

Decision-making preceding transcatheter aortic valve implantation in frail older adults

Vulnerable autonomy, novel frailty scoring and clinical outcomes important to treatment strategy. A mixed method study

Elisabeth Skaar

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2020

UNIVERSITY OF BERGEN



Decision-making preceding transcatheter aortic valve implantation in frail older adults

Vulnerable autonomy, novel frailty scoring and clinical
outcomes important to treatment strategy. A mixed
method study

Elisabeth Skaar



Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 24.04.2020

© Copyright Elisabeth Skaar

The material in this publication is covered by the provisions of the Copyright Act.

Year: 2020

Title: Decision-making preceding transcatheter aortic valve implantation in frail older adults

Name: Elisabeth Skaar

Print: Skipnes Kommunikasjon / University of Bergen

*“...for the
old ones are
like tigers and
polar bears*

irreplaceable

*even so
soon
gone”*

Scientific environment

This research project was performed in the Department of Heart Disease at Haukeland University Hospital and the Department of Clinical Science at the University of Bergen, Norway. Kavli Research Centre for Geriatrics and Dementia, Haraldsplass Deaconess Hospital, Bergen, provided regular seminars and opportunities to present and discuss the project with senior researchers.

Main supervisor:

Margrethe Aase Schaufel, PhD. Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway. Cardiologist and consultant in Thoracic Medicine.

Co-supervisors:

Anette Hysten Ranhoff, Professor, Department of Clinical Science, University of Bergen and Kavli Research Centre for Geriatrics and Dementia, Haraldsplass Deaconess Hospital, Bergen, Norway. Geriatrician.

Jan Erik Nordrehaug, Professor Emeritus, Department of Clinical Science, University of Bergen, Norway. Previously head of the Department of Heart Disease, Haukeland University Hospital. Interventional cardiologist.

I participated in PhD courses at the University of Bergen and attended the European Academy for Medicine of Ageing (EAMA), an advanced postgraduate course in geriatric medicine.

Funded by

The Grieg Foundation (main contributor), Bergen

The Western Norway Regional Health Authority

Department of Heart Disease, Haukeland University Hospital, Helse Bergen

Kavli Research Centre for Geriatrics and Dementia, Haraldsplass Deaconess Hospital, Bergen, Norway.

Acknowledgements

First of all, many thanks to the participants in the studies for allowing me to examine them at a crucial time in their lives. Special thanks go to the ten participants in the qualitative study for making me more aware of the decision-making process and affecting how I practice medicine by encouraging me to involve patients to a greater degree and actively seek their values and goals. I feel privileged for having got to know you.

Margrethe Aase Schaufel (MAS) is the best main supervisor I could ever have wished for, always inspiring me to work hard and improve (by her example, not by telling me to). In addition to regular meetings, we have had supervision in the most peculiar places like cycling to work, on staircases, on the bus or during Margrethe's maternity leave with her baby as a sometimes loud participant. You have supported me all the way, even when it meant taking the train to Oslo (500 km) after a late shift at the hospital to assess my first oral presentation. When I struggled, you always found a solution; you have a bright brain and a warm heart and I envy your future PhD candidates.

My deepest gratitude to Jan Erik Nordrehaug (JEN), without whom this project would not have taken place. You have the ability to rapidly grasp complex problems, such as providing substantial input on the frailty score without extensive knowledge of geriatric medicine. When I asked you to be my supervisor for this thesis you told me you would be like a "good father", and you have been precisely that. I am very grateful for your caring comments as well as your important input at all stages of the process.

I am so grateful for having had Anette Hylén Ranhoff (AHR) as a co-supervisor. You were enthusiastic about this project from the beginning and your extensive knowledge of research in geriatric medicine made this thesis possible. For many years you have been the Director of the Kavli Research Centre for Geriatrics and Dementia at Haraldsplass Deaconess Hospital and Professor of Geriatric Medicine at the University of Bergen. There was little academic geriatric medicine in Bergen before you arrived

and building a sustainable research environment takes years of hard work. I will always be grateful that you chose to commute to Bergen from Oslo for so many years. Your efforts are of great importance in providing better care for frail older adults.

It was challenging to get funding for this project and I am grateful for the financial contributions from the Western Norway Regional Health Authority, the Department of Heart Disease at Haukeland University Hospital, Kavli Research Centre for Geriatrics and Dementia at Haraldsplass Deaconess Hospital and last, but not least, for the substantial contributions from the Grieg Foundation.

Thanks to the head of interventional cardiology at Haukeland University Hospital, Øyvind Bleie (interventional cardiologist and TAVI operator). Without your enthusiasm, this would have been a dissertation for the drawer. You facilitate frailty screening and contribute regularly in informing patients and relatives, also when TAVI is regarded as futile.

