https://doi.org/10.1161/JAHA.116.005070

Pasic, M., Unbehaun, A., Buz, S., Drews, T., & Hetzer, R. (2015). Annular Rupture During Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *8*(1), 1–9. https://doi.org/10.1016/j.jcin.2014.07.020

Passik, C. S., Ackermann, D. M., Pluth, J. R., & Edwards, W. D. (1987). Temporal changes in the causes of aortic stenosis: a surgical pathologic study of 646 cases. *Mayo Clinic Proceedings*, *62*(2), 119–123. https://doi.org/10.1016/s0025-6196(12)61880-1

Pauperio, H. M., Azevedo, A. C., & Ferreira, C. S. (1999). The aortic valve with two leaflets — a study in 2,000 autopsies. *Cardiology in the Young*, *9*(5), 488–498. https://doi.org/10.1017/S1047951100005400

Pawade, T. A., Newby, D. E., & Dweck, M. R. (2015). Calcification in Aortic Stenosis. *Journal of the American College of Cardiology*, *66*(5), 561–577. https://doi.org/10.1016/j.jacc.2015.05.066

Pawade, T., Clavel, M. A., Tribouilloy, C., Dreyfus, J., Mathieu, T., Tastet, L., … Dweck, M. R. (2018). Computed Tomography Aortic Valve Calcium Scoring in Patients with Aortic Stenosis. *Circulation: Cardiovascular Imaging*, *11*(3), 1–11. https://doi.org/10.1161/CIRCIMAGING.117.007146

Pibarot, P., Hahn, R. T., Weissman, N. J., Arsenault, M., Beaudoin, J., Bernier, M., … Kodali, S. (2017). Association of paravalvular regurgitation with 1-year outcomes after transcatheter aortic valve replacement with the SAPIEN 3 valve. *JAMA Cardiology*, *2*(11), 1208–1216. https://doi.org/10.1001/jamacardio.2017.3425

Pibarot, P., Salaun, E., Dahou, A., Avenatti, E., Guzzetti, E., Annabi, M.-S., … Hahn, R. T. (2020a). Echocardiographic Results of Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients. *Circulation*, *141*(19), 1527–1537. https://doi.org/10.1161/CIRCULATIONAHA.119.044574

Pibarot, P., Ternacle, J., Jaber, W. A., Salaun, E., Dahou, A., Asch, F. M., … Hahn, R. T. (2020b). Structural Deterioration of Transcatheter Versus Surgical Aortic Valve Bioprostheses in the PARTNER-2 Trial. *Journal of the American College of Cardiology*, *76*(16), 1830–1843. https://doi.org/https://doi.org/10.1016/j.jacc.2020.08.049

Popma, J. J., Deeb, G. M., Yakubov, S. J., Mumtaz, M., Gada, H., O'Hair, D., … Reardon, M. J. (2019). Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *New England Journal of Medicine*, *380*(18), 1706–1715. https://doi.org/10.1056/NEJMoa1816885

Puls, M., Sobisiak, B., Bleckmann, A., Jacobshagen, C., Danner, B. C., Hünlich, M., … Schillinger, W. (2014). Impact of frailty on short- and long-term morbidity and mortality after transcatheter aortic valve implantation: risk assessment by Katz Index of activities of daily living. *EuroIntervention*, *10*(5), 609–619. https://doi.org/10.4244/EIJY14M08_03

Puri, R., Iung, B., Cohen, D. J., & Rodés-Cabau, J. (2016). TAVI or No TAVI: Identifying patients unlikely to benefit from transcatheter aortic valve implantation. *European Heart Journal*, *37*(28), 2217–2225. https://doi.org/10.1093/eurheartj/ehv756

Rader, F., Sachdev, E., Arsanjani, R., & Siegel, R. J. (2015). Left Ventricular Hypertrophy in Valvular Aortic Stenosis: Mechanisms and Clinical Implications. *The American Journal of Medicine*, *128*(4), 344–352. https://doi.org/10.1016/j.amjmed.2014.10.054

Reardon, M. J., Adams, D. H., Kleiman, N. S., Yakubov, S. J., Coselli, J. S., Deeb, G. M., … Popma, J. J. (2015). 2-Year Outcomes in Patients Undergoing Surgical or Self-Expanding Transcatheter Aortic Valve Replacement. *Journal of the American College of Cardiology*, *66*(2), 113–121. https://doi.org/10.1016/j.jacc.2015.05.017

Reardon, M. J., Van Mieghem, N. M., Popma, J. J., Kleiman, N. S., Søndergaard, L., Mumtaz, M., … Kappetein, A. P. (2017). Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *New England Journal of Medicine*, *376*(14), 1321–1331. https://doi.org/10.1056/NEJMoa1700456

Ringle, A., Castel, A.-L., Le Goffic, C., Delelis, F., Binda, C., Bohbot, Y., … Maréchaux, S. (2018). Prospective assessment of the frequency of low gradient severe aortic stenosis with preserved left ventricular ejection fraction: Critical impact of aortic flow misalignment and pressure recovery phenomenon. *Archives of Cardiovascular Diseases*, *111*(8–9), 518–527. https://doi.org/10.1016/j.acvd.2017.11.004

Roberts, W. C., & Ko, J. M. (2005). Frequency by Decades of Unicuspid, Bicuspid, and Tricuspid Aortic Valves in Adults Having Isolated Aortic Valve Replacement for Aortic Stenosis, With or Without Associated Aortic Regurgitation. *Circulation*, *111*(7), 920–925. https://doi.org/10.1161/01.CIR.0000155623.48408.C5

Robicsek, F., Thubrikar, M. J., Cook, J. W., & Fowler, B. (2004). The congenitally bicuspid aortic valve: how does it function? Why does it fail? *The Annals of Thoracic Surgery*, *77*(1), 177–185. https://doi.org/10.1016/S0003-4975(03)01249-9

Rocha, R. V, Friedrich, J. O., Hong, K., Lee, J., Cheema, A., Bagai, A., … Yanagawa, B. (2019). Aortic valve replacement with pulmonary hypertension: Meta-analysis of 70 676 patients. *Journal of Cardiac Surgery*, *34*(12), 1617–1625. https://doi.org/10.1111/jocs.14309

Rockwood, K., Stadnyk, K., MacKnight, C., McDowell, I., Hebert, R., & Hogan, D. B. (1999). A brief clinical instrument to classify frailty in elderly people. *Lancet*, *353*(9148), 205–206. https://doi.org/10.1016/S0140-6736(98)04402-X

Rodriguez-Gabella, T., Catalá, P., Muñoz-García, A. J., Nombela-Franco, L., Del Valle, R., Gutiérrez, E., … Amat-Santos, I. J. (2019). Renin-Angiotensin System Inhibition

Following Transcatheter Aortic Valve Replacement. *Journal of the American College of Cardiology*, *74*(5), 631–641. https://doi.org/10.1016/j.jacc.2019.05.055

Rong, L. Q., Hameed, I., Di Franco, A., Rahouma, M., Khan, F. M., Demetres, M., … Gaudino, M. (2020). Aortic Valve Area in Aortic Stenosis. *JACC: Cardiovascular Imaging*, *13*(2), 634–635. https://doi.org/10.1016/j.jcmg.2019.08.015

Roques, F., Nashef, S. A. M., Michel, P., Gauducheau, E., de Vincentiis, C., Baudet, E., … Thulin, L. (1999). Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *European Journal of Cardio-Thoracic Surgery*, *15*(6), 816–823. https://doi.org/10.1016/S1010-7940(99)00106-2

Roques, F., Michel, P., Goldstone, A. R., & Nashef, S. A. M. (2003). The logistic EuroSCORE. *European Heart Journal*, *24*(9), 882–883. https://doi.org/10.1016/S0195-668X(02)00799-6

Rosato, S., Santini, F., Barbanti, M., Biancari, F., D'Errigo, P., Onorati, F., … Seccareccia, F. (2016). Transcatheter aortic valve implantation compared with surgical aortic valve replacement in low-risk patients. *Circulation: Cardiovascular Interventions*, *9*(5), 1–8. https://doi.org/10.1161/CIRCINTERVENTIONS.115.003326

Rosenhek, R., Binder, T., Porenta, G., Lang, I., Christ, G., Schemper, M., … Baumgartner, H. (2000). Predictors of Outcome in Severe, Asymptomatic Aortic Stenosis. *New England Journal of Medicine*, *343*(9), 611–617. https://doi.org/10.1056/NEJM200008313430903

Rosenhek, R., Zilberszac, R., Schemper, M., Czerny, M., Mundigler, G., Graf, S., … Maurer, G. (2010). Natural History of Very Severe Aortic Stenosis. *Circulation*, *121*(1), 151–156. https://doi.org/10.1161/CIRCULATIONAHA.109.894170

Ross, J., & Braunwald, E. (1968). Aortic Stenosis. *Circulation*, *38*(1s5), V-61-V–67. https://doi.org/10.1161/01.CIR.38.1S5.V-61

Rossebø, A. B., Pedersen, T. R., Boman, K., Brudi, P., Chambers, J. B., Egstrup, K., … Willenheimer, R. (2008). Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. *New England Journal of Medicine*, *359*(13), 1343–1356. https://doi.org/10.1056/NEJMoa0804602

Saia, F., Gandolfo, C., Palmerini, T., Berti, S., Doshi, S., Laine, M., Marcelli, C., Piva, T., Ribichini, F., De Benedictis, M., Cardaioli, F., Cannata, S., Tarantini G. (2020a). In-hospital and thirty-day outcomes of the SAPIEN 3 Ultra balloon-expandable transcatheter aortic valve: the S3U registry. *Eurointervention*, 15(14):1240-1247. doi: 10.4244/EIJ-D-19-00541

Saia, F., Palmerini, T., Compagnone, M., Battistini, P., Moretti, C., Taglieri, N., … Rapezzi, C. (2020b). Coronary artery disease and reasonably incomplete coronary revascularization in high-risk patients undergoing transcatheter aortic valve implantation. *Catheterization and Cardiovascular Interventions*, *95*(1), 19–27. https://doi.org/10.1002/ccd.28211

Saitoh, T., Shiota, M., Izumo, M., Gurudevan, S. V., Tolstrup, K., Siegel, R. J., & Shiota, T. (2012). Comparison of Left Ventricular Outflow Geometry and Aortic Valve Area in Patients With Aortic Stenosis by 2-Dimensional Versus 3-Dimensional Echocardiography. *The American Journal of Cardiology*, *109*(11), 1626–1631. https://doi.org/10.1016/j.amjcard.2012.01.391

Sathananthan, J., Fraser, R., Hatoum, H., Barlow, A. M., Stanová, V., Allen, K. B., … Webb, J. G. (2020). A bench test study of bioprosthetic valve fracture performed before versus after transcatheter valve-in-valve intervention. *EuroIntervention*, *15*(16), 1409–1416. https://doi.org/10.4244/EIJ-D-19-00939

Schaefer, A., Schofer, N., Goßling, A., Seiffert, M., Schirmer, J., Deuschl, F., … Westermann, D. (2019). Transcatheter aortic valve implantation versus surgical aortic valve replacement in low-risk patients: a propensity score-matched analysis. *European Journal of Cardio-Thoracic Surgery*, *56*(6), 1131–1139. https://doi.org/10.1093/ejcts/ezz245

Schelbert, E. B., Vaughan-Sarrazin, M. S., Welke, K. F., & Rosenthal, G. E. (2008). Valve type and long-term outcomes after aortic valve replacement in older patients. *Heart*, *94*(9), 1181–1188. https://doi.org/10.1136/hrt.2007.127506

Schiller, W., Barnewold, L., Kazmaier, T., Beckmann, A., Masseli, F., Welz, A., … Heller, G. (2017). The German Aortic Valve Score II. *European Journal of Cardio-Thoracic Surgery*, *52*(5), 881–887. https://doi.org/10.1093/ejcts/ezx282

Schoenenberger, A. W., Stortecky, S., Neumann, S., Moser, A., Jüni, P., Carrel, T., … Wenaweser, P. (2013). Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *European Heart Journal*, *34*(9), 684–692. https://doi.org/10.1093/eurheartj/ehs304

Schymik, G., Varsami, C., Bramlage, P., Conzelmann, L. O., Würth, A., Luik, A., … Tzamalis, P. (2018). Two-Year Outcomes of Transcatheter Compared With Surgical Aortic Valve Replacement in "Minimal-Risk" Patients Lacking EuroSCORE Co-morbidities (from the TAVIK Registry). *American Journal of Cardiology*, *122*(1), 149–155. https://doi.org/10.1016/j.amjcard.2018.02.053

Schymik, G., Wendler, O., Hengstenberg, C., Ohlmann, P., Gilard, M., Digne, F., … Tarantini, G. (2019). Outcomes of transfemoral balloon expandable transcatheter aortic valve implantation: Comparison of two subsequent valve generations. *Catheterization and Cardiovascular Interventions*, ccd.28621. https://doi.org/10.1002/ccd.28621

Serruys, P. W., Modolo, R., Reardon, M., Miyazaki, Y., Windecker, S., Popma, J., … van Mieghem, N. (2018). One-year outcomes of patients with severe aortic stenosis and an STS PROM of less than three percent in the SURTAVI trial. *EuroIntervention*, *14*(8), 877–883. https://doi.org/10.4244/EIJ-D-18-00460

Shahian, D. M., O'Brien, S. M., Filardo, G., Ferraris, V. A., Haan, C. K., Rich, J. B., … Anderson, R. P. (2009a). The Society of Thoracic Surgeons 2008 Cardiac Surgery Risk Models: Part 1—Coronary Artery Bypass Grafting Surgery. *The Annals of Thoracic Surgery*, *88*(1, Supplement), S2–S22. https://doi.org/https://doi.org/10.1016/j.athoracsur.2009.05.053

Shahian, D. M., O'Brien, S. M., Filardo, G., Ferraris, V. A., Haan, C. K., Rich, J. B., … Anderson, R. P. (2009b). The Society of Thoracic Surgeons 2008 Cardiac Surgery Risk Models: Part 3—Valve Plus Coronary Artery Bypass Grafting Surgery. *The Annals of Thoracic Surgery*, *88*(1, Supplement), S43–S62. https://doi.org/https://doi.org/10.1016/j.athoracsur.2009.05.055

Shahian, D. M., Jacobs, J. P., Badhwar, V., Kurlansky, P. A., Furnary, A. P., Cleveland, J. C., … O'Brien, S. M. (2018). The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1—Background, Design Considerations, and Model Development. *Annals of Thoracic Surgery*, *105*(5), 1411–1418. https://doi.org/10.1016/j.athoracsur.2018.03.002

Sharma, S. K., Rao, R. S., Chandra, P., Goel, P. K., Bharadwaj, P., Joseph, G., … Seth, A. (2020). First-in-human evaluation of a novel balloon-expandable transcatheter heart valve in patients with severe symptomatic native aortic stenosis: the MyVal-1 study. *EuroIntervention*, *16*(5), 421–429. https://doi.org/10.4244/EIJ-D-19-00413

Smith, C. R., Leon, M. B., Mack, M. J., Miller, D. C., Moses, J. W., Svensson, L. G., … Pocock, S. J. (2011). Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. *New England Journal of Medicine*, *364*(23), 2187–2198. https://doi.org/10.1056/NEJMoa1103510

Sohn, S. H., Jang, M. jin, Hwang, H. Y., & Kim, K. H. (2018). Rapid deployment or sutureless versus conventional bioprosthetic aortic valve replacement: A meta-analysis. *Journal of Thoracic and Cardiovascular Surgery*, *155*(6), 2402-2412.e5. https://doi.org/10.1016/j.jtcvs.2018.01.084

Søndergaard, L., Steinbrüchel, D. A., Ihlemann, N., Nissen, H., Kjeldsen, B. J., Petursson, P., … Thyregod, H. G. H. (2016). Two-Year Outcomes in Patients With Severe Aortic Valve Stenosis Randomized to Transcatheter Versus Surgical Aortic Valve Replacement. *Circulation: Cardiovascular Interventions*, *9*(6), e003665. https://doi.org/10.1161/CIRCINTERVENTIONS.115.003665

Søndergaard, L., Rodés-Cabau, J., Hans-Peter Linke, A., Fichtlscherer, S., Schäfer, U., Kuck, K.-H., … Maisano, F. (2018). Transcatheter Aortic Valve Replacement With a Repositionable Self-Expanding Prosthesis. *Journal of the American College of Cardiology*, *72*(23), 2859–2867. https://doi.org/10.1016/j.jacc.2018.09.014

Søndergaard, L., Ihlemann, N., Capodanno, D., Jørgensen, T. H., Nissen, H., Kjeldsen, B. J., … Thyregod, H. G. H. (2019a). Durability of Transcatheter and Surgical Bioprosthetic Aortic Valves in Patients at Lower Surgical Risk. *Journal of the American College of Cardiology*, *73*(5), 546–553. https://doi.org/10.1016/j.jacc.2018.10.083

Søndergaard, L., Popma, J. J., Reardon, M. J., Van Mieghem, N. M., Deeb, G. M., Kodali, S., … Mangi, A. (2019b). Comparison of a Complete Percutaneous Versus Surgical Approach to Aortic Valve Replacement and Revascularization in Patients at Intermediate Surgical Risk. *Circulation*, *140*(16), 1296–1305. https://doi.org/10.1161/CIRCULATIONAHA.118.039564

Sponga, S., Perron, J., Dagenais, F., Mohammadi, S., Baillot, R., Doyle, D., … Voisine, P. (2012). Impact of residual regurgitation after aortic valve replacement. *European Journal of Cardio-Thoracic Surgery*, *42*(3), 486–492. https://doi.org/10.1093/ejcts/ezs083

Stassano, P., Di Tommaso, L., Monaco, M., Iorio, F., Pepino, P., Spampinato, N., & Vosa, C. (2009). Aortic Valve Replacement. *Journal of the American College of Cardiology*, *54*(20), 1862–1868. https://doi.org/10.1016/j.jacc.2009.07.032

Stefanini, G. G., Stortecky, S., Cao, D., Rat-Wirtzler, J., O'Sullivan, C. J., Gloekler, S., … Windecker, S. (2014). Coronary artery disease severity and aortic stenosis: clinical outcomes according to SYNTAX score in patients undergoing transcatheter aortic valve implantation. *European Heart Journal*, *35*(37), 2530–2540. https://doi.org/10.1093/eurheartj/ehu074

Stortecky, S., Schoenenberger, A. W., Moser, A., Kalesan, B., Jüni, P., Carrel, T., … Wenaweser, P. (2012). Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *JACC: Cardiovascular Interventions*, *5*(5), 489–496. https://doi.org/10.1016/j.jcin.2012.02.012

Strange, G., Stewart, S., Celermajer, D., Prior, D., Scalia, G. M., Marwick, T., … Playford, D. (2019). Poor Long-Term Survival in Patients With Moderate Aortic Stenosis. *Journal of the American College of Cardiology*, *74*(15), 1851–1863. https://doi.org/10.1016/j.jacc.2019.08.004

Tamburino, C., Capodanno, D., Ramondo, A., Petronio, A. S., Ettori, F., Santoro, G., … Ussia, G. P. (2011). Incidence and Predictors of Early and Late Mortality After Transcatheter Aortic Valve Implantation in 663 Patients With Severe Aortic Stenosis. *Circulation*, *123*(3), 299–308. https://doi.org/10.1161/CIRCULATIONAHA.110.946533

Tanawuttiwat, T., O'Neill, B. P., Cohen, M. G., Chinthakanan, O., Heldman, A. W., Martinez, C. A., … Myerburg, R. J. (2014). New-onset atrial fibrillation after aortic valve replacement: comparison of transfemoral, transapical, transaortic, and surgical approaches. *Journal of the American College of Cardiology*, *63*(15), 1510–1519. https://doi.org/10.1016/j.jacc.2013.11.046

Tchetche, D., Van der Boon, R. M. A., Dumonteil, N., Chieffo, A., Van Mieghem, N. M., Farah, B., … Fajadet, J. (2012). Adverse impact of bleeding and transfusion on the outcome post-transcatheter aortic valve implantation: Insights from the Pooled-RotterdAm-

Milano-Toulouse In Collaboration Plus (PRAGMATIC Plus) initiative. *American Heart Journal*, *164*(3), 402–409. https://doi.org/10.1016/j.ahj.2012.07.003

Thaden, J. J., Nkomo, V. T., Lee, K. J., & Oh, J. K. (2015). Doppler Imaging in Aortic Stenosis: The Importance of the Nonapical Imaging Windows to Determine Severity in a Contemporary Cohort. *Journal of the American Society of Echocardiography*, *28*(7), 780–785. https://doi.org/10.1016/j.echo.2015.02.016

Thalji, N. M., Suri, R. M., Daly, R. C., Greason, K. L., Dearani, J. A., Stulak, J. M., … Schaff, H. V. (2015). The prognostic impact of concomitant coronary artery bypass grafting during aortic valve surgery: Implications for revascularization in the transcatheter era. *Journal of Thoracic and Cardiovascular Surgery*, *149*(2), 451–460. https://doi.org/10.1016/j.jtcvs.2014.08.073

Thanassoulis, G., Massaro, J. M., Cury, R., Manders, E., Benjamin, E. J., Vasan, R. S., … Kathiresan, S. (2010). Associations of Long-Term and Early Adult Atherosclerosis Risk Factors With Aortic and Mitral Valve Calcium. *Journal of the American College of Cardiology*, *55*(22), 2491–2498. https://doi.org/10.1016/j.jacc.2010.03.019

Thanassoulis, G. (2016). Lipoprotein (a) in calcific aortic valve disease: from genomics to novel drug target for aortic stenosis. *Journal of Lipid Research*, *57*(6), 917–924. https://doi.org/10.1194/jlr.R051870

Thourani, V. H., Keeling, W. B., Sarin, E. L., Guyton, R. A., Kilgo, P. D., Dara, A. B., … Lattouf, O. M. (2011). Impact of preoperative renal dysfunction on long-term survival for patients undergoing aortic valve replacement. *Annals of Thoracic Surgery*, *91*(6), 1798–1806. https://doi.org/10.1016/j.athoracsur.2011.02.015

Thourani, V. H., Suri, R. M., Gunter, R. L., Sheng, S., O'Brien, S. M., Ailawadi, G., … Mack, M. J. (2015). Contemporary Real-World Outcomes of Surgical Aortic Valve Replacement in 141,905 Low-Risk, Intermediate-Risk, and High-Risk Patients. *The Annals of Thoracic Surgery*, *99*(1), 55–61. https://doi.org/10.1016/j.athoracsur.2014.06.050

Thourani, V. H., Forcillo, J., Beohar, N., Doshi, D., Parvataneni, R., Ayele, G. M., … Leon, M. B. (2016a). Impact of Preoperative Chronic Kidney Disease in 2,531 High-Risk and Inoperable Patients Undergoing Transcatheter Aortic Valve Replacement in the PARTNER Trial. *The Annals of Thoracic Surgery*, *102*(4), 1172–1180. https://doi.org/10.1016/j.athoracsur.2016.07.001

Thourani, V. H., Kodali, S., Makkar, R. R., Herrmann, H. C., Williams, M., Babaliaros, V., … Leon, M. B. (2016b). Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *The Lancet*, *387*(10034), 2218–2225. https://doi.org/10.1016/S0140-6736(16)30073-3

Thourani, V. H., Forcillo, J., Szeto, W. Y., Kodali, S. K., Blackstone, E. H., Lowry, A. M., … Mack, M. J. (2018). Outcomes in 937 Intermediate-Risk Patients Undergoing Surgical Aortic Valve Replacement in PARTNER-2A. *The Annals of Thoracic Surgery*, *105*(5), 1322–1329. https://doi.org/10.1016/j.athoracsur.2017.10.062

Thyregod, H. G. H., Steinbrüchel, D. A., Ihlemann, N., Nissen, H., Kjeldsen, B. J., Petursson, P., … Søndergaard, L. (2015). Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis. *Journal of the American College of Cardiology*, *65*(20), 2184–2194. https://doi.org/10.1016/j.jacc.2015.03.014

Thyregod, H. G. H., Ihlemann, N., Jørgensen, T. H., Nissen, H., Kjeldsen, B. J., Petursson, P., … Søndergaard, L. (2019). Five-Year Clinical and Echocardiographic Outcomes From the NOTION Randomized Clinical Trial in Patients at Lower Surgical Risk. *Circulation*, *139*(24), 2714–2723. https://doi.org/10.1161/CIRCULATIONAHA.118.036606

Toutouzas, K., Benetos, G., Voudris, V., Drakopoulou, M., Stathogiannis, K., Latsios, G., … Tousoulis, D. (2019). Pre-Dilatation Versus No Pre-Dilatation for Implantation of a Self-

Expanding Valve in All Comers Undergoing TAVR: The DIRECT Trial. *JACC: Cardiovascular Interventions*, *12*(8), 767–777. https://doi.org/10.1016/j.jcin.2019.02.005

Turina, J., Hess, O., Sepulcri, F., & Krayenbuehl, H. P. (1987). Spontaneous course of aortic valve disease. *European Heart Journal*, *8*(5), 471–483. https://doi.org/10.1093/oxfordjournals.eurheartj.a062307

Utsunomiya, H., Yamamoto, H., Horiguchi, J., Kunita, E., Okada, T., Yamazato, R., … Kihara, Y. (2012). Underestimation of aortic valve area in calcified aortic valve disease: Effects of left ventricular outflow tract ellipticity. *International Journal of Cardiology*, *157*(3), 347–353. https://doi.org/10.1016/j.ijcard.2010.12.071

van Geldorp, M. W. A., Eric Jamieson, W. R., Kappetein, A. P., Ye, J., Fradet, G. J., Eijkemans, M. J. C., … Takkenberg, J. J. M. (2009). Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: Weighing lifetime anticoagulant-related event risk against reoperation risk. *The Journal of Thoracic and Cardiovascular Surgery*, *137*(4), 881-886.e5. https://doi.org/10.1016/j.jtcvs.2008.09.028

van Rosendael, P. J., Delgado, V., & Bax, J. J. (2018). Pacemaker implantation rate after transcatheter aortic valve implantation with early and new-generation devices: a systematic review. *European Heart Journal*, *39*(21), 2003–2013. https://doi.org/10.1093/eurheartj/ehx785

Varadarajan, P., Kapoor, N., Bansal, R. C., & Pai, R. G. (2006). Clinical Profile and Natural History of 453 Nonsurgically Managed Patients With Severe Aortic Stenosis. *The Annals of Thoracic Surgery*, *82*(6), 2111–2115. https://doi.org/10.1016/j.athoracsur.2006.07.048

Vassiliou, V. S., Perperoglou, A., Raphael, C. E., Joshi, S., Malley, T., Everett, R., … Prasad, S. K. (2017). Midwall Fibrosis and 5-Year Outcome in Moderate and Severe Aortic Stenosis. *Journal of the American College of Cardiology*, *69*(13), 1755–1756. https://doi.org/10.1016/j.jacc.2017.01.034

Vavilis, G., Bäck, M., Occhino, G., Trevisan, M., Bellocco, R., Evans, M., … Carrero, J. J. (2019). Kidney Dysfunction and the Risk of Developing Aortic Stenosis. *Journal of the American College of Cardiology*, *73*(3), 305–314. https://doi.org/10.1016/j.jacc.2018.10.068

Viktorsson, S. A., Helgason, D., Orrason, A. W., Aspelund, T., Sigurdsson, M. I., Geirsson, A., & Gudbjartsson, T. (2016). Favorable Survival after Aortic Valve Replacement Compared to the General Population. *The Journal of Heart Valve Disease*, *25*(1), 8–13.

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *PLoS Medicine*, *4*(10), e296. https://doi.org/10.1371/journal.pmed.0040296

Vora, A. N., Dai, D., Matsuoka, R., Harrison, J. K., Hughes, G. C., Sherwood, M. W., … Vemulapalli, S. (2018). Incidence, Management, and Associated Clinical Outcomes of New-Onset Atrial Fibrillation Following Transcatheter Aortic Valve Replacement: An Analysis From the STS/ACC TVT Registry. *JACC: Cardiovascular Interventions*, *11*(17), 1746–1756. https://doi.org/10.1016/j.jcin.2018.05.042

Waksman, R., Rogers, T., Torguson, R., Gordon, P., Ehsan, A., Wilson, S. R., … Corso, P. J. (2018). Transcatheter Aortic Valve Replacement in Low-Risk Patients with Symptomatic Severe Aortic Stenosis. *Journal of the American College of Cardiology*, *72*(18), 2095–2105. https://doi.org/10.1016/J.JACC.2018.08.1033

Walston, J., Buta, B., & Xue, Q.-L. (2018). Frailty Screening and Interventions: Considerations for Clinical Practice. *Clinics in Geriatric Medicine*, *34*(1), 25–38. https://doi.org/10.1016/j.cger.2017.09.004

Walther, T., Simon, P., Dewey, T., Wimmer-Greinecker, G., Falk, V., Kasimir, M. T., … Mack, M. (2007). Transapical minimally invasive aortic valve implantation: multicenter

experience. *Circulation*, *116*(11 Suppl), I240-5. https://doi.org/10.1161/CIRCULATIONAHA.106.677237

Walther, T., Hamm, C. W., Schuler, G., Berkowitsch, A., Kötting, J., Mangner, N., … Möllmann, H. (2015). Perioperative results and complications in 15,964 transcatheter aortic valve replacements: Prospective data from the GARY registry. *Journal of the American College of Cardiology*, *65*(20), 2173–2180. https://doi.org/10.1016/j.jacc.2015.03.034

Wang, M., Furnary, A. P., Li, H. F., & Grunkemeier, G. L. (2017). Bioprosthetic Aortic Valve Durability: A Meta-Regression of Published Studies. *Annals of Thoracic Surgery*, *104*(3), 1080–1087. https://doi.org/10.1016/j.athoracsur.2017.02.011

Wang, T. K. M., Wang, M. T. M., Gamble, G. D., Webster, M., & Ruygrok, P. N. (2017). Performance of contemporary surgical risk scores for transcatheter aortic valve implantation: A meta-analysis. *International Journal of Cardiology*, *236*, 350–355. https://doi.org/10.1016/j.ijcard.2016.12.188

Watkins, D. A., Johnson, C. O., Colquhoun, S. M., Karthikeyan, G., Beaton, A., Bukhman, G., … Roth, G. A. (2017). Global, regional, & national burden of rheumatic heart disease, 1990-2015. *New England Journal of Medicine*, *377*(8), 713–722. https://doi.org/10.1056/NEJMoa1603693

Webb, J. G., Chandavimol, M., Thompson, C. R., Ricci, D. R., Carere, R. G., Munt, B. I., … Lichtenstein, S. (2006). Percutaneous Aortic Valve Implantation Retrograde From the Femoral Artery. *Circulation*, *113*(6), 842–850. https://doi.org/10.1161/CIRCULATIONAHA.105.582882

Wenaweser, P., Stortecky, S., Schütz, T., Praz, F., Gloekler, S., Windecker, S., & Elsässer, A. (2016). Transcatheter aortic valve implantation with the NVT Allegra transcatheter heart valve system: first-in-human experience with a novel self-expanding transcatheter heart valve. *EuroIntervention*, *12*(1), 71–77. https://doi.org/10.4244/EIJV12I1A13

Wendler, O., Schymik, G., Treede, H., Baumgartner, H., Dumonteil, N., Ihlberg, L., … Vahanian, A. (2017). SOURCE 3 Registry. *Circulation*, *135*(12), 1123–1132. https://doi.org/10.1161/CIRCULATIONAHA.116.025103

Wernly, B., Jirak, P., Lichtenauer, M., Veulemans, V., Zeus, T., Piayda, K., … Jung, C. (2020). Systematic Review and Meta-Analysis of Interventional Emergency Treatment of Decompensated Severe Aortic Stenosis. *The Journal of Invasive Cardiology*, *32*(1), 30–36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31611428

Weyman, A. E., & Scherrer-Crosbie, M. (2005). Aortic Stenosis: Physics and Physiology - What Do the Numbers Really Mean? *Reviews in Cardiovascular Medicine*. Retrieved from https://rcm.imrpress.com

Witberg, G., Regev, E., Chen, S., Assali, A., Barbash, I. M., Planer, D., … Kornowski, R. (2017). The Prognostic Effects of Coronary Disease Severity and Completeness of Revascularization on Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*, *10*(14), 1428–1435. https://doi.org/10.1016/j.jcin.2017.04.035

Xu, Y.-N., Xiong, T.-Y., Li, Y.-J., Liao, Y.-B., Zhao, Z.-G., Wei, X., … Chen, M. (2020). Balloon sizing during transcatheter aortic valve implantation. *Herz*, *45*(2), 192–198. https://doi.org/10.1007/s00059-018-4714-2

Yadgir, S., Johnson, C. O., Aboyans, V., Adebayo, O. M., Adedoyin, R. A., Afarideh, M., … Roth, G. A. (2020). Global, Regional, and National Burden of Calcific Aortic Valve and Degenerative Mitral Valve Diseases, 1990–2017. *Circulation*, *141*(21), 1670–1680. https://doi.org/10.1161/CIRCULATIONAHA.119.043391

Yan, A. T., Koh, M., Chan, K. K., Guo, H., Alter, D. A., Austin, P. C., … Ko, D. T. (2017). Association Between Cardiovascular Risk Factors and Aortic Stenosis. *Journal of the*

American College of Cardiology, *69*(12), 1523–1532. https://doi.org/10.1016/j.jacc.2017.01.025

Yanagawa, B., Butany, J., & Verma, S. (2016). Update on rheumatic heart disease. *Current Opinion in Cardiology*, *31*(2), 162–168. https://doi.org/10.1097/HCO.0000000000000269

Zhao, D. F., Seco, M., Wu, J. J., Edelman, J. B., Wilson, M. K., Vallely, M. P., … Bannon, P. G. (2016). Mechanical Versus Bioprosthetic Aortic Valve Replacement in Middle-Aged Adults: A Systematic Review and Meta-Analysis. *The Annals of Thoracic Surgery*, *102*(1), 315–327. https://doi.org/10.1016/j.athoracsur.2015.10.092

PUBLICATIONS

PUBLICATION I

Comparison of Outcomes After Transcatheter Aortic Valve Replacement vs Surgical Aortic Valve Replacement Among Patients With Aortic Stenosis at Low Operative Risk.

Virtanen MPO, Eskola M, Jalava MP, Husso A, Laakso T, Niemelä M, Ahvenvaara T, Tauriainen T, Maaranen P, Kinnunen EM, Dahlbacka S, Jaakkola J, Vasankari T, Airaksinen J, Anttila V, Rosato S, D'Errigo P, Savontaus M, Juvonen T, Laine M, Mäkikallio T, Valtola A, Raivio P, Biancari F.

JAMA Netw Open. 2019;2(7):e198352. doi:10.1001/jamanetworkopen.2019.5742.

JAMA Network Open

Original Investigation | Cardiology

Comparison of Outcomes After Transcatheter Aortic Valve Replacement vs Surgical Aortic Valve Replacement Among Patients With Aortic Stenosis at Low Operative Risk

Marko P. O. Virtanen, MD; Markku Eskola, MD, PhD; Maina P. Jalava, MD; Annastiina Husso, MD, PhD; Teemu Laakso, MD; Matti Niemelä, MD, PhD; Tuomas Ahvenvaara, MD; Tuomas Tauriainen, MD, PhD; Pasi Maaranen, MD; Eeva-Maija Kinnunen, MD, PhD; Sebastian Dahlbacka, MD, PhD; Jussi Jaakkola, MD, PhD; Tuija Vasankari, RN; Juhani Airaksinen, MD, PhD; Vesa Anttila, MD, PhD; Stefano Rosato, MSc; Paola D'Errigo, MSc; Mikko Savontaus, MD, PhD; Tatu Juvonen, MD, PhD; Mika Laine, MD, PhD; Timo Mäkikallio, MD, PhD; Antti Valtola, MD, PhD; Peter Raivio, MD, PhD; Fausto Biancari, MD, PhD

Abstract

IMPORTANCE Transcatheter aortic valve replacement (TAVR) has been shown to be a valid alternative to surgical aortic valve replacement (SAVR) in patients at high operative risk with severe aortic stenosis (AS). However, the evidence of the benefits and harms of TAVR in patients at low operative risk is still scarce.

OBJECTIVE To compare the short-term and midterm outcomes after TAVR and SAVR in low-risk patients with AS.

DESIGN, SETTING, AND PARTICIPANTS This retrospective comparative effectiveness cohort study used data from the Nationwide Finnish Registry of Transcatheter and Surgical Aortic Valve Replacement for Aortic Valve Stenosis of patients at low operative risk who underwent TAVR or SAVR with a bioprosthesis for severe AS from January 1, 2008, to November 30, 2017. Low operative risk was defined as a Society of Thoracic Surgeons Predicted Risk of Mortality score less than 3% without other comorbidities of clinical relevance. One-to-one propensity score matching was performed to adjust for baseline covariates between the TAVR and SAVR cohorts.

EXPOSURES Primary TAVR or SAVR with a bioprosthesis for AS with or without associated coronary revascularization.

MAIN OUTCOMES AND MEASURES The primary outcomes were 30-day and 3-year survival.

RESULTS Overall, 2841 patients (mean [SD] age, 74.0 [6.2] years; 1560 [54.9%] men) fulfilled the inclusion criteria and were included in the analysis; TAVR was performed in 325 patients and SAVR in 2516 patients. Propensity score matching produced 304 pairs with similar baseline characteristics. Third-generation devices were used in 263 patients (86.5%) who underwent TAVR. Among these matched pairs, 30-day mortality was 1.3% after TAVR and 3.6% after SAVR ($P = .12$). Three-year survival was similar in the study cohorts (TAVR, 85.7%; SAVR, 87.7%; $P = .45$). Interaction tests found no differences in terms of 3-year survival between the study cohorts in patients younger than vs older than 80 years or in patients who received recent aortic valve prostheses vs those who did not.

(continued)

Key Points

Question Does transcatheter aortic valve replacement achieve similar results compared with surgical aortic valve replacement in patients at low operative risk with severe aortic stenosis?

Findings In this comparative effectiveness cohort study of 2841 low-risk patients with aortic stenosis from Finland, propensity score–matching analysis showed similar 30-day and 3-year survival after transcatheter aortic valve replacement and surgical aortic valve replacement.

Meaning Patients with severe aortic stenosis at low operative risk may be offered transcatheter aortic valve replacement instead of surgical aortic valve replacement.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE Transcatheter aortic valve replacement using mostly third-generation devices achieved similar short- and mid-term survival compared with SAVR in low-risk patients. Further studies are needed to assess the long-term durability of TAVR prostheses before extending their use to low-risk patients.

JAMA Network Open. 2019;2(6):e195742.
Corrected on July 12, 2019. doi:10.1001/jamanetworkopen.2019.5742

Introduction

The development of transcatheter aortic valve replacement (TAVR) has made the treatment of severe aortic stenosis (AS) feasible with similar short- and mid-term outcomes compared with surgical aortic valve replacement (SAVR) in patients with high[1-3] or intermediate[4-6] operative risk. Clinical practice has recently turned toward treating even low-risk patients with TAVR, and 3 recent randomized clinical trials reported favorable short-term results with TAVR in these patients.[7-9] The Evolut Low Risk Trial[7] documented a 2-year mortality of 4.5% after either TAVR or SAVR. The PARTNER 3 Trial[8] reported a 1-year mortality of 1.0% after TAVR and 2.5% after SAVR. The Nordic Aortic Valve Intervention Trial (NOTION)[9,10] randomized patients to receive TAVR or SAVR, and 82% of the patients were at low risk for surgical operations, ie, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score less than 4%. Similar outcomes were achieved in both TAVR and SAVR treatment arms at 6 years.[9,10] A 2018 study[11] showed that transfemoral TAVR using mainly a third-generation balloon-expandable TAVR device was associated with no deaths at 30 days compared with 1.7% in a historical, propensity-matched SAVR cohort. However, the long-term durability of TAVR prostheses in low-risk populations is questionable based on registry data, to our knowledge.[12] This leaves uncertainty whether TAVR is an acceptable treatment for low-risk patients. The aim of this study was to compare the short-term and midterm survival of low-risk patients treated with TAVR and SAVR in a nationwide study.

Methods

Study Design and Participants

The Nationwide Finnish Registry of Transcatheter and Surgical Aortic Valve Replacement for Aortic Valve Stenosis (FinnValve registry) is a study (ClinicalTrials.gov identifier, NCT03385915) that includes retrospectively collected data from consecutive and unselected patients treated with TAVR or SAVR with bioprostheses for AS from January 1, 2008, to November 30, 2017, at all 5 university hospitals in Finland (Helsinki University Hospital, Helsinki, Finland; Kuopio University Hospital, Kuopio, Finland; Oulu University Hospital, Oulu, Finland; Tampere University Hospital, Tampere, Finland; and Turku University Hospital, Turku, Finland). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The study protocol was approved by the institutional review boards of all participating centers. Informed consent was waived because of the retrospective nature of this study. The inclusion criteria for study entry were age older than 18 years, previous primary aortic valve procedure with a bioprosthesis for AS with or without associated regurgitation, and TAVR or SAVR with or without associated coronary revascularization. The exclusion criteria were any prior TAVR or surgical intervention on the aortic valve; a concomitant major procedure on the mitral valve, tricuspid valve, or ascending aorta; active endocarditis; or any procedure for isolated aortic valve regurgitation. The operative risk of patients was stratified according to STS-PROM[13] and updated European System for Cardiac Operative Risk Evaluation (EuroSCORE II)[14] scores. Exclusion criteria included having an STS-PROM score of 3% or higher, undergoing an urgent or emergency procedure, having previously undergone a cardiac surgical operation, being older than 85 years, undergoing chronic dialysis, having a functioning kidney transplant, having severe frailty, having an

active malignancy, having had a recent episode of acute heart failure, having a porcelain aorta, being treated with oxygen therapy, having a left ventricular ejection fraction of 30% or below, having a severe mitral valve regurgitation, or not having transfemoral access for TAVR (eFigure in the Supplement).