Daniel E. Forman and Andreas W. Schoenenberger, thank you for our extensive meetings: discussing and planning this project at the Norwegian Society of Cardiology's spring meeting in Bergen 2014 (Forman), the EuGMS in Oslo in 2015 (both) and the EuGMS in Lisbon in 2016 (Schoenenberger). Being international leaders in the field of geriatric cardiology you have both contributed substantially to the papers of this thesis and I am very grateful for all your work.

Leslie Sofia Pareja Eide and Tone Norekvål, thank you for inviting me to use data from the CARDELIR studies in this project, and thanks for considerable input as co-authors. Karl Ove Hufthammer, you are not only an eminent statistician, you are also good at English grammar and spelling, and have contributed substantially in both areas. Thanks to Karel Kuiper, who with his wise comments during the whole project has contributed significantly to both the planning and writing of the papers. Thanks to my other co-authors, Jørund Langørgen (cardiologist working in intensive care medicine), Rune Haaverstad (cardiac surgeon), Erik Packer and Anja Øksnes (both

interventional cardiologists and TAVI operators). You have all contributed to discussion and planning of the study and writing the manuscript; thank you for your time and effort.

I also wish to thank the Department of Heart Disease for funding and Kjell Vikenes, Nils Walde, Geir Atle Myrmoen, Eivind Solheim and Torbjørn Lunde of the Department for facilitating my research in a busy hospital environment and allowing me to concentrate on finishing the thesis in autumn 2019.

Thanks to the members of Kavli Research Centre Advisory Board, Anette Hylene Ranhoff, Anne-Rita Øksengård, Simon Conroy, Olav Sletvold, Boo Johansson, Marie Ernsth Brawell and Ingvild Saltvedt, for allowing me to discuss the thesis from when it was just an idea and throughout the process. And thanks to the Bergen Research Group in Geriatric Medicine/BOLD/Kavli network with Anette, Susanne, Marit, Ole Martin, Ida, Mala, Katinka, Ragnhild, Randi, Bård, Frøydis and Charlotte.

Lectures during medical school at the University of Oslo held by Knut Laake† and Knut Engedal aroused my interest in geriatric medicine. This interest was nourished at Olaviken Hospital for Old Age Psychiatry, with Harald A. Nygaard, Synnøve Grønn, Åslaug Mjøs† and Tor Jacob Moe. Thanks also to Haraldsplass Deaconess Hospital with its inspiring geriatricians Tor Magne, Paal, Mala, Sabine, Charlotte and Kyrre.

To the British-Nordic EAMA group, Esa, Hanna, Rannveig, Susanne, Thomas and Marit, who combined friendship and academia in a perfect mix, thank you for everything, I feel so privileged to know you.

Thanks also to the university librarians Regina Lein and Randi Bolstad for your help with the PubMed search and EndNote. Thanks to Irene Lavik Hjelmaas of the University of Bergen for following up my PhD programme and giving friendly reminders of important dates.

I want to thank the TAVI frailty team (including the leaders), bringing research from papers to patients; we started screening for frailty in TAVI patients during spring 2016. Julie Drevdal, Kari Henriksen, Siren Dahl, Astri Frantzen, Kjersti Hopland, Sissel Hindenes, Maren Eriksen, Vegard Solhaug, Rune Olsen, Anne-Grethe Danielsen, Carina Slettestøl, Hilde Døskeland, Elfrid Staveland, Renate Solheimsnes, Daghild Dencker, Gøril Drag Isaksen and Kristin Espelid. Thanks also to Chandru Punwani.

Thanks go to Kirsti Malterud, for significant input on the qualitative paper and for lectures in qualitative research, and to Ole Fritjof Norheim for recommendations of important theory.

To my colleagues in the Department of Heart Disease, Haukeland University Hospital, I feel privileged to work with you all. Thanks to the interventional cardiologists and TAVI operators Erlend Eriksen and Jon Herstad, and to cardiac surgeon Vegard Ellensen for participating in discussions on when TAVI might be futile. Thanks to Vegard Tuseth as head of the research group in interventional cardiology.

I would also like to thank the patient partners Svein Kristoffersen and Hjørdis Dahle for interesting discussions of the thesis.

I started out by being a girl scout in the YMCA/YWCA in Os, where my mother Solveig was the “meisemor” (leader of the group), during primary school. I continued as a member of the YMCA/YWCA in Ten Sing in my teenage and young adult years. During these years I participated in regular discussions on ethics and I would not have had a focus on ethics in this thesis if it had not been for those important years.

Thanks to my beloved family, my brother John and sister Anne Catherine, my mother Solveig and my father Knut Magnus. A very special thanks to my best friend Erle, who also feels like part of my family. Thanks to my dear friends, my in-laws, nieces and nephews.

Thanks to my husband Håvard, whose bad jokes I have enjoyed for 30 years (and still do). You are the rock of my life. You have contributed by reading manuscripts, providing statistical input and in general being very supportive. And thanks to our children Ingeborg, Sunniva and Magnus for bringing so much to my life and for being so wonderful.