Data were retrospectively collected in a dedicated electronic case report form by cardiologists, cardiac surgeons, and trained research nurses from December 1, 2017, to July 31, 2018, and underwent robust checking of its completeness and quality. Data on mortality were retrieved from the Finnish national registry Statistics Finland. Follow-up was considered complete for all patients, but follow-up was truncated at hospital discharge for those not residing in Finland. Analyses were conducted October 29, 2018, through November 7, 2018.

Baseline Risk Factors

Baseline variables were defined according to the EuroSCORE II criteria.[14] Severe frailty was defined as Geriatric Status Scale[15] grades 2 and 3. Coronary artery disease (CAD) was defined as any stenosis of 50% or more of the main coronary branches. Recent acute heart failure was defined as new-onset or worsening of heart failure requiring hospital admission within 60 days prior to intervention.

Outcome Measures

The primary outcomes were 30-day and 3-year survival. The secondary outcomes were stroke, blood transfusion, bleeding, resternotomy for bleeding, paravalvular regurgitation, new permanent pacemaker implantation, acute kidney injury, renal replacement therapy, conversion to cardiac surgical procedure, coronary artery occlusion, aortic dissection or rupture, major vascular complication, atrial fibrillation, postoperative length of stay in the hospital where the procedure was performed, and repeated aortic valve replacement.

Stroke and major vascular complications were defined according to the Valvular Academic Research Consortium-2 criteria.[16] Major bleeding was defined as European Multicenter Study on Coronary Artery Bypass Grafting bleeding grades 2 or 3, ie, transfusion of more than 4 units of red blood cells or resternotomy for excessive bleeding.[17] In this study, the Valvular Academic Research Consortium-2 definition of major and life-threatening bleeding was not applied because, unlike patients undergoing TAVR, a significant decrease of hemoglobin level is observed in most patients undergoing SAVR, and this does not always reflect a condition of major perioperative blood loss. Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes classification criteria,[18] ie, stage 1 is an increase in serum creatinine levels of at least 1.5-fold the baseline level or a serum creatinine level increase of at least 0.3 mg/dL (to convert to micrograms per liter, multiply by 88.4); stage 2 is an increase in serum creatinine level 2.0- to 2.9-fold the baseline; and stage 3 is defined as an increase in serum creatinine concentration at least 3-fold the baseline level or a serum creatinine concentration increase at least 4.0 mg/dL during the hospital stay or de novo renal replacement therapy during the hospital stay.

Statistical Analysis

Statistical analysis was performed using SAS statistical software version 9.2 (SAS Institute) and SPSS statistical software version 25.0 (IBM). Continuous variables are reported as means and SDs as well as median and interquartile ranges, while categorical variables are reported as counts and percentages. Mann-Whitney *U* test, Fisher exact test, and χ^2 test were used for univariate analysis in the unmatched population. Missing data were not replaced. A propensity score was estimated using a nonparsimonious logistic regression model, including age, sex, body mass index, hemoglobin, estimated glomerular filtration rate, diabetes, stroke, transient ischemic attack, pulmonary disease, extracardiac arteriopathy, New York Heart Association class 4 symptoms, left ventricular ejection fraction of 50% or less, atrial fibrillation, pulmonary artery pressure, recent myocardial infarction, CAD, left main coronary stenosis, number of diseased coronary arteries, moderate mitral valve regurgitation, and prior pacemaker as covariates. One-to-one propensity score matching was performed using the nearest-neighbor method and a caliper width of 0.2 of the SD of the logit of the

propensity score. Furthermore, 3 different propensity score–matching analyses were performed addressing exact matching of patients older than 80 years, with CAD, and with selected valve prostheses (ie, third-generation TAVR prostheses and their variants (ie, EvolutR, Sapien 3, ACURATE neo, and Lotus) and selected SAVR prostheses and their variants with proven durability (ie, Trifecta, Perimount).[19] These matched data sets were used for interaction tests analyses. 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 less than 0.10 were considered an acceptable imbalance between the treatment groups. Early outcomes in the propensity score–matched cohorts were evaluated using the *t* test for paired samples for continuous variables and the McNemar test for dichotomous variables. These tests were used to evaluate any difference in the adverse events of propensity score–matched pairs. Differences in the long-term survival of matched pairs were evaluated using the Kaplan-Meier method with the Klein-Moeschberger stratified log-rank test. *P* values were 2-tailed, and a *P* value less than .10 was considered statistically significant for interaction tests of matched cohorts. A *P* value less than .05 was considered statistically significant for all the other tests.

Results

The FinnValve registry includes data from 6463 patients who underwent primary TAVR or SAVR with a bioprosthesis for severe AS. Of these, 2841 patients (mean [SD] age, 74.0 [6.2] years; 1560 [54.9%] men) fulfilled the inclusion criteria and were included in analysis (eFigure in the Supplement). Surgical aortic valve replacement was performed in 2516 patients, and TAVR was performed in 325 patients. A significant interinstitutional difference in the prevalence of low-risk patients undergoing TAVR was observed (Helsinki, 102 patients [11.0%]; Kuopio, 75 patients [18.7%]; Oulu, 74 patients [13.2%]; Tampere, 20 patients [3.4%]; Turku, 54 patients [14.8%]; *P* < .001). The mean (SD) follow-up of this series was 4.0 (2.7) years (TAVR cohort, 1.7 [1.4] years; SAVR cohort, 4.3 [2.7] years).

Characteristics and Outcomes of the Unmatched Cohorts

The baseline characteristics of the low-risk patients in the unmatched TAVR and SAVR groups are shown in **Table 1**. Patients who underwent SAVR were younger, more often men, and had lower STS-PROM and EuroSCORE II risk scores compared with patients in the TAVR cohort (Table 1). Before matching, the prevalence of previous stroke, pulmonary disease, peripheral arteriopathy, atrial fibrillation, and mitral regurgitation was higher in the TAVR cohort compared with the SAVR cohort. Patients in the SAVR cohort had a higher prevalence of CAD and more often underwent concomitant revascularization.

In unmatched cohorts, 4 patients (1.2%) in the TAVR cohort and 50 patients (2.0%) in the SAVR cohort died within 30 days (*P* = .52). Early outcomes of the unadjusted cohorts are presented in **Table 2**. Three-year survival was lower for the TAVR cohort (85.5%) compared with the SAVR cohort (92.0%), but the difference was not statistically significant (*P* = .20).

Characteristics and Outcomes of the Propensity Score–Matched Cohorts

Propensity score matching produced 304 pairs of patients with similar baseline characteristics (**Table 3**). The standardized differences between groups were less than the prespecified margin indicating good balance of covariates. The rate of planned concomitant revascularization was lower in the TAVR group compared with the SAVR group (6 patients [2.0%] vs 49 patients [16.1%]; *P* < .001). The prevalence of CAD (57 patients in each group [18.8%]) and the frequency of previous percutaneous coronary intervention (TAVR, 51 patients [16.8%]; SAVR, 49 patients [16.1%]) were similar between the matched cohorts. Selected, more recent prostheses were used for 263 patients (86.5%) undergoing TAVR procedures and 150 patients (49.3%) undergoing SAVR procedures.

Among the matched pairs, 30-day mortality included 4 patients (1.3%) after TAVR and 11 patients (3.6%) after SAVR (*P* = .12) (**Table 4**). Three-year survival was similar in the study cohorts (85.7% vs 87.7% for TAVR and SAVR, respectively; *P* = .45) (**Figure**).

Patients who underwent TAVR had a shorter mean (SD) hospital stay (4.1 [3.2] days vs 7.9 [5.7] days; *P* < .001) and lower rates of atrial fibrillation (92 patients [30.3%] vs 194 patients [63.4%]; *P* < .001), resternotomy for bleeding (1 patient [0.3%] vs 18 patients [5.9%]; *P* < .001), and European Multicenter Study on Coronary Artery Bypass Grafting bleeding grades 2 or 3 (7 patients [2.3%] vs 51 patients [16.9%]; *P* < .001) compared with patients who underwent SAVR (Table 4). Two patients

Table 1. Characteristics of Unmatched Patients With Low Operative Risk Undergoing Transcatheter or Surgical Aortic Valve Replacement[a]

Characteristic	No. (%)		Standardized Difference (95% CI)	*P* Value
	TAVR (n = 325)	SAVR (n = 2516)		
Age, y				
Mean (SD)	78.1 (6.0)	73.4 (6.0)	0.77 (0.66 to 0.77)	<.001
Median (IQR)	80.0 (75.7-82.1)	74.0 (69.9-77.7)		
Men	153 (47.1)	1407 (55.9)	0.18 (0.06 to 0.29)	.003
Body mass index[b]				
Mean (SD)	28.6 (5.1)	28.0 (4.7)	0.12 (0.01 to 0.24)	.05
Median (IQR)	27.9 (24.7-31.9)	27.4 (24.6-30.8)		
Hemoglobin, g/dL[c]				
Mean (SD)	13.0 (1.5)	13.4 (1.3)	0.38 (0.27 to 0.50)	<.001
Median (IQR)	13.1 (12.1-14.0)	13.6 (12.7-14.5)		
eGFR, mL/min/1.73 m^2[c]				
Mean (SD)	76 (21)	80 (20)	0.20 (0.09 to 0.32)	<.001
Median (IQR)	73 (62-88)	79 (66-92)		
Diabetes	75 (23.1)	555 (22.1)	0.02 (−0.09 to 0.14)	.68
Stroke	29 (8.9)	127 (5.0)	0.15 (0.04 to 0.27)	.004
Transient ischemic attack	22 (6.8)	107 (4.3)	0.11 (−0.01 to 0.23)	.04
Pulmonary disease	60 (18.5)	275 (10.9)	0.21 (0.10 to 0.33)	<.001
Extracardiac arteriopathy	41 (12.6)	207 (8.2)	0.14 (0.03 to 0.26)	.008
LVEF ≤50%	47 (14.5)	298 (11.8)	0.08 (−0.04 to 0.19)	.18
Atrial fibrillation	118 (36.3)	457 (18.2)	0.42 (0.30 to 0.53)	<.001
NYHA class 4	7 (2.2)	20 (0.8)	0.11 (−0.002 to 0.23)	.02
SPAP, mm Hg				
31-55	109 (33.5)	799 (31.8)	0.12 (0 to 0.23)	.11
>55	18 (5.5)	86 (3.4)		
Moderate mitral regurgitation	25 (7.7)	77 (3.1)	0.22 (0.10 to 0.33)	<.001
Recent myocardial infarction	4 (1.2)	20 (0.8)	0.04 (−0.08 to 0.16)	.42
Coronary artery disease	60 (18.5)	877 (34.9)	0.38 (0.26 to 0.49)	<.001
Left main coronary stenosis	2 (0.6)	76 (3.0)	0.18 (0.07 to 0.30)	.01
No. of diseased vessels				
Mean (SD)	0.2 (0.5)	0.6 (0.9)	0.47 (0.36 to 0.59)	<.001
Median (IQR)	0 (0)	0 (0-1.0)		
Prior PCI	65 (20.0)	200 (7.9)	0.35 (0.24 to 0.47)	<.001
Permanent pacemaker	24 (7.4)	90 (3.6)	0.17 (0.05 to 0.28)	.001
Planned concomitant PCI or CABG	9 (2.8)	812 (32.3)	0.84 (0.72 to 0.96)	<.001
EuroSCORE II, %				
Mean (SD)	2.6 (1.5)	2.1 (1.1)	0.42 (0.31 to 0.54)	<.001
Median (IQR)	2.2 (1.7-3.2)	1.8 (1.3-2.6)		
STS-PROM score, %				
Mean (SD)	2.1 (0.5)	1.8 (0.6)	0.63 (0.51 to 0.74)	<.001
Median (IQR)	2.2 (1.8-2.5)	1.7 (1.3-2.2)		

Abbreviations: CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; EuroSCORE II, updated European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional classification; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; SPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR, transcatheter aortic valve replacement.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.

[a] Clinical variables are according to the EuroSCORE II definition criteria.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Calculated using the original Modification of Diet in Renal Disease equation.

in each cohort had coronary ostium occlusion, and conversion to cardiac surgical operations was necessary for 3 patients in the TAVR cohort. Major vascular complications were more frequent in the TAVR cohort than the SAVR cohort (27 patients [8.9%] vs 7 patients [2.3%]; *P* = .001), and patients who received TAVR experienced higher rates of paravalvular regurgitation with SAVR (mild regurgitation: TAVR, 46 patients [15.1%]; SAVR, 17 patients [5.6%]; moderate regurgitation: TAVR, 9 patients [3.0%]; SAVR, 2 patients [0.7%]; *P* < .001).

No significant difference was observed in the rates of stroke between the cohorts. There was a higher rate of acute kidney injury in the SAVR cohort (15 patients [5.0%]) compared with the TAVR cohort (6 patients [2.0%]), but the difference was not significant (*P* = .12). Permanent pacemaker implantation was needed more often among patients who underwent TAVR than those who underwent SAVR (29 patients [9.5%] vs 14 patients [4.6%]; *P* = .03).

The interaction test for type of procedure and CAD was statistically significant and demonstrated unfavorable intermediate survival in patients with CAD who underwent SAVR (eTable in the Supplement). Interaction tests found that survival in the TAVR cohort was similar to that of the SAVR cohort for patients younger than vs older than 80 years (*P* for interaction = .23) and for patients who received selected valve prostheses vs those who did not (*P* for interaction = .26) (eTable in the Supplement).

Discussion

This nationwide study represents one of the largest studies of low-risk patients who underwent TAVR or SAVR, to our knowledge. We found that short-term and midterm mortality in low-risk patients was low and similar after TAVR or SAVR, TAVR was associated with shorter hospital stays and a favorable safety profile in terms of major perioperative bleeding, and SAVR was associated with lower rates of severe vascular complication, paravalvular regurgitation, and need of permanent pacemaker.

Table 2. Early Outcomes of Unmatched Low-Risk Patients Undergoing TAVR or SAVR

Outcome	No. (%)		*P* Value
	TAVR (n = 325)	SAVR (n = 2516)	
Deaths within 30 d	4 (1.2)	50 (2.0)	.52
Conversion to cardiac surgery	3 (0.9)	NA	NA
Coronary ostium occlusion	2 (0.6)	9 (0.4)	.36
Aortic dissection/rupture	2 (0.6)	19 (0.8)	>.99
Major vascular complication	28 (8.6)	36 (1.4)	<.001
Stroke	6 (1.8)	76 (3.0)	.23
RBC transfusion, units			
Mean (SD)	0.4 (1.2)	2.3 (3.3)	<.001
Median (IQR)	0 (0)	2.0 (0-3.0)	
RBC transfusion >4 units	8 (2.5)	353 (14.2)	<.001
Resternotomy for bleeding	1 (0.3)	190 (7.6)	<.001
E-CABG bleeding grades 2-3	8 (2.5)	418 (16.8)	<.001
KDIGO acute kidney injury grades 2-3	6 (1.9)	111 (4.4)	.03
Renal replacement therapy	1 (0.3)	39 (1.6)	.08
Paravalvular regurgitation			
Mild	48 (14.8)	135 (5.4)	<.001
Moderate	9 (2.8)	10 (0.4)	
Severe	0	4 (0.2)	
Atrial fibrillation	100 (30.8)	1330 (52.9)	<.001
Permanent pacemaker	35 (10.8)	98 (3.9)	<.001
Hospital stay, d			
Mean (SD)	4.1 (3.2)	7.7 (5.7)	<.001
Median (IQR)	4.0 (2.0-5.0)	7.0 (5.0-8.0)	

Abbreviations: E-CABG, European Coronary Artery Bypass Grafting registry; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not applicable; RBC, red blood cells; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

This study represents a nationwide practice demonstrating that from January 1, 2008, to November 30, 2017, 325 of 2841 patients (11.4%) with AS and low operative risk were treated with TAVR in Finland. Slightly lower proportions of low-risk patients during a similar time frame was reported by Schymik et al.[20] An STS-PROM score less than 3.0% was selected as the cutoff value for

Table 3. Characteristics of Propensity Score–Matched Patients With Low Operative Risk Who Underwent TAVR or SAVR[a]

Characteristic, No. (%)	TAVR (n = 304)	SAVR (n = 304)	Standardized Difference (95% CI)	*P* Value
Age, y				
Mean (SD)	77.9 (6.0)	78.1 (4.8)	0.036 (−0.123 to 0.195)	.95
Median (IQR)	79.8 (75.4 to 82.0)	79.0 (74.4-82.1)		
Women	161 (53.0)	153 (50.3)	0.053 (−0.106 to 0.212)	.57
Body mass index[b]				
Mean (SD)	28.5 (5.1)	28.7 (4.9)	0.028 (−0.131 to 0.187)	.33
Median (IQR)	27.8 (24.7 to 31.9)	28.0 (24.8-31.6)		
Hemoglobin, g/dL				
Mean (SD)	13.1 (1.5)	13.0 (1.4)	0.04 (−0.12 to 0.20)	.60
Median (IQR)	13.2 (12.1 to 14.0)	13.0 (12.1-13.9)		
eGFR, mL/min/1.73 m^2[c]				
Mean (SD)	76 (21)	76 (20)	0.01 (−0.15 to 0.17)	.95
Median (IQR)	73 (26)	74 (26)		
Diabetes	68 (22.4)	68 (22.4)	0 (−0.16 to 0.16)	>.99
Stroke	26 (8.6)	24 (7.9)	0.02 (−0.14 to 0.18)	.89
Transient ischemic attack	20 (6.6)	19 (6.3)	0.01 (−0.15 to 0.20)	>.99
Pulmonary disease	54 (17.8)	59 (19.4)	0.04 (−0.12 to 0.20)	.68
Extracardiac arteriopathy	39 (12.8)	42 (13.8)	0.03 (−0.13 to 0.19)	.81
LVEF ≤50%	41 (13.5)	40 (13.2)	0.01 (−0.15 to 0.17)	>.99
Atrial fibrillation	107 (35.2)	105 (34.5)	0.01 (−0.15 to 0.17)	.93
NYHA class 4	5 (1.6)	8 (2.6)	0.07 (−0.09 to 0.23)	.58
SPAP, mm Hg				
31-55	101 (33.2)	95 (31.3)	0.06 (−0.10 to 0.22)	.12
>55	15 (4.9)	18 (5.9)		
Moderate mitral regurgitation	20 (6.6)	19 (6.3)	0.04 (−0.12 to 0.20)	.80
Recent myocardial infarction	3 (1.0)	2 (0.7)	0.09 (−0.07 to 0.24)	>.99
Coronary artery disease	57 (18.8)	57 (18.8)	0 (−0.16 to 0.16)	>.99
Left main coronary stenosis	2 (0.7)	5 (1.6)	0.09 (−0.07 to 0.25)	.45
No. of diseased vessels				
Mean (SD)	0.2 (0.6)	0.3 (0.6)	0.03 (−0.13 to 0.19)	.92
Median (IQR)	0 (0)	0 (0)		
Prior PCI	51 (16.8)	49 (16.1)	0.02 (−0.14 to 0.18)	.91
Permanent pacemaker	21 (6.9)	15 (4.9)	0.08 (−0.08 to 0.24)	.41
Planned concomitant PCI or CABG	6 (2.0)	49 (16.1)	0.51 (0.35 to 0.67)	<.001
EuroSCORE II score, %				
Mean (SD)	2.6 (1.4)	2.5 (1.3)	0.04 (−0.12 to 0.20)	.65
Median (IQR)	2.2 (1.7 to 3.2)	2.2 (1.6 to 3.0)		
STS-PROM score, %				
Mean (SD)	2.1 (0.9)	2.1 (0.5)	0.03 (−0.14 to 0.18)	.82
Median (IQR)	2.2 (1.7 to 2.5)	2.2 (1.7 to 2.6)		

Abbreviations: CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; EuroSCORE-II, updated European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional classification; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; SPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR, transcatheter aortic valve replacement.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.