Bergen, January 2020

Abbreviations

ACC American College of Cardiology

ACP Advance Care Planning

ADL Activity/Activities of Daily Living

AS Aortic Stenosis

BMI Body Mass Index

CCS Canadian Cardiovascular Society

CGA Comprehensive Geriatric Assessment

d days

ESC European Society of Cardiology

EuroSCORE European System for Cardiac Operative Risk Evaluation

GA Geriatric Assessment

HADS Hospital Anxiety and Depression Scale

LOS Length of stay

MMSE Mini Mental Status Examination

NEADL Nottingham Extended Activities of Daily Living

NORIC Norwegian Registry of Interventional Cardiology

NYHA New York Heart Association

REK Regional Committee for Medical Research Ethics

ROC receiver operating characteristic

SAVR Surgical Aortic Valve Replacement

SD Standard Deviation

SDM Shared Decision-Making

SPPB Short Physical Performance Battery

SOF Study of Osteoporotic Fracture

STC Systematic Text Condensation

STS score Society of Thoracic Surgeons score

TAVI Transcatheter Aortic Valve Implantation

VHD Valvular Heart Disease

List of publications

Paper 1: Conditions for autonomous choice: a qualitative study of older adults' experience of decision-making in TAVR. Elisabeth Skaar, Anette Hylen Ranhoff, Jan Erik Nordrehaug, Daniel E Forman, Margrethe Aase Schaufel. *Journal of Geriatric Cardiology* (2017) 14: 42-48.

Paper 2: A novel Geriatric Assessment frailty score predicts two-year mortality after Transcatheter Aortic Valve Implantation. Skaar, E, Eide, L.S.P, Norekvål, T.M, Ranhoff, A.H, Nordrehaug, J.E, Forman, D.E, Schoenenberger, A.W, Hufthammer, K.O, Kuiper, K.K.J, Bleie, Ø, Packer, E.J.S, Langørgen, J, Haaverstad, R, Schaufel, M.A. *European Heart Journal - Quality of Care and Clinical Outcomes* (2018) 00, 1–8. doi:10.1093/ehjqcco/qcy044

Paper 3: Baseline frailty status and outcomes important for shared decision-making in older adults receiving Transcatheter Aortic Valve Implantation, a prospective observational study. Skaar, E, Øksnes, A., Eide, L.S.P, Norekvål, T.M, Ranhoff, A.H, Nordrehaug, J.E, Forman, D.E, Schoenenberger, A.W, Hufthammer, K.O, Kuiper, K.K.J, Bleie, Ø, Packer, E.J.S, Langørgen, J, Haaverstad, R, Schaufel, M.A. Under review.

Abstract

Introduction

Transcatheter aortic valve implantation (TAVI), also known as transcatheter aortic valve replacement (TAVR), is a new technique for treating severe, symptomatic aortic stenosis. The mean age for TAVI patients is over 80 years and most of the patients have comorbidities and frailty. Some patients may be too frail and have a short life expectancy even after the intervention, and will benefit more from a palliative approach. Established surgical scores have limitations in determining risk among candidates for TAVI. Assessment of frailty might help to estimate the mortality risk and identify patients likely to benefit from treatment. On the other hand, there is a risk of ageism and undertreating older adults. How can we select the right patients for the procedure? Patient autonomy is a leading principle in bioethics and a basis for shared decision-making. In the light of the increasing focus on patient-centred care, this project has explored TAVI patients' experience of the decision-making process preceding intervention. This thesis consists of three studies focusing on the decision-making process prior to TAVI. Paper 1 focuses on the patient perspective, paper 2 takes the doctors' viewpoint and paper 3 includes both perspectives.

Aims

The aim of paper one was to explore conditions for autonomous choice as experienced by older adults who recently underwent transcatheter aortic valve implantation.

The aim of paper two was to develop a frailty score to guide the decision for TAVI.

The aim of paper three was to examine baseline characteristics and clinical outcomes important to older adults and their doctors to enhance shared decision-making prior to transcatheter aortic valve implantation.

Materials and methods

We conducted a mixed method study, with one qualitative sub-study (paper 1) and two quantitative sub-studies (papers 2 and 3). All patients underwent TAVI due to severe and symptomatic aortic stenosis. The qualitative study involved semi-structured interviews of a purposive sample of ten older adults after the procedure. Analysis was by systematic text condensation.

In paper 2 we conducted a prospective observational study in 82 patients ≥ 70 years accepted for TAVI from 2013 to 2015 and 65 patients ≥ 80 years (from a concomitant study on delirium) accepted from 2011 to 2013, giving a total of 147 patients. Prior to the procedure, a geriatric assessment (GA) was completed in 142 patients (missing data for calculating frailty score in five patients). Based on this, an eight-element frailty score with a 0–9 (least frail to most frail) scale was developed. In paper 3 we conducted a prospective, observational study of 82 TAVI patients ≥ 70 years (the last cohort of study 2), with two-year follow-up focusing on baseline frailty status (including cognitive deficits) and outcome measures important for shared decision-making prior to the procedure.