[a] Clinical variables are according to the EuroSCORE II definition criteria.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Calculated using the original Modification of Diet in Renal Disease equation.

low-risk patients, which is supported by earlier studies.[10,21] Patients who have generally a higher operative risk, such as patients older than 85 years with severe frailty and a recent acute heart failure episode, were excluded, leaving a small proportion of patients with comorbidities.

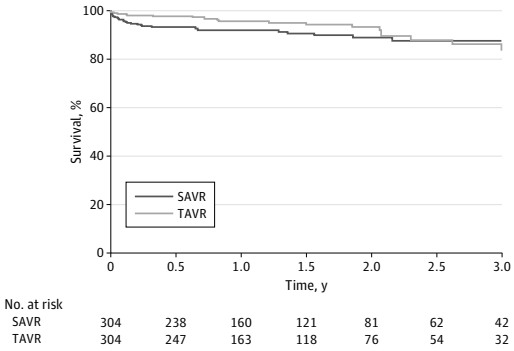
Initially, TAVR was indicated only for inoperable or high–operative risk patients, but accepted clinical practice has expanded to perform TAVR in patients at lower operative risk[7,8,22] and requires more data on long-term outcomes in these populations. To our knowledge, the longest follow-up data on similar survival after TAVR or SAVR extend 5 years for high-risk patients,[1,3] while data on intermediate survival among low-risk patients are limited.[5,6,10] Despite the short-term results

Table 4. Early Outcomes in Propensity Score–Matched Low-Risk Patients Undergoing TAVR and SAVR

Outcome	No. (%)		*P* Value
	TAVR (n = 304)	SAVR (n = 304)	
Deaths at 30 d	4 (1.3)	11 (3.6)	.12
Conversion to cardiac surgery	3 (1.0)	NA	NA
Coronary ostium occlusion	2 (0.7)	2 (0.7)	>.99
Aortic dissection or rupture	2 (0.7)	5 (1.6)	.45
Major vascular complication	27 (8.9)	7 (2.3)	.001
Stroke	6 (2.0)	16 (5.3)	.12
RBC transfusion, units			
Mean (SD)	0.4 (1.2)	2.5 (2.9)	<.001
Median (IQR)	0 (0)	2.0 (0-4.0)	
RBC transfusion >4 units	7 (2.3)	46 (15.1)	<.001
Resternotomy for bleeding	1 (0.3)	18 (5.9)	<.001
E-CABG bleeding grades 2-3	7 (2.3)	51 (16.9)	<.001
KDIGO acute kidney injury grades 2-3	6 (2.0)	15 (5.0)	.12
Renal replacement therapy	1 (0.3)	5 (1.7)	.22
Paravalvular regurgitation			
Mild	46 (15.1)	17 (5.6)	<.001
Moderate	9 (3.0)	2 (0.7)	
Severe	0	0	
Atrial fibrillation	92 (30.3)	194 (63.4)	<.001
Permanent pacemaker	29 (9.5)	14 (4.6)	.03
Hospital stay, d			
Mean (SD)	4.1 (3.3)	7.9 (5.2)	<.001
Median (IQR)	3.0 (2.0-5.0)	7.0 (5.0-9.0)	

Abbreviations: E-CABG, European Coronary Artery Bypass Grafting registry; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not applicable; RBC, red blood cells; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Figure. Kaplan-Meier Estimate of Survival in Low-Risk Patients With Aortic Stenosis Who Underwent Transcatheter (TAVR) or Surgical Aortic Valve Replacement (SAVR)



documented with TAVR compared with SAVR in low-risk patients from two 2019 randomized clinical trials,[7,8] there are limited data on the midterm and long-term outcomes after TAVR in low-risk patients. Our data suggest that similar and excellent survival can be expected 3 years after TAVR (85.7%) and SAVR (87.7%) in patients deemed to have low operative risk. Indeed, the 3-year survival of patients who underwent TAVR was higher than reported in a low-risk series from the 2016 Observational Study of Effectiveness of SAVR-TAVI Procedures for Severe Aortic Stenosis Treatment (OBSERVANT),[12] in which the TAVR cohort had inferior midterm survival compared with the SAVR cohort. However, OBSERVANT gathered data from 2010 to 2012 with limited operator experience and using only second-generation TAVR devices.[12] The higher rate of significant paravalvular regurgitation might have been negatively associated with long-term outcomes observed in OBSERVANT, a phenomenon well documented in other studies.[3,4,23] Indications for TAVR expanded to include low-risk patients only in recent years; therefore, 86.5% of low-risk patients in the FinnValve registry who underwent TAVR received third-generation TAVR devices and were treated by more experienced operators. Minimal-risk patients in the TAVIK registry[20] had a lower 2-year survival after TAVR (90.9%) compared with SAVR (95.7%; $P = .001$), a difference that was likely associated with older age in the TAVR cohort. The NOTION trial randomized mainly low-risk patients (mean STS-PROM score, 3%; mean EuroSCORE II score, 2%) to receive TAVR or SAVR and demonstrated similar survival rates at 6 years (57.5% vs 62.3%), despite a 15% rate of moderate aortic regurgitation in the TAVR arm.[9,10]

To our knowledge, this study is one of few providing 3-year follow-up survival after TAVR and SAVR in low-risk patients with AS. Numerically higher 30-day mortality was observed after SAVR in the overall (50 of 2516 patients [2.0%]) and matched (11 of 304 patients [3.6%]) populations. It is worth noting that 30-day mortality after TAVR was lower than predicted by the STS-PROM and EuroSCORE II scores in the overall (4 of 325 patients [1.2%]) and matched (4 of 304 patients [1.3%]) populations. The same was not observed in the SAVR cohort. These findings are similar to those of previous studies in low-risk populations, which reported in-hospital 30-day mortality of 1% to 2% in both TAVR and SAVR populations.[11,20,24] A 2018 study by Waksman et al[11] found no mortality at 30 days among low-risk patients who underwent TAVR. However, the study by Waksman et al[11] consisted of patients much younger than other studies. Overall, current data suggest that very low operative mortality can be expected when treating low-risk patients older than 70 years with TAVR or SAVR techniques. Indeed, in the 2019 Placement of Aortic Transcatheter Valves (PARTNER) 3 trial,[8] 30-day mortality was 0.5% after TAVR and 1.3% after SAVR, and in the Evolut Low Risk trial,[7] 30-day mortality was 0.4% after TAVR and 1.1% after SAVR.

Nearly half of patients treated for AS have concomitant CAD.[25] In our study of selected low-risk patients, less than 1 of 5 patients had significant CAD. The prevalence of CAD and history of percutaneous coronary intervention were comparable in the study cohorts. However, only 15% of patients with CAD undergoing TAVR underwent any planned coronary revascularization, while 93% of patients with CAD undergoing SAVR underwent a concomitant revascularization. This reflects the contemporary practice of accomplishing revascularization concomitantly with SAVR if CAD is detected by a preoperative coronary angiography, as supported by the 2017 European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines[26] and the 2014 American Heart Association and American College of Cardiology guideline.[27] Patients undergoing combined SAVR and coronary surgery procedures are potentially exposed to a higher risk of early mortality, most likely owing to CAD itself as well as to prolonged intraoperative myocardial ischemia. In these patients, cardiac surgeons are prone to perform coronary artery bypass grafting and administer antegrade cardioplegia through vein grafts to avoid suboptimal myocardial protection during prolonged cardiopulmonary bypass and to decrease the risk of possible ischemic complications early after SAVR. The risk of myocardial ischemia is lower after TAVR because of the minimally invasive nature of this treatment, which does not require the use of cardiac arrest during cardiopulmonary bypass. It is worth noting that leaving CAD untreated during SAVR impairs long-term survival regardless of the severity of CAD.[28] In the present study, we observed that concomitant

CAD was associated with worse outcomes in patients undergoing SAVR (eTable in the Supplement). It is also possible that increased operative mortality in the SAVR cohort was partly owing to a higher proportion of combined procedures, although the revascularization rate was performed in only 16% of the matched patients in the SAVR cohort. The association of concomitant CAD with long-term mortality after TAVR is controversial,[25,29] and the indication of percutaneous coronary intervention prior to or during TAVR is commonly discussed before valve intervention. The severity of CAD and success of revascularization may have a role in survival after TAVR, and these components have to be considered during decision making.[30] Interpreting the results of studies about AS and coexisting CAD becomes more difficult when considering the hemodynamic severity of CAD,[31,32] and hopefully the ongoing Percutaneous Coronary Intervention Prior to Transcatheter Aortic Valve Implantation ACTIVATION (ISRCTN75836930) and NOTION-3 (NCT03058627) trials will provide conclusive data on the potential benefits of percutaneous coronary intervention during TAVR.

The distribution of periprocedural complications in our study was typical compared with another low-risk study by Witberg et al.[33] Bleeding and atrial fibrillation were less frequent in the TAVR cohort, and less vascular complications and new permanent pacemaker implantations were observed in the SAVR cohort. Higher rates of acute kidney injury and stroke were observed after SAVR, but severe intraprocedural complications were infrequent. Major bleeding events were significantly higher in the SAVR cohort than the TAVR cohort.

Limitations

The main limitation of this study is its retrospective nature. Second, the definition of low risk was based on a cutoff value of 3% for operative mortality as estimated by the STS-PROM scoring system and by excluding patients deemed at increased risk because of significant comorbidities. Despite these inclusion criteria, it is possible that some patients included or excluded from this analysis were incorrectly classified. Third, comparative analysis of the study cohorts was based on propensity score matching, and its results are potentially biased by unmeasured confounders despite well-balanced covariates. Fourth, the relatively small size of the matched study cohorts may affect the reliability of these results. Fifth, the limited length of follow-up of patients with low operative risk prevented more conclusive results on the durability of TAVR in this patient population.

Conclusions

This nationwide registry analysis found that TAVR using mostly third-generation devices achieved similar early and intermediate survival compared with SAVR in low-risk patients. Before extending the use of TAVR to low-risk patients, further studies are needed to assess the long-term durability of transcatheter aortic valve prostheses.

ARTICLE INFORMATION

Accepted for Publication: April 25, 2019.

Published: June 14, 2019. doi:10.1001/jamanetworkopen.2019.5742

Correction: This article was corrected on July 12, 2019, to fix a typographical error in the Key Points and transposed 3-year survival rates for the propensity score–matched cohorts in the Results section.

Corresponding Author: Fausto Biancari, MD, PhD, Heart Center, Turku University Hospital, PO Box 52, 20521 Turku, Finland (faustobiancari@yahoo.it).

Author Affiliations: Heart Hospital, Tampere University Hospital, Faculty of Medicine and Health Technology, Tampere, Finland (Virtanen, Eskola, Maaranen); Heart Center, Turku University Hospital, Turku, Finland (Jalava, Jaakkola, Vasankari, Airaksinen, Anttila, Savontaus, Biancari); Heart Center, Kuopio University Hospital, Kuopio, Finland (Husso, Valtola); Heart Center, Helsinki University Hospital, Helsinki, Finland (Laakso, Kinnunen,

Dahlbacka, Juvonen, Laine, Raivio); Department of Internal Medicine, Oulu University Hospital, Oulu, Finland (Niemelä, Mäkikallio); Department of Surgery, Oulu University Hospital, University of Oulu, Oulu, Finland (Ahvenvaara, Tauriainen, Biancari); National Centre of Global Health, Istituto Superiore di Sanità, Rome, Italy (Rosato, D'Errigo); Department of Surgery, University of Turku, Turku, Finland (Biancari).

Author Contributions: Dr Biancari had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Virtanen, Eskola, Husso, Niemelä, Ahvenvaara, Kinnunen, Vasankari, Airaksinen, Anttila, Juvonen, Laine, Mäkikallio, Valtola, Raivio, Biancari.

Acquisition, analysis, or interpretation of data: Virtanen, Jalava, Laakso, Niemelä, Tauriainen, Maaranen, Kinnunen, Dahlbacka, Jaakkola, Airaksinen, Rosato, D'Errigo, Savontaus, Mäkikallio, Valtola, Raivio, Biancari.

Drafting of the manuscript: Virtanen, Jalava, Husso, Ahvenvaara, Anttila, Rosato, Juvonen, Mäkikallio, Biancari.

Critical revision of the manuscript for important intellectual content: Virtanen, Eskola, Jalava, Laakso, Niemelä, Ahvenvaara, Tauriainen, Maaranen, Kinnunen, Dahlbacka, Jaakkola, Vasankari, Airaksinen, Anttila, D'Errigo, Savontaus, Laine, Mäkikallio, Valtola, Raivio, Biancari.

Statistical analysis: Virtanen, Rosato, D'Errigo, Mäkikallio, Biancari.

Administrative, technical, or material support: Jalava, Husso, Vasankari, Airaksinen, Anttila, Savontaus, Juvonen, Laine, Valtola, Raivio.

Supervision: Eskola, Airaksinen, Anttila, Valtola, Raivio, Biancari.

Conflict of Interest Disclosures: Dr Airaksinen reported receiving grants from Finnish Foundation for Cardiovascular Research outside the submitted work. Dr Savontaus reported receiving personal fees from Medtronic and Boston Scientific during the conduct of the study. Dr Juvonen reported receiving grants from the Finnish Foundation for Cardiovascular research outside the submitted work. Dr Laine reported receiving personal fees from Boston Scientific during the conduct of the study. No other disclosures were reported.

REFERENCES

1. Gleason TG, Reardon MJ, Popma JJ, et al; CoreValve U.S. Pivotal High Risk Trial Clinical Investigators. 5-Year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol*. 2018;72(22):2687-2696. doi:10.1016/j.jacc.2018.08.2146

2. Smith CR, Leon MB, Mack MJ, et al; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364(23):2187-2198. doi:10.1056/NEJMoa1103510

3. Mack MJ, Leon MB, Smith CR, et al; PARTNER 1 trial investigators. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385(9986):2477-2484. doi:10.1016/S0140-6736(15)60308-7

4. Leon MB, Smith CR, Mack MJ, et al; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374(17):1609-1620. doi:10.1056/NEJMoa1514616

5. Reardon MJ, Van Mieghem NM, Popma JJ, et al; SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376(14):1321-1331. doi:10.1056/NEJMoa1700456

6. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet*. 2016;387(10034):2218-2225. doi:10.1016/S0140-6736(16)30073-3

7. Popma JJ, Deeb GM, Yakubov SJ, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380(18):1706-1715. doi:10.1056/NEJMoa1816885

8. Mack MJ, Leon MB, Thourani VH, et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380(18):1695-1705. doi:10.1056/NEJMoa1814052

9. Thyregod HGH, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol*. 2015;65(20):2184-2194. doi:10.1016/j.jacc.2015.03.014

10. Søndergaard L, Ihlemann N, Capodanno D, et al. Durability of transcatheter and surgical bioprosthetic aortic valves in patients at lower surgical risk. *J Am Coll Cardiol*. 2019;73(5):546-553. doi:10.1016/j.jacc.2018.10.083

11. Waksman R, Rogers T, Torguson R, et al. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2018;72(18):2095-2105. doi:10.1016/j.jacc.2018.08.1033

12. Rosato S, Santini F, Barbanti M, et al; OBSERVANT Research Group. Transcatheter aortic valve implantation compared with surgical aortic valve replacement in low-risk patients. *Circ Cardiovasc Interv*. 2016;9(5):e003326. doi:10.1161/CIRCINTERVENTIONS.115.003326

13. Society of Thoracic Surgeons. STS short-term risk calculator. https://www.sts.org/resources/risk-calculator. Accessed May 7, 2019.

14. Nashef SAM, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41(4):734-744. doi:10.1093/ejcts/ezs043

15. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hébert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. *Lancet*. 1999;353(9148):205-206. doi:10.1016/S0140-6736(98)04402-X

16. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J*. 2012;33(19):2403-2418. doi:10.1093/eurheartj/ehs255

17. Biancari F, Ruggieri VG, Perrotti A, et al. European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG registry): study protocol for a prospective clinical registry and proposal of classification of postoperative complications. *J Cardiothorac Surg*. 2015;10:90. doi:10.1186/s13019-015-0292-z

18. Acute Kidney Injury Work Group. Section 2: AKI definition. *Kidney Int Suppl*. 2012;2:19-36. doi:10.1038/kisup.2011.32

19. Wang SV, He M, Jin Y, et al. A review of the performance of different methods for propensity score matched subgroup analyses and a summary of their application in peer-reviewed research studies. *Pharmacoepidemiol Drug Saf*. 2017;26(12):1507-1512. doi:10.1002/pds.4328

20. Schymik G, Varsami C, Bramlage P, et al. Two-year outcomes of transcatheter compared with surgical aortic valve replacement in "minimal-risk" patients lacking EuroSCORE co-morbidities (from the TAVIK registry). *Am J Cardiol*. 2018;122(1):149-155. doi:10.1016/j.amjcard.2018.02.053

21. Serruys PW, Modolo R, Reardon M, et al. One-year outcomes of patients with severe aortic stenosis and an STS PROM of less than three percent in the SURTAVI trial. *EuroIntervention*. 2018;14(8):877-883. doi:10.4244/EIJ-D-18-00460

22. De Backer O, Luk NHV, Olsen NT, Olsen PS, Søndergaard L. Choice of treatment for aortic valve stenosis in the era of transcatheter aortic valve replacement in Eastern Denmark (2005 to 2015). *JACC Cardiovasc Interv*. 2016;9(11):1152-1158. doi:10.1016/j.jcin.2016.02.028

23. Généreux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel: a comprehensive review of the literature. *J Am Coll Cardiol*. 2013;61(11):1125-1136. doi:10.1016/j.jacc.2012.08.1039

24. Frerker C, Bestehorn K, Schlüter M, et al. In-hospital mortality in propensity-score matched low-risk patients undergoing routine isolated surgical or transfemoral transcatheter aortic valve replacement in 2014 in Germany. *Clin Res Cardiol*. 2017;106(8):610-617. doi:10.1007/s00392-017-1097-y

25. Snow TM, Ludman P, Banya W, et al. Management of concomitant coronary artery disease in patients undergoing transcatheter aortic valve implantation: the United Kingdom TAVI Registry. *Int J Cardiol*. 2015;199:253-260. doi:10.1016/j.ijcard.2015.06.166

26. Baumgartner H, Falk V, Bax JJ, et al; ESC Scientific Document Group. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38(36):2739-2791. doi:10.1093/eurheartj/ehx391

27. Nishimura RA, Otto CM, Bonow RO, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(23):e521-e643. doi:10.1161/CIR.0000000000000031

28. Thalji NM, Suri RM, Daly RC, et al. The prognostic impact of concomitant coronary artery bypass grafting during aortic valve surgery: implications for revascularization in the transcatheter era. *J Thorac Cardiovasc Surg*. 2015;149(2):451-460. doi:10.1016/j.jtcvs.2014.08.073

29. Sankaramangalam K, Banerjee K, Kandregula K, et al. Impact of coronary artery disease on 30-day and 1-year mortality in patients undergoing transcatheter aortic valve replacement: a meta-analysis. *J Am Heart Assoc*. 2017;6(10):e006092. doi:10.1161/JAHA.117.006092

30. Witberg G, Regev E, Chen S, et al. The prognostic effects of coronary disease severity and completeness of revascularization on mortality in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10(14):1428-1435. doi:10.1016/j.jcin.2017.04.035

31. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010; 55(25):2816-2821. doi:10.1016/j.jacc.2009.11.096

32. Di Gioia G, Scarsini R, Strisciuglio T, et al. Correlation between angiographic and physiologic evaluation of coronary artery narrowings in patients with aortic valve stenosis. *Am J Cardiol*. 2017;120(1):106-110. doi:10.1016/j.amjcard.2017.03.250

33. Witberg G, Lador A, Yahav D, Kornowski R. Transcatheter versus surgical aortic valve replacement in patients at low surgical risk: a meta-analysis of randomized trials and propensity score matched observational studies. *Catheter Cardiovasc Interv*. 2018;92(2):408-416. doi:10.1002/ccd.27518

SUPPLEMENT.

eFigure. Study Flowchart

eTable. Interaction Tests for Intermediate Mortality in Subgroups of Low-Risk Patients Undergoing Transcatheter or Surgical Aortic Valve Replacement

Supplementary Online Content

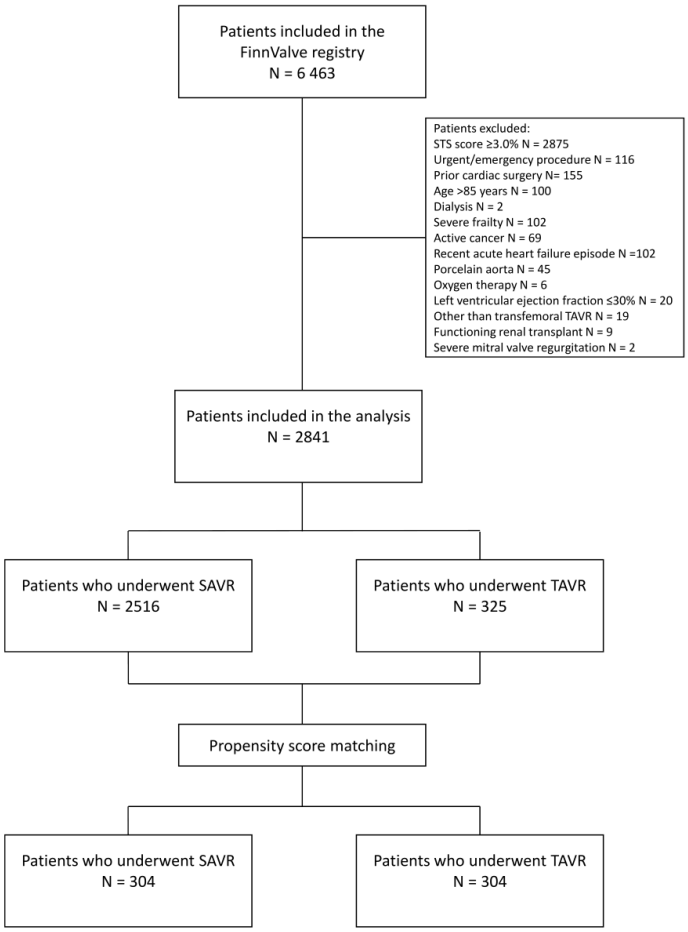
Virtanen MPO, Eskola M, Jalava MP, et al. Comparison of outcomes after transcatheter aortic valve replacement vs surgical aortic valve replacement among patients with aortic stenosis at low operative risk. *JAMA Netw Open*. 2019;2(6):e195742. doi:10.1001/jamanetworkopen.2019.5742

eFigure. Study Flowchart

eTable. Interaction Tests for Intermediate Mortality in Subgroups of Low-Risk Patients Undergoing Transcatheter or Surgical Aortic Valve Replacement

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Study Flowchart



eTable. Interaction Tests for Intermediate Mortality in Subgroups of Low-Risk Patients Undergoing Transcatheter or Surgical Aortic Valve Replacement

	Covariates	SAVR No. of pts	TAVR No. of pts	Hazard ratio	95% confidence interval		Interaction p-value
SAVR vs. TAVR	Overall	304	304	1.393	0.784	2.472	
SAVR vs. TAVR	Coronary artery disease	57	57	3.242	0.736	14.273	0.078
SAVR vs. TAVR	No coronary artery disease	247	247	0.753	0.385	1.473	
SAVR vs. TAVR	Age ≥80 years	143	142	1.502	0.608	3.713	0.234
SAVR vs. TAVR	Age <80 years	161	162	0.64	0.217	1.887	
SAVR vs. TAVR	Other than selected prostheses	154	41	0.492	0.135	1.783	0.264
SAVR vs. TAVR	Selected prostheses	150	263	1.138	0.559	2.316	

SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

PUBLICATION
II

Comparison of Survival of Transfemoral Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement for Aortic Stenosis in Low-Risk Patients Without Coronary Artery Disease.

Virtanen MPO, Airaksinen J, Niemelä M, Laakso T, Husso A, Jalava MP, Tauriainen T, Maaranen P, Kinnunen EM, Dahlbacka S, Rosato S, Savontaus M, Juvonen T, Laine M, Mäkikallio T, Valtola A, Raivio P, Eskola M, Biancari F.

Am J Cardiol 2020;125(4):589-596. doi:10.1016/j.amjcard.2019.11.002.

Comparison of Survival of Transfemoral Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement for Aortic Stenosis in Low-Risk Patients Without Coronary Artery Disease

Marko P.O. Virtanen, MD[a], Juhani Airaksinen, MD, PhD[b], Matti Niemelä, MD, PhD[c], Teemu Laakso, MD[d], Annastiina Husso, MD, PhD[e], Maina P. Jalava, MD[b], Tuomas Tauriainen, MD, PhD[f], Pasi Maaranen, MD[a], Eeva-Maija Kinnunen, MD, PhD[d], Sebastian Dahlbacka, MD, PhD[d], Stefano Rosato, MSc[g], Mikko Savontaus, MD, PhD[b], Tatu Juvonen, MD, PhD[d], Mika Laine, MD, PhD[d], Timo Mäkikallio, MD, PhD[c], Antti Valtola, MD, PhD[e], Peter Raivio, MD, PhD[d], Markku Eskola, MD, PhD[a], and Fausto Biancari, MD, PhD[b,f,*]

Increasing data support transcatheter aortic valve implantation (TAVI) as a valid option over surgical aortic valve replacement (SAVR) in the treatment for severe aortic stenosis (AS) also in patients with low operative risk. However, limited data exist on the outcome of TAVI and SAVR in low-risk patients without coronary artery disease (CAD). The FinnValve registry included data on 6463 patients who underwent TAVI or SAVR with bioprosthesis between 2008 and 2017. Herein, we evaluated the outcome of low operative risk as defined by STS-PROM score <3% and absence of CAD, previous stroke and other relevant co-morbidities. Only patients who underwent TAVI with third-generation prostheses and SAVR with Perimount Magna Ease or Trifecta prostheses were included in this analysis. The primary endpoints were 30-day and 3-year all-cause mortality. Overall, 1,006 patients (175 TAVI patients and 831 SAVR patients) met the inclusion criteria of this analysis. Propensity score matching resulted in 140 pairs with similar baseline characteristics. Among these matched pairs, 30-day mortality was 2.1% in both TAVI and SAVR cohorts (p = 1.00) and 3-year mortality was 17.0% after TAVI and 14.6% after SAVR (p = 0.805). Lower rates of bleeding and atrial fibrillation, and shorter hospital stay were observed after TAVI. The need of new permanent pacemaker implantation and the incidence of early stroke did not differ between groups. In conclusion, TAVI using third-generation prostheses achieved similar early and mid-term survival compared with SAVR in low-risk patients without CAD. **(Am J Cardiol 2020;125:589−596)**

After the first-in-man transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS),[1] this treatment method has proven to be a valid alternative to surgical aortic valve replacement (SAVR) in intermediate- and high-risk AS patients.[2−5] Based on the results of recent trials,[6−8] the indication of TAVI has been expanded to low-risk patients. However, data on the long-term outcomes in these low-risk patients are still limited, particularly in those without coronary artery disease (CAD). Indeed, the prevalence of CAD is higher than 60% in intermediate-risk AS patients, whereas up to 28% of low-risk patients has concomitant CAD.[4−7,9] CAD may negatively affect the outcome after TAVI and SAVR,[10−13] and it may be a major confounding factor in the analysis of the benefits and risks of TAVI and SAVR. Still, only a few studies compared these treatment methods in patients without significant CAD.[14,15] This issue has been investigated in the present nationwide study.

Methods

The FinnValve registry is a nationwide study (ClinicalTrials.gov Identifier: NCT03385915), which includes data on consecutive and unselected patients who underwent TAVI or SAVR for severe AS, between January 2008 and October 2017, at all 5 Finnish University Hospitals. The

[a]Heart Hospital, Tampere University Hospital and Faculty of Medicine and Health Technology, University of Tampere, Tampere, Finland; [b]Heart Center, Turku University Hospital and Department of Surgery, University of Turku, Turku, Finland; [c]Department of Internal Medicine, Oulu University Hospital, Oulu, Finland; [d]Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland; [e]Heart Center, Kuopio University Hospital, Kuopio, Finland; [f]Department of Surgery, Oulu University Hospital and Research Unit of Surgery, Anesthesia and Intensive Care, Faculty of Medicine, University of Oulu, Oulu, Finland; and [g]National Centre of Global Health, Istituto Superiore di Sanità, Rome, Italy. Manuscript received September 23, 2019; revised manuscript received and accepted November 5, 2019.

Sources of funding and support: This study was not supported by any external funding.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT03385915.

See page 594 for disclosure information.

*Corresponding author: Tel: 358407333973.

E-mail address: faustobiancari@yahoo.it (F. Biancari).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.11.002

study protocol was approved by the Institutional Review Boards of all participating centers. The FinnValve registry included data on patients who underwent primary TAVI or SAVR for AS with or without coronary revascularization. Data were collected retrospectively into a dedicated electronic case report form by physicians and trained research nurses. Data on mortality were obtained from the Finnish Population Register Centre and data on cardiovascular interventions were retrieved from the registry of the Finnish National Institute for Health and Welfare. Follow-up was considered complete for all patients, but for those not residing in Finland whose follow-up was truncated at the time of hospital discharge. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[16]

This analysis included patients with low operative risk (Figure 1), which was defined as a Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) <3% along with the following exclusion criteria: age >85 years, CAD, previous coronary revascularization, previous cardiac surgery, stroke, estimated glomerular filtration rate <30 mL/min/m^2, dialysis, functioning renal transplant, severe frailty, active malignancy, critical preoperative state, acute heart failure within 60 days from the index procedure, porcelain aorta, oxygen therapy, left ventricular ejection fraction ≤30%, severe mitral valve regurgitation, nontransfemoral access for TAVI, and urgent/emergency procedure. The analysis was limited to third-generation TAVI prostheses (Sapien 3, Evolut R, Acurate Neo, Lotus) and SAVR pericardial prostheses (Perimount Magna Ease and Trifecta) in order to avoid any

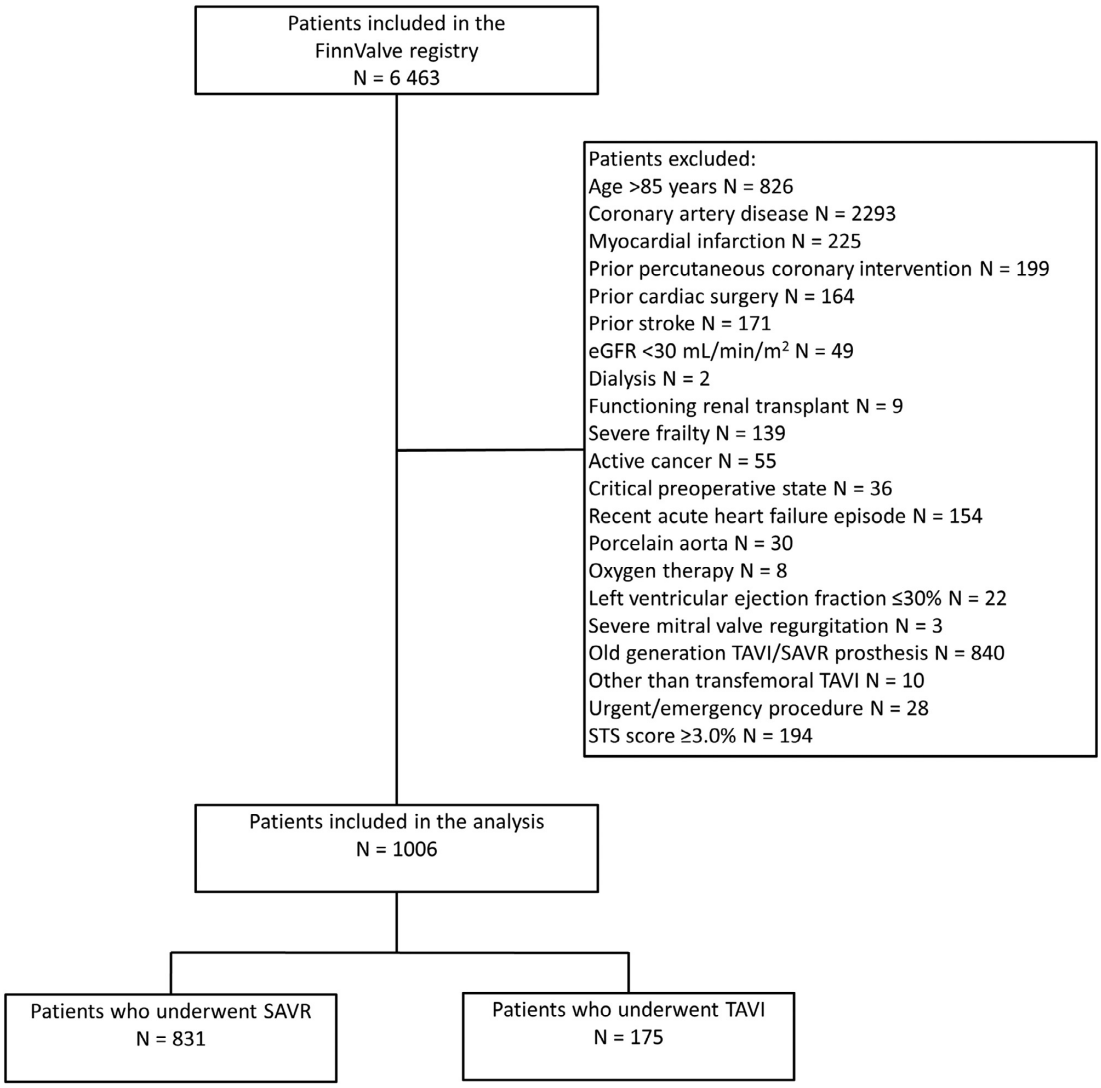


Figure 1. Study flow-chart.

potential bias related to previous generation valve technology. CAD was defined as a stenosis of 50% or more in at least one of the main coronary arteries. Severe frailty was defined as Geriatric Status Scale 2 to 3 (GCS).[17] Baseline variables were defined according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II criteria.[18]

The primary outcomes of this study were 30-day and 3-year all-cause mortality. Secondary early outcomes were stroke, transfusion, reoperation for bleeding, paravalvular regurgitation, new permanent pacemaker implantation (PPI), acute kidney injury (AKI), new dialysis, conversion to cardiac surgery, coronary artery occlusion, aortic dissection/rupture, major vascular complication, atrial fibrillation, and postoperative length of stay in the hospital where the index procedure was performed. Late secondary outcomes were repeat operation on the aortic valve prosthesis, prosthetic valve endocarditis, coronary revascularization, and new PPI.

VARC-2 criteria[19] were applied for stroke, major vascular complication, and perioperative bleeding. Severe bleeding was also defined according to European Coronary Artery Bypass Grafting (E-CABG) bleeding scores 2 to 3, that is transfusion of more than 4 units of red blood cells and/or reoperation for mediastinal and/or peripheral bleeding.[20] AKI was defined according to the KDIGO criteria.[21]

Statistical analyses were performed using Stata v. 15.1 (StataCorp LLC, Texas) and SPSS v. 25.0 (IBM Corporation, New York) statistical softwares. Continuous variables are reported as means and standard deviations. Categorical variables are summarized as counts and percentages. The Mann-Whitney, Fisher's and Chi-square tests were used for univariate analysis in the unmatched population. A propensity score was estimated using a nonparsimonious logistic regression model including the following covariates: Age, gender, body mass index, hemoglobin, estimated glomerular filtration rate, diabetes, pulmonary disease, extracardiac arteriopathy, New York Heart Association class 4 symptoms, left ventricular ejection fraction ≤50%, atrial fibrillation, systolic pulmonary artery pressure, mitral valve regurgitation, and previous pacemaker.

One-to-one propensity score matching was performed using the psmatch2 Stata module with a caliper width of 0.01. Standardized differences lower than 0.10 were considered for adequate balance between the study cohorts. The paired *t* test, the McNemar test, and the Fleiss-Everitt test were used to assess the differences between preoperative variables and the early outcomes in the propensity score matched pairs. Differences in late mortality were evaluated by the Kaplan-Meier method with the log-rank test. Competing risk analysis with the Fine-Gray's test was performed for late nonfatal adverse events because patient's death might have hindered the observation of these events. Statistical significance was set at $p < 0.05$.

Results

Of 6,463 patients included in the FinnValve registry, 1,006 patients (mean age, 73.1 ± 7.0 years; female gender, 53%) fulfilled the inclusion criteria of the current analysis (Figure 1). TAVI was performed in 175 patients and SAVR in 831 patients. The mean follow-up of this series was 3.7 ± 2.0 years (TAVI cohort, 2.2 ± 0.9 years; SAVR cohort 4.0 ± 2.0 years).

The baseline characteristics of the unmatched cohorts are presented in Table 1. Thirty-day mortality was 1.7% in TAVI and 1.6% in SAVR ($p = 0.885$). Other early outcomes of the unmatched cohorts are presented in Table 2. Three-year all-cause mortality was higher after TAVI (16.6%) compared with SAVR (6.8%) ($p = 0.003$; Table 3).

The propensity score matching resulted in 140 pairs. These cohorts had balanced baseline covariates except for hemoglobin and systolic pulmonary pressure whose standardized differences were slightly over 0.1, without reaching statistically significance in paired tests (Table 1). The mean age of the patients was 76.5 ± 6.8 in the TAVI cohort and 76.9 ± 4.7 in the SAVR cohort ($p = 0.458$). The predicted risk of operative mortality according to EuroSCORE II and STS score was similar between TAVI and SAVR. In the TAVI group, 62% of the patients received a balloon expandable prosthesis, 21% a self-expanding prosthesis, and 16% a mechanically expandable prosthesis. In the surgical group, the Perimount Magna Ease bioprosthesis was implanted in 59% of the patients and the Trifecta bioprosthesis in the others.

Three patients (2.1%) died in both cohorts at 30 days after the procedure (Table 2). The late all-cause mortality was not different between the TAVI and SAVR cohorts (1-year: 5.0% for both; 2-year: 8.2% vs 8.7%; 3-year: 17.0% vs 14.6%, $p = 0.805$, respectively) (Table 3, Figure 2).

Three patients (2.1%) in both cohorts suffered stroke immediately after the procedure. Major vascular complication occurred in 7.9% of TAVI patients and in 0.7% SAVR patients ($p = 0.006$). Similar rates of paravalvular regurgitation were observed in the study cohorts. Atrial fibrillation, bleeding, and red blood cell transfusion were more frequent in the SAVR cohort (Table 2). Patients treated with TAVI had shorter hospital stay compared with the surgical cohort (3.7 ± 3.4 days after TAVI and 7.5 ± 3.4 days after SAVR; $p < 0.0001$). No statistically significant differences were observed in terms of AKI (Table 2). A new PPI was needed immediately after the procedure in 13 patients after TAVI (9.8%) and in 8 patients after SAVR (6.1%) ($p = 0.481$). The rate of new PPI was numerically higher in the TAVI cohort compared with the SAVR cohort during follow-up, but the difference did not reach statistical significance (Table 3). Coronary revascularization and repeat aortic valve replacement were rare in these cohorts. No prosthetic valve endocarditis was observed in this series (Table 3).

Discussion

Our study group has previously reported similar results after TAVI and SAVR in patients with low operative risk from the nationwide FinnValve registry.[22] In the present study, we report on updated survival along with prostheses-related adverse events of patients without CAD and other significant co-morbidities who underwent isolated TAVI and SAVR. This selected patient population is expected to provide unbiased information on TAVI and SAVR device-related events, because the outcomes of interest are less

Table 1
Characteristics of unmatched and propensity score matched patients

Variable	Unmatched cohorts				Propensity score matched cohorts			
	TAVI (n = 175)	SAVR (n = 831)	Standardized difference	p-value	TAVI (n = 140)	SAVR (n = 140)	Standardized difference	p Value
Age (years)	77.4 ± 6.4	72.2 ± 6.8	0.790	<0.0001	76.5 ± 6.8	76.9 ± 4.7	0.068	0.458
Women	101 (57.7%)	431 (51.9%)	0.117	0.159	79 (56.4%)	75 (53.6%)	0.057	0.731
Body mass index (kg/m^2)	29 ± 5	28 ± 5	0.151	0.114	29 ± 5	29 ± 5	0.073	0.555
Hemoglobin (mg/L)	130 ± 16	135 ± 13	0.370	<0.0001	130 ± 16	129 ± 14	0.113	0.364
Estimated glomerular filtration rate (mL/min/1.73m^2)	75 ± 21	80 ± 19	0.261	0.001	75 ± 21	74 ± 20	0.038	0.764
Diabetes mellitus	46 (26.3%)	170 (20.5%)	0.138	0.088	35 (25.0%)	37 (26.4%)	0.033	0.883
Pulmonary disease	30 (17.1%)	90 (10.8%)	0.183	0.019	22 (15.7%)	26 (18.6%)	0.076	0.643
Extracardiac arteriopathy	13 (7.4%)	46 (5.5%)	0.077	0.333	11 (7.9%)	10 (7.1%)	0.027	1.000
Ejection fraction ≤50%	29 (16.7%)	88 (10.6%)	0.178	0.023	19 (13.6%)	21 (15.0%)	0.048	0.860
Atrial fibrillation	63 (36.0%)	139 (16.7%)	0.448	<0.0001	47 (33.6%)	46 (32.9%)	0.015	1.000
New York Heart Association Class 4	1 (0.6%)	5 (0.6%)	0.004	1.000	1 (0.7%)	2 (1.4%)	0.069	1.000
Systolic pulmonary artery pressure (mmHg)			0.089	0.519			0.166	0.933
31-55	58 (33.1%)	286 (34.4%)			45 (32.1%)	39 (27.9%)		
>55	9 (5.1%)	28 (3.4%)			6 (4.3%)	11 (7.9%)		
Mitral regurgitation			0.437	<0.0001			0.047	0.944
Mild	54 (33.3%)	174 (21.9%)			46 (32.9%)	43 (30.7%)		
Moderate	14 (8.6%)	15 (1.9%)			7 (5.0%)	7 (5.0%)		
Prior permanent pace-maker	12 (6.9%)	30 (3.6%)	0.146	0.051	7 (5.0%)	8 (5.7%)	0.032	1.000
European System for Cardiac Operative Risk Evaluation II (%)	2.3 ± 1.0	1.6 ± 0.8	0.717	<0.0001	2.1 ± 0.9	2.1 ± 1.1	0.020	0.398
Society of Thoracic Surgeons score (%)	2.1 ± 0.6	1.6 ± 0.6	0.832	<0.0001	2.0 ± 0.6	2.0 ± 0.6	0.089	0.845

SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation. Values are number (%) or mean ± standard deviation.