Results

In paper 1, the median age of the included patients was 83.5 years (range 73–89 years). Even when choice seemed difficult or lacking, TAVI patients deliberately took the chance presented to them by taking into account risk assessment, ambivalence and fate. They regarded declining the treatment as worse than accepting the risk related to the procedure. The experience of being carefully advised by their doctor formed the basis of autonomous trust. This trust mitigated ambivalence about the procedure and risks. TAVI patients claimed that it had to be their decision and expressed feelings consistent with self-empowerment. Despite this, choosing the procedure as an obligation to their family or passively accepting it were also reported.

In paper 2, patients had a mean age of 83 (SD 4) years, and 54% were women. The novel GA frailty score predicted two-year mortality in Cox analysis, also when adjusted for gender, age and logistic EuroSCORE (HR 1.75, 95% CI: 1.28–2.42, $P < 0.001$). A ROC curve analysis indicated that a GA frailty cut-off score of ≥ 4 predicted

two-year mortality with a specificity of 80% (95% CI: 73%–86%) and a sensitivity of 60% (95% CI: 36%–80%), and the area under the curve was 0.81 (CI 0.71–0.90). All-cause two-year mortality was 11%.

In paper 3, mean age was 83 years (SD 4.7) and 48% were women. Fifteen patients (18%) had a Mini Mental Status Examination (MMSE) score below 24 points at baseline, indicating cognitive impairment or dementia, while five patients had an MMSE below 20 points. At baseline and six months, mean New York Heart Association (NYHA) class was 2.5 (SD 0.6) and 1.4 (SD 0.6) ($p < 0.001$) respectively. Between baseline and six months there was no change in the mean scores on the Nottingham Extended Activities of Daily Living (NEADL) scale, with 54.2 (SD 11.5) and 54.5 (SD 10.3) points, mean difference 0.3 ($p = 0.7$). At two years, six patients (7%) had died, four (5%, $n = 79$) lived in a nursing home, six (7%) had contracted infective endocarditis, and four (5%) had had a disabling stroke.

Conclusion

This study provides empirically-based descriptions of the conditions for TAVI patients' autonomy as experienced in the decision-making process, to assist clinicians obtaining valid informed consent. We found that a frailty scale based on geriatric assessment predicted two-year mortality in TAVI patients beyond the established risk score. Patients had symptom improvement and could maintain activities of daily living six months after TAVI, and had low mortality after two years. Rarely, severe complications occurred, such as stroke and endocarditis. Some patients had cognitive impairment or dementia at baseline, which might have influenced the decision-making process. Our findings provide support to identify patients with higher risk and lower expected benefit after TAVI, and circumstances under which the procedure might be futile. The decision to offer the procedure should be a careful evaluation by the heart team, and involve considering frailty, symptom burden and technical challenges, and exploring patient preferences, before offering TAVI.

CONTENTS

1. Introduction	1
1.1 Aortic stenosis and treatment options	1
1.1.1 Aortic stenosis (AS)	1
1.1.2 Surgical aortic valve replacement	1
1.1.2 Transcatheter aortic valve implantation	2
1.1.3 Conservative strategy and transition to palliative care	3
1.2 The decision-making process	4
1.2.1 The heart team	4
1.2.2 Established risk scores	5
1.2.3 Autonomy and shared decision-making	5
1.2.4 Cognitive impairment and informed consent	6
1.2.5 Futility	7
1.3 Frailty	7
1.3.1 Definition of frailty	7
1.3.2. Comprehensive geriatric assessment and geriatric assessment	8
1.3.3 Predictive value of frailty assessment before TAVI	9
2. Aims	10
3. Methods	11
3.1 Study setting (all three papers)	11
3.2 Ethical considerations	11
3.3 Study design and analysis, study 1	12
3.3.1 Data collection	12
3.3.2 Participants	14
3.3.3 Analysis by systematic text condensation	14
3.4 Study design and analysis (studies 2 and 3)	16
3.4.1 Study period and data collection	16
3.4.2. Assessment tools	17
3.4.3 Developing a novel frailty scale	20
3.4.4 Statistics	21
3.4.5 Missing variables	22
4. Summary of results	23

5. Discussion	26
5.1 Methodological aspects (study 1)	26
5.1.1 <i>Internal validity</i>	26
5.1.2 <i>External validity</i>	28
5.1.3 <i>Sample size</i>	28
5.1.4 <i>Reflexivity</i>	29
5.2 Methodological aspects (studies 2 and 3)	30
5.2.1 <i>Study design</i>	30
5.2.2 <i>Power calculations</i>	31
5.2.3 <i>The cost of dichotomizing continuous variables</i>	32
5.2.4 <i>Cut-offs for variables in the novel frailty score</i>	32
5.3 Discussion of main results	34
5.3.1 <i>Benefit and risk</i>	34
5.3.2 <i>Shared decision-making, autonomy and trust</i>	40
5.3.3 <i>Vulnerable autonomy and the impact of cognitive impairment and dementia</i>	44
5.3.4 <i>Geriatric cardiology facilitating comprehensive decision-making</i>	46
6. Conclusions	47
7. Implications and suggestions	48
7.1 <i>Clinical practice</i>	48
7.2 <i>Future research</i>	48
8. References	49

1. Introduction

Due to the demography of an ageing population, decision-making in the oldest patients is increasingly important. Severe and symptomatic aortic stenosis has a high mortality rate without a new valve implantation. With advancing age, frailty and comorbidity, life expectancy might be short even after TAVI, and some patients may benefit from a palliative approach. The European Society of Cardiology (ESC) recommends an objective assessment of frailty before treatment decisions in patients with severe, symptomatic aortic stenosis; however, it has not been established which frailty assessments and which cut-offs should be used. Little is known about TAVI patients' motivation for the procedure and their experiences of autonomy in the preceding decision-making process. Shared decision-making is recommended to address these issues but can be difficult to achieve, and there may be limitations to the concept in certain circumstances.

1.1 Aortic stenosis and treatment options

1.1.1 Aortic stenosis (AS)

Degenerative calcific aortic stenosis is a common valve disease, with increasing prevalence due to the ageing population [1]. The prevalence of AS increases from 4% in 70- to 79-year-olds to 10% in the 80-89 age group [2]. Classification of the severity of AS is based on echocardiography; high gradient aortic stenosis with a valve area < 1 cm² and mean gradient > 40 mmHg, low-flow, low-gradient aortic stenosis with reduced or preserved ejection fraction and normal-flow, low-gradient aortic stenosis with preserved ejection fraction. Details of this assessment will be found in the ESC guideline documents [1]. When patients with severe AS develop typical symptoms like syncope, angina or dyspnoea, the prognosis is poor without intervention [1], usually stated as a two-year survival rate of 50% [3, 4].

1.1.2 Surgical aortic valve replacement

Surgical aortic valve replacement (SAVR) has been a treatment option for AS since the 1960s. However, about 30% of the patients were denied surgery due to high risk,

and most were older adults [5]. Multivariate risk scores evaluating both cardiac and extra-cardiac factors are used to define high-risk patients, such as the Society of Thoracic Surgeons score [6] and the EuroSCORE [7]. SAVR involves splitting of the sternum, a general anaesthetic, a heart-lung machine, an operating time of 3-5 hours, a hospital stay of 5-10 days and 2-3 months recovery time [8].

1.1.2 Transcatheter aortic valve implantation

Since it was first performed in 2002 [9], TAVI has emerged as an option for inoperable or high-risk patients with severe, symptomatic aortic stenosis. TAVI is non-inferior or superior to SAVR in high-risk patients [10], and superior to standard care (which often included balloon aortic valvuloplasty) in inoperable patients [3]. Later studies have proven TAVI superior to SAVR when femoral TAVI access is used in intermediate-risk patients. For low-risk and younger patients, recent studies demonstrated comparable safety and efficiency of TAVI and SAVR, with one-year all-cause mortality, short-term and one-year stroke and myocardial infarction similar in both groups [11]. At present, transcatheter aortic valve implantation is not recommended in asymptomatic patients by the European valve guidelines [1]. The concept of frailty, as defined below, has been related to TAVI from the beginning, as TAVI was initially developed for patients with severe aortic stenosis considered too frail for surgery [12]. The ESC states: “*criteria for when TAVI should no longer be performed since it would be futile need to be further defined*” [1]. The procedure takes under two hours, hospital stay is usually 2-5 days and recovery time is about one month [8].