Table 2
Early outcomes of unmatched and propensity score matched patients

Variable	Unmatched cohorts			Propensity score matched pairs		
	TAVI (n = 175)	SAVR (n = 831)	p Value	TAVI (n = 140)	SAVR (n = 140)	p Value
30-day death	3 (1.7%)	13 (1.6%)	0.885	3 (2.1%)	3 (2.1%)	1.000
Stroke	4 (2.3%)	20 (2.4%)	1.000	3 (2.1%)	3 (2.1%)	1.000
Conversion to cardiac surgery	2 (1.1%)	-	-	2 (1.4%)	-	-
Deep sternal wound infection/mediastinitis	0	11 (1.3%)	0.228	0	2 (1.4%)	0.500
Coronary revascularization	0	6 (0.7%)	0.597	0	1 (0.7%)	1.000
Coronary ostium occlusion	0	3 (0.4%)	1.000	0	1 (0.7%)	1.000
Aortic dissection/rupture	1 (0.1%)	4 (0.5%)	1.000	1 (0.7%)	0	1.000
Major vascular complication	15 (8.6%)	7 (0.7%)	<0.0001	11 (7.9%)	1 (0.7%)	0.006
Red blood cell transfusion	17 (9.9%)	439 (53.9%)	<0.0001	13 (9.6%)	94 (69.1%)	<0.0001
Red blood cell transfusion (units)	0.4 ± 1.7	1.7 ± 2.5	<0.0001	0.4 ± 1.8	2.3 ± 2.7	<0.0001
Red blood cell transfusion >4 units	3 (1.8%)	84 (10.3%)	<0.0001	3 (2.2%)	19 (14.0%)	<0.0001
Resternotomy/thoracotomy for bleeding	2 (1.1%)	65 (7.8%)	<0.0001	2 (1.4%)	11 (7.9%)	0.022
E-CABG bleeding grades 2-3*	9 (5.3%)	110 (13.5%)	0.003	7 (5.1%)	23 (16.9%)	0.002
VARC-2 bleeding			<0.0001			<0.0001
Major bleeding	36 (20.8%)	360 (43.3%)		27 (19.6%)	68 (48.6%)	
Life-threatening or disabling	9 (5.2%)	415 (49.9%)		7 (5.1%)	59 (42.1%)	
Acute kidney injury grades 2-3	4 (2.3%)	31 (3.8%)	0.494	4 (2.9%)	7 (5.0%)	0.549
New renal replacement therapy	0	11 (1.3%)	0.228	0	3 (2.1%)	0.250
Paravalvular regurgitation			<0.0001			0.431
Mild	16 (9.1%)	46 (5.5%)		13 (9.3%)	9 (6.4%)	
Moderate	5 (2.9%)	1 (0.1%)		3 (2.1%)	1 (0.7%)	
Severe	0	1 (0.1%)		0	0	
Atrial fibrillation	56 (32.0%)	430 (51.7%)	<0.0001	43 (30.7%)	82 (58.6%)	<0.0001
Permanent pacemaker,†	16 (9.8%)	30 (3.7%)	0.001	13 (9.8%)	8 (6.1%)	0.481
Hospital stay (days)	3.8 ± 3.1	7.2 ± 4.3	<0.0001	3.7 ± 3.2	7.5 ± 3.4	<0.0001

E-CABG = European Coronary Artery Bypass Grafting study; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; VARC = Valve Academic Research Consortium.

* It includes also intervention for peripheral bleeding;

† It excludes patients with previous pacemaker implantation.

Values are number (%) or mean ± standard deviation.

Table 3
Late outcomes of unmatched and propensity score matched patients

Variable	Unmatched cohorts			Propensity score matched pairs		
	TAVI (n = 175)	SAVR (n = 831)	p Value	TAVI (n = 140)	SAVR (n = 140)	p Value
All-cause mortality			0.003			0.805
1-year	4.0%	3.4%		5.0%	5.0%	
2-year	8.6%	4.5%		8.2%	8.7%	
3-year	16.6%	6.8%		17.0%	14.6%	
Coronary revascularization			0.858			0.679
1-year	0.6%	1.1%		0.7%	0.7%	
2-year	0.6%	1.3%		0.7%	0.7%	
3-year	2.6%	1.5%		3.6%	1.7%	
Prosthetic valve endocarditis			-			-
1-year	0	0		0	0	
2-year	0	0		0	0	
3-year	0	0		0	0	
Repeat aortic valve replacement			-			-
1-year	0	0.2%		0	0.8%	
2-year	0	0.6%		0	0.8%	
3-year	0	0.8%		0	0.8%	
New pace-maker implantation			<0.0001			0.082
1-year	13.3%	4.1%		13.8%	6.2%	
2-year	15.4%	5.1%		14.6%	6.2%	
3-year	15.4%	6.0%		14.6%	9.3%	

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement. p-values are from Kaplan-Meier and competing risk analysis.

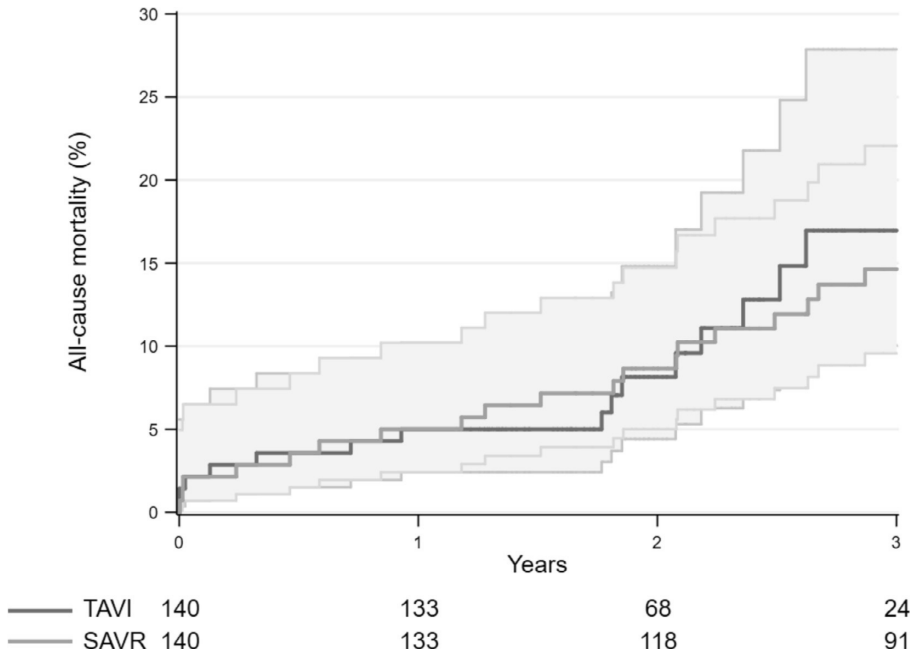


Figure 2. Kaplan-Meier estimate of survival in propensity score matched pairs of low-risk patients with severe aortic stenosis without coronary artery disease who underwent transcatheter (TAVI) or surgical aortic valve replacement (SAVR).

likely affected by other confounders such as CAD, depressed ventricular function, cerebrovascular disease, and renal failure. Indeed, our study cohort is somewhat similar to that of recent randomized controlled trials with low prevalence of atherosclerotic cardiovascular disease.[6,7] Furthermore, the inclusion of patients who received newest generations of TAVI and SAVR prostheses may prevent bias related to less recent valve technology.

The main findings of this study are: (1) 30-day and 3-year survival were similar after TAVI or SAVR; (2) TAVI was associated with shorter hospital stay, lower rates of bleeding and atrial fibrillation compared with SAVR, but major vascular complications were more frequent after TAVI than after SAVR; (3) no differences in the incidence of early stroke and new PPI was observed between these 2 treatment strategies; (4) the intermediate-term risk for aortic valve reoperation is very low after TAVI and SAVR.

Thirty-day mortality was similar in the study cohorts (2.1%). This means that despite its less invasive nature, TAVI was not safer than SAVR in these very low-risk patients. In the propensity score matched cohorts, 3-year survival was 83% after TAVI and 85.4% after SAVR, which demonstrates the clinical efficacy of both treatment methods at intermediate follow-up. Only patients who received most recent TAVI and SAVR prostheses were included in analysis, with low rates paravalvular regurgitation and structural valve deterioration.

Our results are balanced with those of previous studies.[8] Randomized trials including low-risk patients and using composite primary outcomes confirmed TAVI as noninferior treatment over SAVR.[6,7,14] Still there is no clear evidence of a survival benefit of TAVI over SAVR in low-risk populations.[23] Early mortality in our study (30-day: 2.1%, 1-year: 5.0%) was slightly higher than in the PARTNER 3[6] and the Evolut Low Risk Trial[7] (30-day: 0.4% to 0.5% for TAVI, 1.1% and 1.3% for SAVR; 1-year: 1.0% to 2.4% for TAVI, 2.5% to 3.0% for SAVR), but similar to the results of the NOTION trial[14] (30-day: 2.1% for TAVI, 3.7% for SAVR; 1-year: 4.9% for TAVI, 7.5% for SAVR). Such differences are likely related to different age profiles of the study cohorts. The outcome of low-risk patients (STS score <4%) undergoing isolated aortic valve procedure from the German Aortic Valve Registry (GARY) showed a significantly lower 30-day mortality of patients undergoing TAVI compared with SAVR (1.7% after transvascular TAVI vs 3.0% after SAVR, $p = 0.002$), whereas 1-year survival was similar with these treatment methods (90.4% after TAVI vs 91.2% after SAVR, $p = 0.368$).[15] Nonrandomized data are also available from the Low Risk Trial, which reported at 30-day nil mortality after TAVI and 1.7% mortality after SAVR ($p = 0.079$).[24] One-year survival rate was 97% in TAVI cohort.[25] However, the patients in the Low Risk Trial were younger compared with other studies (age 73.6 years, STS 1.8%). The longest follow-up of low-risk patients' outcome is available from the NOTION trial, which demonstrated a 5-year survival of about 72% in the TAVI and SAVR cohorts.[8]

Our results indicate that despite the low operative risk and the minimally invasive nature of TAVI, these patients are still exposed to a certain risk of early mortality and severe adverse events. Stroke, AKI stage 3, and severe bleeding were not infrequent after TAVI and might have had a negative impact on the longer-term survival after TAVI.[26,27] Importantly, the early outcome of patients who underwent TAVI was affected by a significantly higher rate of major vascular complications, whereas blood transfusion was required frequently after SAVR (Table 2). Such differences are due to the different nature of these treatment methods. In fact, the risk of vascular complications at the access site is the Achille's heel of TAVI, even in these low-risk patients. On the contrary, SAVR may increase the risk of exposure to blood products due to significant bleeding from the operative field and to the marked hemodilution occurring during cardiopulmonary bypass. In this study, almost 70% of SAVR patients received blood transfusion, which might be partly explained by a policy of liberal perioperative blood transfusion adopted in our country. Still only 14% of patients required transfusion of more than 4 units of red blood cell. The risk of stroke after TAVI has remained relatively stable during past years with a rate of 2.0% and 2.5% as shown in a large database.[28] The present study confirmed that such a risk of stroke exists also in low-risk patients, although previous studies reported on lower stroke rates.[6,7,14]

The risk of PPI was 9.8% after TAVI, which can be considered satisfactory considering that about 60% of TAVI devices were balloon-expandable prostheses.[29] The rate of new PPI after SAVR was 6.1% and remained relatively stable during 3-year follow-up (9.3%). On the contrary, the rate of new PPI after TAVI increased to 14.6% at 3-years ($p = 0.082$ for TAVI vs SAVR). Late coronary revascularization was rare in both the study cohorts and prosthetic valve endocarditis was not observed in this series.

The retrospective nature is the main limitation of this study. Second, the definition of low operative risk was based on STS score <3% and by excluding patients with significant co-morbidities. Still, it is possible that some patients were incorrectly classified. Third, comparative analysis of the study cohorts is based on propensity score matching and its results are potentially biased by unmeasured confounders. Fourth, the small size and limited follow-up of this series prevent conclusive results on the efficacy and durability of TAVI in this patient population.

In conclusion, TAVI or SAVR with the most recent prostheses achieve similar early and mid-term outcome in low-risk patients without CAD. Potentially life-threatening complications can be expected in very low-risk patients despite the minimally invasive nature of transfemoral TAVI.

Disclosures

Disclosure of potential conflicts of interest: Dr Mikko Savontaus is a proctor for Medtronic, the relationship is significant; Dr Mika Laine is a proctor for Boston Scientific, the relationship is significant. The other coauthors do not have any conflict of interest related to this study.

1. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 2002;106:3006–3008.

2. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2477–2484.
3. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, Kleiman NS, Chetcuti S, Hermiller JB, Heiser J, Merhi W, Zorn GL, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte JV, Mumtaz M, Oh JK, Huang J, Adams DH. 5-year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol* 2018;72:2687–2696.
4. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609–1620.
5. Reardon MJ, Mieghem NM Van, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PWJC, Kappetein AP. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376:1321–1331.
6. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–1705.
7. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL, Forrest JK, Tchétché D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380:1706–1715.
8. Thyregod HGH, Ihlemann N, Jørgensen TH, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrøm T, Clemmensen P, Hansen PB, Andersen LW, Steinbruüchel DA, Olsen PS, Søndergaard L. Five-year clinical and echocardiographic outcomes from the NOTION randomized clinical trial in patients at lower surgical risk. *Circulation* 2019;139:2714–2723.
9. Sankaramangalam K, Banerjee K, Kandregula K, Mohananey D, Parashar A, Jones BM, Jobanputra Y, Mick S, Krishnaswamy A, Svensson LG, Kapadia SR. Impact of coronary artery disease on 30-day and 1-year mortality in patients undergoing transcatheter aortic valve replacement: a meta-analysis. *J Am Heart Assoc* 2017;6:e006092.
10. Witberg G, Regev E, Chen S, Assali A, Barbash IM, Planer D, Vaknin-Assa H, Guetta V, Vukasinovic V, Orvin K, Danenberg HD, Segev A, Kornowski R. The prognostic effects of coronary disease severity and completeness of revascularization on mortality in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2017;10:1428–1435.
11. Shamekhi J, Stundl A, Weber M, Mellert F, Welz A, Grube E, Nickenig G, Werner N, Sinning J-M. Impact of coronary artery disease in patients undergoing transfemoral transcatheter aortic valve implantation. *Int J Cardiol* 2017;245:215–221.
12. Stefanini GG, Stortecky S, Cao D, Rat-Wirtzler J, O'Sullivan CJ, Gloekler S, Buellesfeld L, Khattab AA, Nietlispach F, Pilgrim T, Huber C, Carrel T, Meier B, Jüni P, Wenaweser P, Windecker S. Coronary artery disease severity and aortic stenosis: clinical outcomes according to SYNTAX score in patients undergoing transcatheter aortic valve implantation. *Eur Heart J* 2014;35:2530–2540.
13. Beach JM, Mihaljevic T, Svensson LG, Rajeswaran J, Marwick T, Griffin B, Johnston DR, Sabik JF, Blackstone EH. Coronary artery disease and outcomes of aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol* 2013;61:837–848.
14. Thyregod HGH, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrøm T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Søndergaard L. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis. *J Am Coll Cardiol* 2015;65:2184–2194.
15. Bekeredjian R, Szabo G, Balaban Ü, Bleiziffer S, Bauer T, Ensminger S, Frerker C, Herrmann E, Beyersdorf F, Hamm C, Beckmann A, Möllmann H, Karck M, Katus HA, Walther T. Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results from the German Aortic Valve Registry (GARY). *Eur Heart J* 2019;40:1323–1330.
16. Elm E von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007;4:e296.
17. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hebert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. *Lancet* 1999;353:205–206.
18. Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardio-Thorac Surg* 2012;41:734–745.
19. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es G-A, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012;33:2403–2418.
20. Biancari F, Ruggieri VG, Perrotti A, Svenarud P, Dalén M, Onorati F, Faggian G, Santarpino G, Maselli D, Dominici C, Nardella S, Musumeci F, Gherli R, Mariscalco G, Masala N, Rubino AS, Mignosa C, De Feo M, Della Corte A, Bancone C, Chocron S, Gatti G, Gherli T, Kinnunen E-M, Juvonen T. European multicenter study on Coronary Artery Bypass Grafting (E-CABG registry): study protocol for a prospective clinical registry and proposal of classification of postoperative complications. *J Cardiothorac Surg* 2015;10:90.
21. Acute Kidney Injury Work Group. Section 2: AKI definition. *Kidney Int Suppl* 2012;2:19–36.
22. Virtanen MPO, Eskola M, Jalava MP, Husso A, Laakso T, Niemelä M, Ahvenvaara T, Tauriainen T, Maaranen P, Kinnunen E-M, Dahlbacka S, Jaakkola J, Vasankari T, Airaksinen J, Anttila V, Rosato S, D'Errigo P, Savontaus M, Juvonen T, Laine M, Mäkikallio T, Valtola A, Raivio P, Biancari F. Comparison of outcomes after transcatheter aortic valve replacement vs surgical aortic valve replacement among patients with aortic stenosis at low operative risk. *JAMA Netw Open* 2019;2:e195742.
23. Kheiri B, Osman M, Bakhit A, Radaideh Q, Barbarawi M, Zayed Y, Golwala H, Zahr F, Stone GW, Bhatt DL. Meta-analysis of transcatheter aortic valve replacement in low-risk patients. *Am J Med* 2019. https://doi.org/10.1016/j.amjmed.2019.06.020. In press.
24. Waksman R, Rogers T, Torguson R, Gordon P, Ehsan A, Wilson SR, Goncalves J, Levitt R, Hahn C, Parikh P, Bilfinger T, Butzel D, Buchanan S, Hanna N, Garrett R, Asch F, Weissman G, Ben-Dor I, Shults C, Bastian R, Craig PE, Garcia-Garcia HM, Kolm P, Zou Q, Satler LF, Corso PJ. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe aortic stenosis. *J Am Coll Cardiol* 2018;72:2095–2105.
25. Waksman R, Corso PJ, Torguson R, Gordon P, Ehsan A, Wilson SR, Goncalves J, Levitt R, Hahn C, Parikh P, Bilfinger T, Butzel D, Buchanan S, Hanna N, Garrett R, Buchbinder M, Asch F, Weissman G, Ben-Dor I, Shults C, Bastian R, Craig PE, Ali S, Garcia-Garcia HM, Kolm P, Zou Q, Satler LF, Rogers T. TAVR in low-risk patients. *JACC Cardiovasc Interv* 2019;12:901–907.
26. Arnold SV, Zhang Y, Baron SJ, McAndrew TC, Alu MC, Kodali SK, Kapadia S, Thourani VH, Miller DC, Mack MJ, Leon MB, Cohen DJ. Impact of short-term complications on mortality and quality of life after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2019;12:362–369.
27. Maaranen P, Husso A, Tauriainen T, Lahtinen A, Valtola A, Ahvenvaara T, Virtanen M, Laakso T, Kinnunen E-M, Dahlbacka S, Juvonen T, Mäkikallio T, Jalava MP, Jaakkola J, Airaksinen J, Vasankari T, Rosato S, Savontaus M, Laine M, Raivio P, Niemelä M, Mennander

A, Eskola M, Biancari F. Blood transfusion and outcome after transfemoral transcatheter aortic valve replacement. *J Cardiothorac Vasc Anesth* 2019;33:2949–2959.
28. Huded CP, Tuzcu EM, Krishnaswamy A, Mick SL, Kleiman NS, Svensson LG, Carroll J, Thourani VH, Kirtane AJ, Manandhar P, Kosinski AS, Vemulapalli S, Kapadia SR. Association between transcatheter aortic valve replacement and early postprocedural stroke. *JAMA* 2019;321:2306–2315.
29. van Rosendael PJ, Delgado V, Bax JJ. Pacemaker implantation rate after transcatheter aortic valve implantation with early and new-generation devices: a systematic review. *Eur Heart J* 2018;39: 2003–2013.

PUBLICATION III

Mid-term outcomes of Sapien 3 versus Perimount Magna Ease for treatment of severe aortic stenosis.

Virtanen MPO, Eskola M, Savontaus M, Juvonen T, Niemelä M, Laakso T, Husso A, Jalava MP, Tauriainen T, Ahvenvaara T, Maaranen P, Kinnunen EM, Dahlbacka S, Laine M, Mäkikallio T, Valtola A, Raivio P, Rosato S, D'Errigo P, Vento A, Airaksinen J, Biancari F.

J Cardiothorac Surg. 2020;15(1):157. doi:10.1186/s13019-020-01203-1.

Virtanen et al. Journal of Cardiothoracic Surgery (2020) 15:157
https://doi.org/10.1186/s13019-020-01203-1

Journal of Cardiothoracic Surgery

RESEARCH ARTICLE Open Access

Mid-term outcomes of Sapien 3 versus Perimount Magna Ease for treatment of severe aortic stenosis

Marko P. O. Virtanen[1,2*], Markku Eskola[1,2], Mikko Savontaus[3], Tatu Juvonen[4,5], Matti Niemelä[6], Teemu Laakso[4], Annastiina Husso[7], Maina P. Jalava[3], Tuomas Tauriainen[5], Tuomas Ahvenvaara[5], Pasi Maaranen[1,2], Eeva-Maija Kinnunen[4], Sebastian Dahlbacka[4], Mika Laine[4], Timo Mäkikallio[6], Antti Valtola[7], Peter Raivio[4], Stefano Rosato[8], Paola D'Errigo[8], Antti Vento[4], Juhani Airaksinen[3] and Fausto Biancari[3,5]

Abstract

Background: There is limited information on the longer-term outcome after transcatheter aortic valve replacement (TAVR) with new-generation prostheses compared to surgical aortic valve replacement (SAVR). The aim of this study was to compare the mid-term outcomes after TAVR with Sapien 3 and SAVR with Perimount Magna Ease bioprostheses for severe aortic stenosis.

Methods: In a retrospective study, we included patients who underwent transfemoral TAVR with Sapien 3 or SAVR with Perimount Magna Ease bioprosthesis between January 2008 and October 2017 from the nationwide FinnValve registry. Propensity score matching was performed to adjust for differences in the baseline characteristics. The Kaplan-Meir method was used to estimate late mortality.

Results: A total of 2000 patients were included (689 in the TAVR cohort and 1311 in the SAVR cohort). Propensity score matching resulted in 308 pairs (STS score, TAVR 3.5 ± 2.2% vs. SAVR 3.5 ± 2.8%, $p = 0.918$). In-hospital mortality was 3.6% after SAVR and 1.3% after TAVR ($p = 0.092$). Stroke, acute kidney injury, bleeding and atrial fibrillation were significantly more frequent after SAVR, but higher rate of vascular complications was observed after TAVR. The cumulative incidence of permanent pacemaker implantation at 4 years was 13.9% in the TAVR group and 6.9% in the SAVR group ($p = 0.0004$). At 4-years, all-cause mortality was 20.6% for SAVR and 25.9% for TAVR ($p = 0.910$). Four-year rates of coronary revascularization, prosthetic valve endocarditis and repeat aortic valve intervention were similar between matched cohorts.

Conclusions: The Sapien 3 bioprosthesis achieves comparable midterm outcomes to a surgical bioprosthesis with proven durability such as the Perimount Magna Ease. However, the Sapien 3 bioprosthesis was associated with better early outcome.

Trial registration: ClinicalTrials.gov Identifier: NCT03385915.

Keywords: Aortic valve stenosis, Aortic valve replacement, TAVR, SAVR

* Correspondence: marko.virtanen@fimnet.fi
[1]Heart Hospital, Tampere University Hospital, Tampere, Finland
[2]Faculty of Medicine and Health Technology, University of Tampere, Tampere, Finland
Full list of author information is available at the end of the article

Background

Transcatheter aortic valve replacement (TAVR) with balloon-expandable [1–3] and self-expanding [4–7] bioprosthesis has proven its efficacy and safety compared to surgical aortic valve replacement (SAVR) in the treatment of aortic stenosis (AS) regardless of the operative risk. A meta-analysis of randomized controlled trials recently showed that TAVR is associated with significant reduction of all-cause mortality, a lower risk for stroke, atrial fibrillation and bleeding, but a higher risk for permanent pacemaker implantation and major vascular complications at 2 years compared to SAVR [8]. The indications for TAVR are expanding, but it is controversial whether TAVR should be performed on a larger scale because of limited data on the long-term outcome and valve durability of TAVR prostheses compared to SAVR prostheses. Similar longer-term survival after TAVR and SAVR is observed in randomized controlled trials [1, 6, 7], but studies reporting outcomes in the real-world populations have discordant findings [9–12]. Sustained valve hemodynamics and low reintervention rate is associated with the use of first-generation balloon-expandable Sapien bioprosthesis [1, 13]. However, a higher rate of structural valve deterioration leading to hemodynamic compromise was observed with the second-generation Sapien XT valve compared to the third-generation Sapien 3 valve prosthesis and the surgical valves in the PARTNER 2 trial [14]. Importantly, TAVR with different valve types and their iterations may result in discrepant outcomes and valve performance [14–16]. Therefore it is important to compare the outcomes of each TAVR prosthesis separately against SAVR prostheses with proven long-term durability [17, 18].

The third-generation balloon-expandable Sapien 3 (Edwards Lifesciences, Irvine, CA, USA) prosthesis has bovine pericardial leaflets that are attached inside a cobalt-chromium alloy frame, and unlike its predecessors (Sapien, Sapien XT, Edwards Lifesciences, Irvine, CA, USA) has an improved external layer of polyethylene terephthalate fabric seal to minimize the risk of paravalvular regurgitation along with a redesigned frame. During manufacturing, bovine pericardial leaflets undergo the same tissue processing (ThermaFix) intended to reduce the risk of leaflet calcification as in the latest generation surgical Perimount Magna Ease (Edwards Lifesciences, Irvine, CA, USA), which is regarded as the most durable surgical bioprosthesis [17].

The aim of this study was to compare the outcome after TAVR with the Sapien 3 and SAVR with the Perimount Magna Ease bovine pericardial prostheses. To our knowledge, this is the first direct comparison of these TAVR and SAVR bioprostheses.

Methods

Registry design

The FinnValve registry collected data on consecutive patients who underwent TAVR or SAVR with a bioprosthesis for AS at all Finnish university hospitals (Helsinki, Kuopio, Oulu, Tampere, Turku) between January 2008 and October 2017. Inclusion criteria were age > 18 years, primary aortic valve procedure with a bioprosthesis (TAVR or SAVR) for AS with or without associated coronary revascularization. The exclusion criteria were any prior aortic valve procedure, concomitant intervention for other valve or ascending aorta, active endocarditis and a procedure for aortic valve regurgitation. The study protocol was approved by the local Institutional Review Boards in all participating centres. Data was retrospectively collected in a dedicated electronic case report system by physicians and trained research nurses. Data on mortality was obtained from the Finnish Population Register Centre and data on cardiovascular interventions was retrieved from the registry of the Finnish National Institute for Health and Welfare. The follow-up was complete, except for those few patients not residing in Finland follow-up was truncated at hospital discharge. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [19].

Patients and outcomes

Only patients who underwent transfemoral TAVR with Sapien 3 or SAVR with Perimount Magna Ease were included in this analysis. The choice between TAVR and SAVR was based on individual assessment by the local Heart Team. Patients in the TAVR group and concomitant coronary artery disease (CAD) underwent revascularization based on the discretion of the treating physician. Patients who underwent an emergency procedure or with associated severe clinical conditions were excluded (Fig. 1). The primary outcomes were in-hospital and 4-year all-cause mortality. The secondary outcomes were stroke, atrial fibrillation, permanent pacemaker implantation, major vascular complications, acute kidney injury, dialysis, moderate or severe paravalvular regurgitation, severe bleeding, reoperation for bleeding, red blood cell transfusion, annular or aortic rupture/dissection, conversion to cardiac surgery, coronary artery occlusion, deep sternal wound infection, postoperative intra-aortic balloon pump or extracorporeal membrane oxygenation, ventricular wall injury and length of index hospitalization. Late secondary outcomes were permanent pacemaker implantation, coronary revascularization, prosthetic valve endocarditis and reoperation on the implanted aortic bioprosthesis.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) II criteria were applied for

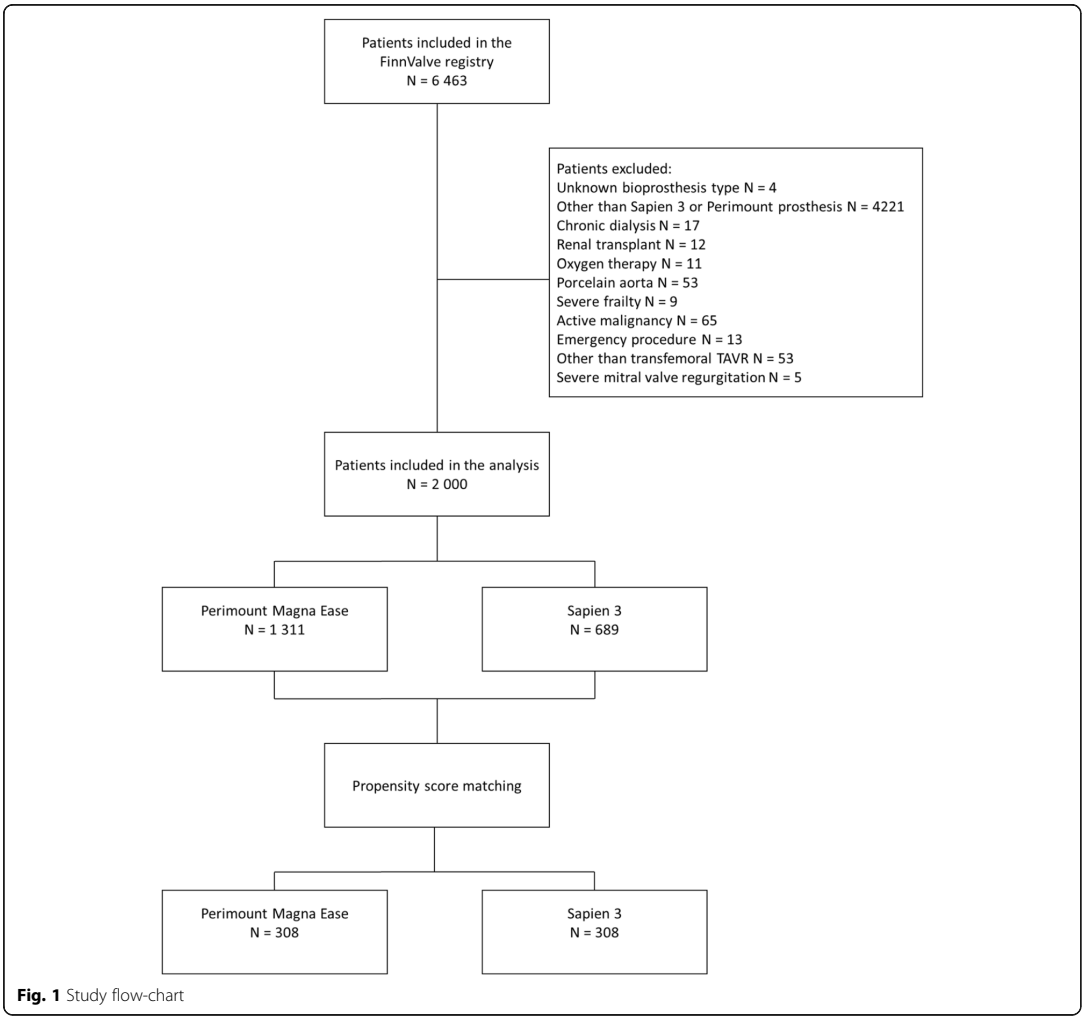


Fig. 1 Study flow-chart

the definition of baseline variables and for surgical risk stratification [20]. Surgical risk was estimated also according to the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score. Coronary artery disease was defined as a ≥ 50% stenosis in a main coronary artery. Severe frailty was defined as Geriatric Status Scale 2–3 [21]. Stroke and major vascular complications were defined according to Valvular Academic Consortium 2 (VARC-2) [22] criteria and severe bleeding according to European Coronary Artery Bypass Grafting (E-CABG) bleeding scores 2–3 [23], i.e. transfusion of more than 4 units of red blood cells and/or reoperation for bleeding. Acute kidney injury was defined according to the KDIGO definition criteria [24].

Statistical analysis

Statistical analyses were performed using SAS v. 9.2 (SAS Institute Inc., Cary, NC) and SPSS v. 25.0 (IBM Corporation, New York, USA) statistical softwares. Data is presented as means ± standard deviation for continuous variables, and as counts and percentages for categorical variables. Mann-Whitney's test was used to compare continuous variables, and the chi -square and Fisher's exact tests were used to compare the categorical variables in the unmatched cohorts. A propensity score was calculated with a non-parsimonious logistic regression model including the following variables**:** age, gender, body mass index, diabetes, atrial fibrillation, extracardiac arteriopathy, chronic lung disease, hemoglobin, estimated glomerular filtration rate, stroke, pre-existing

pacemaker, previous cardiac surgery, previous percutaneous coronary intervention, coronary artery disease, number of diseased coronaries, recent myocardial infarction, New York Heart Association class IV symptoms, acute heart failure or critical preoperative state, urgent procedure, left ventricular ejection fraction, systolic pulmonary pressure, mitral valve regurgitation, frailty and inactive malignancy. One-to-one propensity score matching was performed using the nearest-neighbour method and a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Baseline variables and in-hospital outcomes in the matched population were compared with paired t-test and the McNemar test. Kaplan-Meier method with Klein-Moeschberger log-rank test was used to estimate late mortality. The risk for late adverse events was calculated with competing risk analysis and comparisons were performed using the Gray's k-sample test for equality of cumulative incidence functions. Hazard ratios were calculated with their 95% confidence intervals (CI). $P < 0.05$ was considered statistically significant.

Results

Study population

A total of 6463 patients were included in the FinnValve registry, and after exclusion of 4463 patients (Fig. 1), 2000 patients were subjects for the present analysis. Among them, 689 underwent TAVR with Sapien 3 bioprosthesis and 1311 patients underwent SAVR with Perimount Magna Ease prosthesis. The mean follow-up of the overall series and of the TAVR and SAVR cohorts was 3.6 ± 2.1, 2.4 ± 1.0 and 4.2 ± 2.1 years, respectively. The patients in the TAVR cohort were older (81.3 ± 6.4 vs. 74.0 ± 6.9 years), had more often co-morbidities and higher surgical risk based on the EuroSCORE II and STS-PROM scores (Table 1). After propensity score matching, 308 pairs with balanced baseline variables were identified (Table 1). The standardized difference after matching was < 0.1 for all baseline and operative covariates except for concomitant coronary revascularization, which was more common in SAVR (27.3% vs. 4.5%) despite a similar prevalence of coronary artery disease in the cohorts. The mean STS-PROM score was 3.5 ± 2.2% in the TAVR and 3.5 ± 2.8 in the SAVR cohort ($p = 0.918$) (Table 1). The sizes of implanted prostheses are summarized in Table 2.

Early outcomes

The early outcomes of the unmatched TAVR and SAVR cohorts are summarized in Table 3.

In the propensity matched cohorts, TAVR had a numerically lower in-hospital mortality (1.2% vs. 3.6%, $p = 0.092$) compared to SAVR (Table 3). Moreover, postoperative stroke was significantly less frequent after TAVR (0.3% vs. 3.6%, $p = 0.006$). A trend towards a higher need of permanent pacemaker implantation early after the procedure was observed in the Sapien 3 group. The incidence of moderate or severe paravalvular regurgitation was similar in both cohorts. TAVR was associated with lower rates of postoperative atrial fibrillation, acute kidney injury and severe bleeding compared to SAVR (Table 3). Major vascular complications were significantly more frequent in the TAVR cohort. Annular rupture occurred in one patient after Sapien 3 implantation (Table 3).

Mid-term outcomes after procedures

In the matched cohorts, Kaplan-Meier estimate of all-cause mortality was 7.5 and 6.5% at 1-year, 11.3 and 11.7% at 2-years, 12.9 and 14.7% at 3-years, 20.6 and 25.9% at 4-years in the SAVR and TAVR cohorts, respectively (HR 0.96; 95% CI 0.63–1.46; $p = 0.910$) (Fig. 2). At 4-years, the cumulative incidence of permanent pacemaker implantation was higher after TAVR (13.9% vs. 6.9%; HR 2.16; 95% CI 1.27–3.68). TAVR was associated with similar rates of late coronary revascularization (1.5% vs. 1.4%; HR 0.76; 95% CI 0.17–3.43), prosthetic valve endocarditis (0.6% vs. 0.5%; HR 1.02; 95% CI 0.06–16.10) and repeat aortic valve intervention (0.4% vs. 0.4%; HR 1.02; 95% CI 0.06–16.14) compared to SAVR.

In the matched groups, one patient in the TAVR group underwent aortic valve reintervention for structural valve deterioration and one patient in the SAVR group for paravalvular regurgitation. Additionally, the indications for reoperation in the unmatched cohorts were structural valve deterioration (1 patient with Sapien 3, 1 patient with Perimount), paravalvular regurgitation (5 patients with Perimount), and endocarditis (1 patient with Perimount).

Discussion

The main findings of our study are the following: 1) patients treated for severe AS with the transfemoral TAVR with the Sapien 3 bioprosthesis had similar mid-term mortality compared to patients who underwent SAVR with the Perimount Magna Ease bioprosthesis; 2) the risk for coronary revascularization, repeat aortic valve intervention and prosthetic valve endocarditis at 4 years was low and similar with both bioprostheses; 3) the Sapien 3 was associated with a higher cumulative rate of permanent pacemaker implantation than the Perimount Magna Ease bioprosthesis; 4) procedural safety in terms of stroke, atrial fibrillation, kidney injury and bleeding favoured TAVR, whilst lower rate of major vascular complications was observed with SAVR.