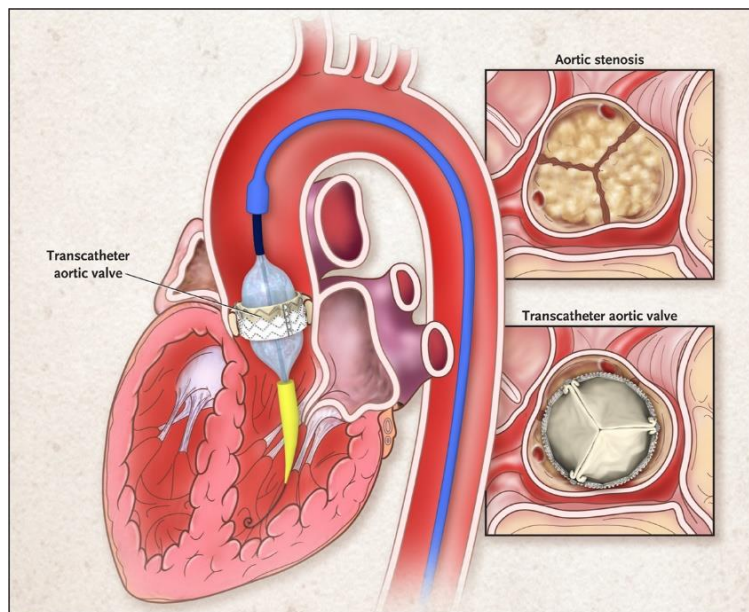


Figure 1: Illustration of the TAVI procedure: “The transcatheter valve is placed at the level of the native aortic valve during the final step of valve replacement, when the balloon is inflated within the native valve during a short period of rapid ventricular pacing. The delivery system is shown when it has traversed the aorta retrograde over a guidewire from its point of insertion in the femoral artery (transfemoral placement). Before balloon inflation, the valve and balloon are collapsed on the catheter (dark blue) and fit inside the sheath (blue). After balloon inflation, the calcified native valve (upper panel) is replaced by the expanded transcatheter valve (lower panel, shown in short-axis view from the aortic side of the valve)”. Reproduced with permission from [10]. Copyright Massachusetts Medical Society.

1.1.3 Conservative strategy and transition to palliative care

The ESC guideline on valvular heart disease has limited recommendations on how to provide care for patients refused for both surgery and TAVI [1]. Most patients with severe aortic stenosis progress to heart failure before death [13], and recommendations for palliative care in heart failure [14] are emphasized to guide clinicians [13]. Palliative care is an approach that improves quality of life for patients with life-limiting conditions and their families, by early identification and treatment of symptoms and other physical, psychosocial and spiritual problems [15]. Some centres have developed palliative care services for patients when TAVI is regarded as futile [13]. However, only a small percentage of heart failure patients are referred to

palliative care [16]. Further research on how to provide palliative care to patients with heart failure is warranted. Traditionally cardiologists have reported an unwillingness to discuss information such as poor prognosis [17]. In a recent expert position statement for people living with heart failure, the authors highlight that palliative care improves quality of life and should complement cardiac care, instead of being seen as an alternative to it [18].

1.2 The decision-making process

1.2.1 The heart team

It is recommended that all decisions on treatment for severe, symptomatic aortic stenosis are discussed in a heart team with particular expertise in valvular heart disease (VHD). The team should consist of “cardiologists, cardiac surgeons, imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians and heart failure, electrophysiology or intensive care specialists” [1].

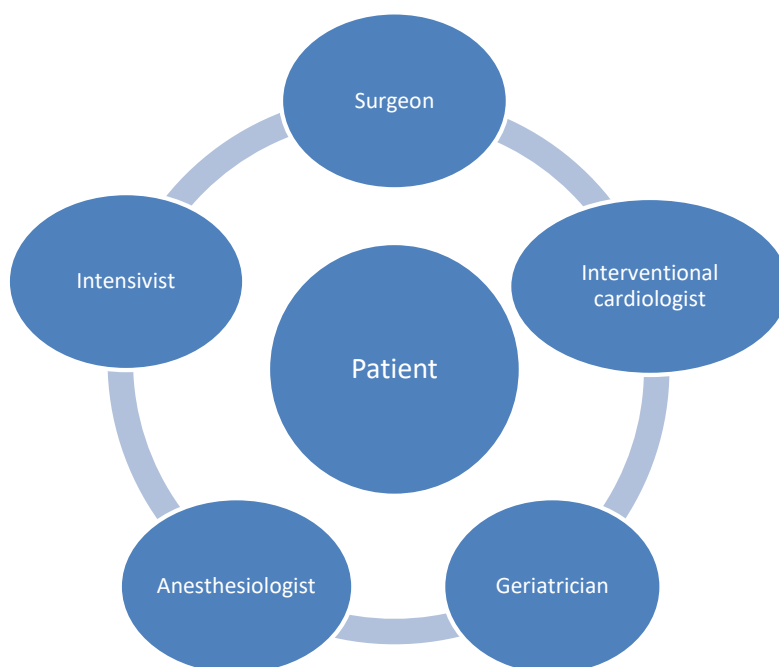


Figure 2: Composition of the heart team tailored to the patient's needs [19].

The ESC recommends a heart team to evaluate the severity and the aetiology of the VHD, the symptom burden and the likelihood that the symptoms are caused by VHD. They also recommended assessing life expectancy, expected quality of life, benefit-risk assumption, optimal treatment modality and patient preferences [1]. Where life expectancy is below one year, it is not recommended to perform TAVI, yet no standard means of prognostication is suggested.

In 2017, the American College of Cardiology (ACC) published an expert consensus pathway for TAVI in aortic stenosis patients [20]. This document discusses in detail the possibility of TAVI being futile and recommends methods to assess frailty, an aspect that is scarcely mentioned in the European Valve Guidelines. The ESC guidelines state that age ≥ 75 years, presence of severe comorbidity and frailty favour TAVI over SAVR [1]. However, there is also an understanding that for the frailest patients TAVI might be futile and a conservative approach is recommended for these patients [21].