We hypothesised that unbiased evaluation on the outcomes after TAVR and SAVR could be feasible by including only the Sapien 3 and the Perimount Magna

Table 1 Baseline characteristics of the unmatched and propensity score matched cohorts

Clinical variables	Unmatched cohort				Propensity score matched cohort			
	Sapien 3 (***N*** = 689)	Perimount Magna Ease (***N*** = 1311)	Standardized difference	***p***-value	Sapien 3 (***N*** = 308)	Perimount Magna Ease (***N*** = 308)	Standardized difference	***p***-value
Age, yrs	81.3 ± 6.4	74.0 ± 6.9	1.1	< 0.0001	78.8 ± 6.9	79.0 ± 5.3	−0.03	0.697
Female	365 (53.0)	556 (42.4)	0.21	< 0.0001	160 (51.9)	165 (53.6)	−0.03	0.674
BMI, kg/m^2	27.4 ± 4.9	28.0 ± 4.8	−0.12	0.012	28.1 ± 5.2	28.0 ± 5.0	0.02	0.848
Diabetes mellitus	207 (30.0)	353 (26.9)	0.07	0.140	93 (30.2)	87 (28.2)	0.04	0.578
Atrial fibrillation	293 (42.5)	255 (19.5)	0.52	< 0.0001	102 (33.1)	99 (32.1)	0.02	0.782
Extracardiac arteriopathy	117 (17.0)	137 (10.5)	0.19	< 0.0001	49 (15.9)	41 (13.3)	0.07	0.383
Chronic lung disease	149 (21.6)	172 (13.1)	0.23	< 0.0001	65 (21.1)	62 (20.1)	0.02	0.761
Hemoglobin, g/l	125.7 ± 15.2	133.6 ± 15.1	−0.53	< 0.0001	128.7 ± 15.2	127.8 ± 15.3	0.06	0.421
eGFR, ml/m^2/min	62.0 ± 18.5	72.6 ± 16.7	−0.60	< 0.0001	65.6 ± 18.1	66.4 ± 16.1	−0.05	0.550
History of stroke	70 (10.2)	70 (5.3)	0.18	0.0001	27 (8.8)	29 (9.4)	−0.02	0.782
Prior pacemaker	65 (9.4)	50 (3.8)	0.23	< 0.0001	20 (6.5)	19 (6.2)	0.01	0.862
Previous cardiac surgery	110 (16.0)	24 (1.8)	0.51	< 0.0001	17 (5.5)	18 (5.8)	−0.01	0.847
Prior PCI	140 (20.3)	130 (9.9)	0.29	< 0.0001	47 (15.3)	40 (13.0)	0.07	0.370
Coronary artery disease	181 (26.3)	563 (42.9)	−0.36	< 0.0001	102 (33.1)	97 (31.5)	0.04	0.665
No. of diseased vessels	0.36 ± 0.7	0.78 ± 1.1	−0.48	< 0.0001	0.47 ± 0.8	0.46 ± 0.8	0.02	0.836
Recent MI	17 (2.5)	72 (5.5)	−0.16	0.0018	9 (2.9)	9 (2.9)	0.00	1.000
NYHA class IV	82 (11.9)	94 (7.2)	0.16	0.0004	31 (10.1)	34 (11.0)	−0.03	0.696
AHF	75 (10.9)	101 (7.7)	0.11	0.017	33 (10.7)	33 (10.7)	0.00	1.000
Urgent procedure	55 (8.0)	148 (11.3)	−0.11	0.020	28 (9.1)	33 (10.7)	−0.05	0.508
Ejection fraction			0.26	< 0.0001			0.08	0.699
> 50%	499 (72.4)	1069 (81.5)			230 (74.7)	239 (77.6)		
31–50%	158 (22.9)	220 (16.8)			68 (22.1)	60 (19.5)		
21–30%	31 (4.5)	22 (1.7)			10 (3.2)	9 (2.9)		
Sys. pulmonary pressure			0.74	< 0.0001			0.09	< 0.0001
31–55 mmHg	245 (35.6)	524 (40.0)			131 (42.5)	121 (39.3)		
> 55 mmHg	75 (10.9)	92 (7.0)			34 (11.0)	39 (12.7)		
Mitral valve regurgitation			0.56	< 0.0001			0.06	0.652
Mild	255 (37.0)	278 (21.2)			116 (37.7)	107 (34.7)		

Table 1 Baseline characteristics of the unmatched and propensity score matched cohorts *(Continued)*

Clinical variables	Unmatched cohort				Propensity score matched cohort			
	Sapien 3 (***N*** = 689)	Perimount Magna Ease (***N*** = 1311)	Standardized difference	***p***-value	Sapien 3 (***N*** = 308)	Perimount Magna Ease (***N*** = 308)	Standardized difference	***p***-value
Moderate	80 (11.6)	39 (3.0)			23 (7.5)	21 (6.8)		
Concomitant coronary revascularization	29 (4.2)	511 (39.0)	−0.78	< 0.0001	14 (4.5)	84 (27.3)	−0.62	< 0.0001
EuroSCORE II, %	6.5 ± 7.1	3.4 ± 4.2	0.52	< 0.0001	5.0 ± 5.2	4.9 ± 5.9	0.02	0.752
STS-PROM, %	4.3 ± 2.9	2.6 ± 2.1	0.67	< 0.0001	3.5 ± 2.2	3.5 ± 2.8	0.01	0.918

Categorical values are reported as counts and percentages. Continuous variables are reported as mean and standard deviation. *AHF* acute heart failure (within 60 days before procedure or critical preoperative state), *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *EuroSCORE* European System for Cardiac Operative Risk Evaluation, *MI* myocardial infarction within 90 days before procedure, *NYHA* New York Heart Association, *PCI* percutaneous coronary intervention, *STS-PROM* Society of Thoracic Surgeons Predicted Risk of Mortality

Ease bioprostheses, because the bioprostheses share some technological features such as bovine pericardial leaflets utilizing similar anti-calcification processes during manufacturing. Furthermore, the Perimount Magna Ease demonstrated an excellent durability among current surgical bioprostheses [17].

Our study showed that TAVR with the Sapien 3 prosthesis resulted in similar survival compared to SAVR with the Perimount Magna Ease at 4-years. Comparable mid-term outcomes between TAVR and SAVR were achieved in randomized controlled trials [1, 6, 7], but strict selection of the patients does not allow generalization of the results into real-life AS patients undergoing invasive treatment. Indeed, several observational studies have shown inferior mid-term outcomes after TAVR compared to SAVR. The findings from the OBSERVANT registry of 1300 matched patients undergoing TAVR with first/second generation prostheses and SAVR showed that TAVR was associated with higher all-cause mortality (44.5% vs. 35.8%) at 5-years. Mortality rate in the OBSERVANT registry exceeded our 4-year mortality already after 2.5 years [11]. Markedly inferior 5-year survival after TAVR was observed also in the analysis from the French Medical Information System database, with all-cause death of 52% after TAVR and 37% after SAVR in the matched patient populations [9].

Table 2 Prosthesis sizes in the unmatched cohorts

Size	Sapien 3 (***N*** = 689)	Size	Perimount Magna Ease (***N*** = 1311)
20 mm	2 (0.3)	19 mm	35 (2.7)
23 mm	221 (32.1)	21 mm	320 (24.4)
26 mm	256 (37.2)	23 mm	551 (42.0)
29 mm	206 (29.9)	25 mm	296 (22.6)
		27 mm	95 (7.2)
		29 mm	10 (0.8)

Categorical values are reported as counts and percentages

There are few possible explanations for such different mid-term outcomes between the studies. Firstly, the Sapien 3 bioprosthesis carried a decreased risk of structural valve deterioration compared to its predecessor the Sapien XT valve, and performed similarly as the surgical valves in the PARTNER 2 study [14]. In addition, a propensity score matched study combining data from the SOURCE XT and the SOURCE 3 registries showed improved survival with Sapien 3 compared to Sapien XT valves [15]. A low incidence (1.9%) of moderate paravalvular regurgitation with Sapien 3 in our study was in concordance with other studies, and potentially impacted the outcomes [25]. Secondly, including different generations of balloon-expandable and self-expanding TAVR prostheses in previous observational studies may have introduced a significant bias [16].

The question of valve durability is becoming more relevant as TAVR is adopted for lower- risk patients. Several studies showed reasonable durability of surgical bioprosthesis up to 15–20 years after SAVR [17], but variable definitions used for structural valve deterioration in surgical prostheses makes benchmarking for transcatheter valves difficult [26]. The incidence of structural valve deterioration cannot be estimated in our study since a comprehensive echocardiographic follow-up data was not available and solely reintervention rate inevitably leads to a major underestimation of its true incidence. This clearly limits the interpretation of our results regarding the durability of the Sapien 3 prosthesis. However, the need for reintervention for aortic valve complications was very low in both cohorts.

The cumulative incidence of permanent pacemaker implantation in the Perimount group remained low and stable, while in the Sapien 3 group permanent pacemaker implantation was increasingly needed along the study period. Since pacing after TAVR may have long-term consequences for the patient [27], we should aim to reduce the risk for permanent pacemaker

Table 3 Outcomes in the unmatched and propensity score matched cohorts

Outcomes	Unmatched cohort			Propensity score matched cohort		
	Sapien 3 (***N*** = 689)	Perimount Magna Ease (***N*** = 1311)	***p***-value	Sapien 3 (***N*** = 308)	Perimount Magna Ease (***N*** = 308)	***p***-value
In-hospital death	8 (1.2)	26 (2.0)	0.177	4 (1.3)	11 (3.6)	0.092
Stroke	9 (1.3)	48 (3.7)	0.003	1 (0.3)	11 (3.6)	0.006
Vascular complications			< 0.0001			< 0.0001
Minor	18 (2.6)	0		8 (2.6)	0	
Major	58 (8.4)	13 (1.0)		29 (9.4)	2 (0.6)	
Annulus rupture	2 (0.3)	0		1 (0.3)	0	
Aortic dissection/rupture	2 (0.3)	7 (0.5)	0.727	1 (0.3)	1 (0.3)	1.000
Coronary ostium occlusion	2 (0.3)	2 (0.2)	0.612	1 (0.3)	2 (0.6)	1.000
Acute kidney injury stages 2–3	5 (0.7)	72 (5.5)	< 0.0001	1 (0.3)	24 (7.8)	< 0.0001
Postoperative dialysis	2 (0.3)	20 (1.5)	0.012	0	7 (2.3)	0.015
Moderate/severe paravalvular regurgitation	8 (1.2)	10 (0.8)	0.370	6 (1.9)	4 (1.3)	0.754
Severe bleeding*	14 (2.1)	282 (21.9)	< 0.0001	4 (1.3)	88 (29.0)	< 0.0001
Reoperation for bleeding	14 (2.0)	129 (9.8)	< 0.0001	7 (2.3)	33 (10.7)	< 0.0001
Red blood cell transfusion, units	0.3 (1.1)	2.6 (3.4)	< 0.0001	0.27 (1.0)	3.2 (3.5)	< 0.0001
Postoperative IABP or ECMO	0	11 (0.8)	0.020	0	3 (1.0)	0.249
Atrial fibrillation	269 (39.0)	733 (55.9)	< 0.0001	102 (33.1)	200 (64.9)	< 0.0001
Permanent pacemaker implantation	52 (7.5)	47 (3.6)	< 0.0001	28 (9.1)	16 (5.2)	0.064
Hospital stay, days	4.0 ± 3.4	7.7 ± 5.5	< 0.0001	4.1 ± 3.7	8.4 ± 6.8	< 0.0001

Categorical values are reported as counts and percentages. Continuous variables are reported as mean and standard deviation. *ECMO* extracorporeal membrane oxygenation, *IABP* intra-aortic balloon pump; * = transfusion of more than 4 units of red blood cells and/or reoperation for bleeding

implantation by adopting higher implantation technique and avoiding excess oversizing with the Sapien 3 prosthesis [28, 29].

The prevalence of coronary artery disease was similar in the matched cohorts, but concomitant coronary revascularization was performed only in 14% of the patients with coronary artery disease in the TAVR group compared to 87% revascularization rate in patients with coronary artery disease in the SAVR group. Complete revascularization during SAVR is recommended to avoid postoperative left ventricular systolic dysfunction and excess mortality after surgery [30], but the best

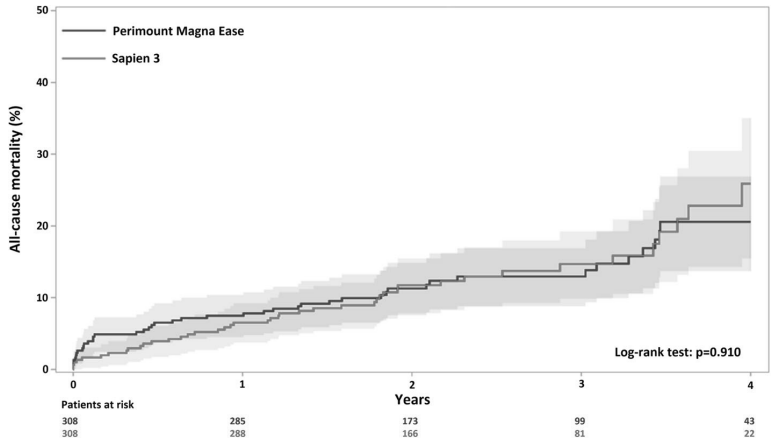


Fig. 2 Kaplan-Meier estimate of all-cause mortality after aortic valve replacement with Sapien 3 and Perimount Magna Ease bioprostheses in the propensity score matched cohorts. *P*-value is from the Klein-Moeschberger log-rank test

revascularization strategy during TAVR is not established yet, which most likely explains the lower revascularization rate in the TAVR group. Interestingly, such a low rate of coronary revascularization at the time of procedure did not expose patients undergoing TAVR to an increased need of revascularization at 4-years with similar mortality rate compared to SAVR. However, we have to interpret this finding with caution because the increased risk related to coronary artery disease in the TAVR patients is driven by its severity [31], and our definition criteria did not capture patients only with the most severe coronary artery disease.

Procedural safety is one of the major concerns in the decision-making process. The present findings indicate that TAVR with balloon-expandable Sapien 3 is safe with very low rates of annular rupture and coronary obstruction. Furthermore, TAVR was associated with lower incidence of stroke, acute kidney injury, atrial fibrillation and bleeding compared to SAVR. However, the rate of major vascular complications was still higher in TAVR compared to SAVR. This favourable safety profile of TAVR over SAVR is in alignment with current knowledge [8].

Limitations

The retrospective nature is the major limitation of this study. Secondly, the mean follow-up in the TAVR cohort was shorter than in the SAVR cohort. Third, comparative analysis of the TAVR and SAVR cohorts was based on propensity score matching and unrecognized confounders might have had an impact on the results. Finally, the lack of complete echocardiographic follow-up prevented an analysis of structural valve deterioration which might have occurred in these cohorts.

Conclusions

In this nationwide study, transfemoral TAVR with Sapien 3 prosthesis achieved similar mid-term outcomes with better procedural safety compared to SAVR with Perimount Magna Ease bioprosthesis.

Abbreviations

EuroSCORE: European System for Cardiac Operative Risk Evaluation; PARTNER: Placement of Aortic Transcatheter Valves; SAVR: Surgical aortic valve replacement; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR: Transcatheter aortic valve replacement

Acknowledgements

Not applicable.

Authors' contributions

MPOV, ME and FB designed the study, collected and analysed data and drafted the manuscript. MN, AVa, PR, JA: designed the study, interpreted data and revised the manuscript; MS, TJ, TL, AH, MPJ, TT, TA, PM, E-MK, SD, ML, TM, AVe collected and interpreted data, and revised the manuscript; SR, PD'E performed the statistical analyses. All authors read and accepted the final manuscript.

Funding

This study was financially partly supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital. MPOV received personal research grants from Aarne Koskelo Foundation and from Paavo Ilmari Ahvenainen Foundation.

Availability of data and materials

The datasets used during the current study are not available due to legal restrictions.

Ethics approval and consent to participate

This study was approved by the local Institutional Review Boards in each participating centre.

Consent for publication

Not applicable.

Competing interests

MS is a proctor for Medtronic; ML is a proctor for Boston Scientific All the other authors declare that they have no competing interests.

Author details

[1]Heart Hospital, Tampere University Hospital, Tampere, Finland. [2]Faculty of Medicine and Health Technology, University of Tampere, Tampere, Finland. [3]Heart Center, Turku University Hospital, and Department of Surgery, University of Turku, Turku, Finland. [4]Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland. [5]Department of Surgery, Oulu University Hospital and Research Unit of Surgery, Anesthesia and Intensive Care, Faculty of Medicine, University of Oulu, Oulu, Finland. [6]Department of Internal Medicine, Oulu University Hospital, Oulu, Finland. [7]Heart Center, Kuopio University Hospital, Kuopio, Finland. [8]National Centre of Global Health, Istituto Superiore di Sanità, Rome, Italy.

Received: 18 March 2020 Accepted: 22 June 2020
Published online: 29 June 2020

References

1. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385:2477–84.
2. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374:1609–20.
3. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695–705.
4. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or Transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2017;376:1321–31.
5. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019;380:1706–15.
6. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-year outcomes of self-expanding Transcatheter versus surgical aortic valve replacement in high-risk patients. J Am Coll Cardiol. 2018;72:2687–96.
7. Søndergaard L, Ihlemann N, Capodanno D, Jørgensen TH, Nissen H, Kjeldsen BJ, et al. Durability of Transcatheter and surgical bioprosthetic aortic valves in patients at lower surgical risk. J Am Coll Cardiol. 2019;73:546–53.
8. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. Eur Heart J. 2019;40:3143–53.
9. Armoiry X, Obadia JF, Pascal L, Polazzi S, Duclos A. Comparison of transcatheter versus surgical aortic valve implantation in high-risk patients: A nationwide study in France. J Thorac Cardiovasc Surg. 2018;156:1017–1025.e4.
10. Schaefer A, Schofer N, Goßling A, Seiffert M, Schirmer J, Deuschl F, et al. Transcatheter aortic valve implantation versus surgical aortic valve

replacement in low-risk patients: a propensity score-matched analysis. Eur J Cardio-Thoracic Surg. 2019;56:1131–9.
11. Barbanti M, Tamburino C, D'Errigo P, Biancari F, Ranucci M, Rosato S, et al. Five-year outcomes of Transfemoral Transcatheter aortic valve replacement or surgical aortic valve replacement in a real world population. Circ Cardiovasc Interv. 2019;12:e007825.
12. Virtanen MPO, Eskola M, Jalava MP, Husso A, Laakso T, Niemelä M, et al. Comparison of outcomes after Transcatheter aortic valve replacement vs surgical aortic valve replacement among patients with aortic stenosis at low operative risk. JAMA Netw Open. 2019;2:e195742.
13. Douglas PS, Leon MB, Mack MJ, Svensson LG, Webb JG, Hahn RT, et al. Longitudinal hemodynamics of transcatheter and surgical aortic valves in the PARTNER trial. JAMA Cardiol. 2017;2:1197–206.
14. Pibarot P, Hahn R. Incidence, predictors and outcome of structural valve deterioration in transcatheter vs. SAVR: five year follow-up from the PARTNER II trials in intermediate-risk patients. Data presented in PCR London Valves 18th November ; London; United Kingdom. https://www.pcronline.com/Cases-resources-images/Resources/Course-videos-slides/2019/Late-Breaking-Trials-at-PCR-London-Valves-2019-Session-2?auth=true. Accessed 17 Mar 2020.
15. Schymik G, Wendler O, Hengstenberg C, et al. Outcomes of transfemoral balloon expandable transcatheter aortic valve implantation: Comparison of two subsequent valve generations. Catheter Cardiovasc Interv. 2019:1–10. https://doi.org/10.1002/ccd.28621.
16. Van Belle E, Vincent F, Labreuche J, Auffret V, Debry N, Lefèvre T, et al. Balloon-expandable versus self-expanding Transcatheter aortic valve replacement. Circulation. 2020;141:243–59.
17. Forcillo J, Pellerin M, Perrault LP, Cartier R, Bouchard D, Demers P, et al. Carpentier-Edwards pericardial valve in the aortic position: 25-years experience. Ann Thorac Surg. 2013;96:486–93.
18. Nielsen PH, Hjortdal V, Modrau IS, Jensen H, Kimose H-H, Terp K, et al. Durability after aortic valve replacement with the Mitroflow versus the Perimount pericardial bioprosthesis: a single-Centre experience in 2393 patients. Eur J Cardio-Thoracic Surg. 2016;49:1705–10.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 2007;4:e296.
20. Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardio-Thoracic Surg. 2012;41:734–45.
21. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hebert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. Lancet. 1999;353:205–6.
22. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research Consortium-2 consensus document†. Eur Heart J. 2012;33:2403–18.
23. Biancari F, Ruggieri VG, Perrotti A, Svenarud P, Dalén M, Onorati F, et al. European multicenter study on coronary artery bypass grafting (E-CABG registry): study protocol for a prospective clinical registry and proposal of classification of postoperative complications. J Cardiothorac Surg. 2015;10:90.
24. Acute Kidney Injury Work Group. Section 2: AKI definition. Kidney Int Suppl. 2012;2:19–36.
25. Pibarot P, Hahn RT, Weissman NJ, Arsenault M, Beaudoin J, Bernier M, et al. Association of paravalvular regurgitation with 1-year outcomes after transcatheter aortic valve replacement with the SAPIEN 3 valve. JAMA Cardiol. 2017;2:1208–16.
26. Fatima B, Mohananey D, Khan FW, Jobanputra Y, Tummala R, Banerjee K, et al. Durability data for bioprosthetic surgical aortic valve. JAMA Cardiol. 2019;4:71–80.
27. Costa G, Zappulla P, Barbanti M, Cirasa A, Todaro D, Rapisarda G, et al. Pacemaker dependency after transcatheter aortic valve implantation: incidence, predictors and long-term outcomes. EuroIntervention. 2019;15:875–83.
28. Husser O, Pellegrini C, Kessler T, Burgdorf C, Thaller H, Mayr NP, et al. Predictors of permanent pacemaker implantations and new-onset conduction abnormalities with the SAPIEN 3 balloon-expandable Transcatheter heart valve. JACC Cardiovasc Interv. 2016;9:244–54.
29. Mauri V, Reimann A, Stern D, Scherner M, Kuhn E, Rudolph V, et al. Predictors of permanent pacemaker implantation after Transcatheter aortic valve replacement with the SAPIEN 3. JACC Cardiovasc Interv. 2016;9:2200–9.
30. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the Management of Patients with Valvular Heart Disease. Circulation. 2014;129:e521–643.
31. D'Ascenzo F, Verardi R, Visconti M, Conrotto F, Scacciatella P, Dziewierz A, et al. Independent impact of extent of coronary artery disease and percutaneous revascularisation on 30-day and one-year mortality after TAVI: a meta-analysis of adjusted observational results. EuroIntervention. 2018;14:e1169–77.

Publisher's Note