1.2.2 Established risk scores

Operative mortality is estimated by different multivariate scoring systems based on combinations of risk factors. The two most common are the European System for Cardiac Operative Risk Evaluation (EuroSCORE), [7, 22] and the Society of Thoracic Surgeons score (STS score) [6]. These successfully distinguish between high-risk and low-risk patients, but lack accuracy in estimating operative mortality in individual patients, and have major limitations in not including risk factors such as frailty [23]. At present there is no established TAVI risk score; however, when deciding between SAVR and TAVI, the ESC guidelines state that $STS \geq 4\%$ and logistic EuroSCORE $\geq 10\%$ favour TAVI [1].

1.2.3 Autonomy and shared decision-making

Previously, paternalism was the common basis for decision-making in medicine, where doctors made treatment decisions without involving the patient. The aims of medicine were defined in objective terms, such as “maximizing health or prolonging life” [24]. Even though paternalism still exists in medicine and may be the preferred

model for instance in emergency care in which shared decision-making has limitations, the latter is now the ideal. This involves the patient in treatment decisions and recognizes that “the patient’s well-being should be the essential aim of medicine, and it has a substantial ‘subjective’ component”, due to the patient’s goals and values [24]. However, treatment decisions for older adults may entail both paternalist and autonomous factors [25]. Autonomy is a core element of shared decision-making and forms the basis of informed consent. Autonomy is defined by Beauchamp and Childress as based on three conditions, *intentionality, understanding and non-control* [26]. Autonomy does not mean, however, that patients freely can choose their treatment. “The authority of the patient to order a particular treatment, however, is more limited than the authority to refuse one” [24]. This will also depend on the health care setting and priorities in the patient’s location.

In Norway, health care is mostly publicly funded, and national priorities will impact patients’ possibilities to choose treatment [27]. Patients are not free to choose between SAVR and TAVI or between TAVI and conservative treatment. Treatment decisions are made in the heart teams at university hospitals, preferably supplemented by doctors who know the patients. The legislation stipulates that patients should be involved in decision-making [28] and the Minister of Health also highlighted this in his speech to the specialist health care services in 2018, with the words: “No decision about me, without me” (first stated by the UK Secretary of State for Health, Andrew Lansley, in 2010 [29]) and the Minister also stated that patient involvement must be the rule in all health care services [28]. However, the extent to which this is implemented is unknown and difficult to measure. We therefore wished to investigate how older adults undergoing TAVI experience conditions for autonomous decisions.

1.2.4 Cognitive impairment and informed consent

The population of older adults is growing and the number of patients with cognitive impairment and dementia increases with higher age [30]. Health care workers need to be aware that some older patients have reduced capacity to give an informed consent to treatment and to participate in shared decision-making [31]. To provide an informed consent the patient needs to communicate a choice, understand the information, be

aware of the situation and its consequences and reason about treatment options [32]. In Norway, when patients lack capacity to participate in decision-making, health care may be provided if it is likely that the patient would have consented to and preferred treatment. If possible, the patient's family should be contacted to provide information of what the patient would have wanted [28]. This thesis also explores the challenges of decision-making regarding TAVI in the context of cognitive impairment in order to assist both clinicians and patients in making the optimal choice.

1.2.5 Futility

Therapeutic futility is defined as lack of medical efficiency, particularly when the therapy is unlikely to produce its intended clinical result, as assessed by the doctor, or lack of a meaningful survival, as considered in relation to the personal values of the patient [33]. It is well-documented that TAVI improves symptoms and prolongs life, and most older adults with severe symptomatic AS would benefit from valve implantation. In some patients, however, judging benefit versus futility in TAVI patients is complex and must integrate different information to facilitate a shared decision [34].

1.3 Frailty

1.3.1 Definition of frailty

Frailty is defined as a state of reduced physiological reserve and diminished resistance to stressors, which increases the risk of adverse outcome [35, 36]. Stressors are classified as acute or chronic disease or iatrogenic, such as surgery or intervention [12]. The prevalence of frailty increases with age and it is more common in women [37]. Most older adults over 85 years are not frail, demonstrating the concept of biological versus chronological age [38] and the considerable variation among the oldest patients. However, there is no consensus on the definition. Several attempts have been made to reach agreement, but have been unsuccessful due to the inability to settle for a "single operational definition of frailty that can satisfy all experts" [39]. Physical frailty based on the Fried criteria [35] or the frailty index of Rockwood [40], based on an accumulation of deficits, are the two most widespread approaches to

frailty. The physical phenotype of frailty shows significant overlap with sarcopenia [41], which is defined as a progressive and generalized muscle disorder. Severe sarcopenia is characterized by low muscle strength, low muscle quantity/quality and low physical performance [42]. Evaluating sarcopenia by measuring psoas muscle area and volume with a validated CT method outperformed other frailty assessments in predicting long-term mortality in TAVI patients [43].

Further, a method based on comprehensive geriatric assessment (CGA), without adopting the strict criteria of the frailty index, has also been used [44, 45]. The concept of frailty is used for different purposes, including identification of older adults in the community to prevent or delay functional decline and to decide which intervention should be implemented at specific time points [46]. In order to inform treatment strategy, the concept of physical frailty is insufficient; assessment of cognition and psychological status is also needed. Frailty defined on the basis of CGA is more applicable in clinical practice and therefore used in this thesis, inspired by the work of Kristjansson et al. and Stortecky et al. [45, 47]. The impact of heterogeneity in older age has been a focus of increasing interest in research, illustrated by the escalation in the number of PubMed papers on “frailty” from 74 in 2001 to 1988 in 2018. Even when procedures have low risk, frail patients still have higher risk of adverse outcomes [48].

1.3.2. Comprehensive geriatric assessment and geriatric assessment

Older adults might have complex, multiple and overlapping problems. Specialist coordinated care was developed to categorize the different components contributing to loss of function and disease. Comprehensive geriatric assessment (CGA) is a systematic examination of independence, physical functioning, comorbidity, polypharmacy, cognition, nutritional state, social network and emotional state in older adults [49]. A variety of different tests are used in a multidisciplinary team, assessing the different domains in order to tailor treatment to patient needs. We chose to use the term geriatric assessment (GA) for the frailty score used in this thesis because this has been used in similar publications focusing on preoperative assessment to identify frailty [50].

1.3.3 Predictive value of frailty assessment before TAVI

In the first paper on frailty screening before TAVI, a frailty index was constructed based on multidimensional geriatric assessment, including independence, cognition, nutrition and mobility. The authors demonstrated that this construct added information to the already existing risk scores in predicting mortality and morbidity [47].

Subsequently, several frailty scores have been advocated, both single-item screening followed by a more thorough examination, and more multifaceted assessments [12, 51]. Guidelines recommend measures of frailty, not subjective “eyeballing” or “end of the bed” assessments, to increase objectivity [1, 38]. In a systematic review on preoperative frailty and outcomes after TAVI from 2017, including 10 studies from Europe and North America and 4592 patients, the authors found that although the frailty instruments varied, measurement of frailty identified a population at double risk of both early (≤ 30 days) and late (>30 days) mortality [38].

Afilalo et al. [52] compared the incremental prognostic value of seven different frailty scores to predict poor outcomes following TAVR or SAVR and found that a brief 4-item scale encompassing lower-extremity weakness, cognitive impairment, anaemia and hypoalbuminemia outperformed other frailty scores. Despite a growing body of publications, there still is a need for research addressing the clinical applicability and reliability of different frailty scores in order to establish common standards in this field.

2. Aims

The overall aim of this thesis was to provide support in treatment strategies for frail older adults with severe aortic stenosis, where the TAVI procedure might be futile. We defined the following objectives to achieve this goal:

1. To explore conditions for autonomous choice as experienced by older adults who recently underwent trans-catheter aortic valve implantation.
2. To develop a frailty score to guide the decision for TAVI.
3. To examine baseline characteristics and clinical outcomes important to older adults and their doctors to enhance shared decision-making prior to transcatheter aortic valve implantation.

3. Methods

3.1 Study setting (all three papers)

All studies were performed in different subsamples of 147 patients admitted to Haukeland University Hospital to undergo TAVI. Eighty-two patients ≥ 70 years were included from October 2013 to April 2015 (studies 2 and 3). Of these 82 patients, 12 were included in the qualitative study (study 1). Another 65 patients ≥ 80 years were also participating in a concomitant study of delirium, between February 2011 to September 2013 (study 2) [53]. Haukeland University Hospital provides all SAVR and TAVI in Western Norway (serving a population of 1.1 million). The TAVI programme at this hospital started in 2010, with an increase in the number of procedures every year since then, reaching 126 TAVI procedures performed in 2018 [54].

The hospital has advanced interventional and surgical expertise. All patients in the study were discussed by a heart team including (as a minimum) cardiac surgeons, interventional cardiologists and imaging specialists, and often a doctor from the ward familiar with the patient, before TAVI treatment was offered.

3.2 Ethical considerations

Older adults are underrepresented in clinical research and considered more vulnerable and complex, making research challenging. In order to provide treatment with beneficence, non-maleficence and justice, we regard it as important also in an ethical perspective to perform studies in this age group. The studies in this thesis follow the principles of the Declaration of Helsinki, and were approved by the Regional Committee for Medical Research Ethics (REK 2010/2936-6 and 2013/1310). The studies included the usual care and no interventions; however, questionnaires and testing of cognition, emotional status and physical frailty (by LPE/ES at baseline) might have distressed patients and we strove to provide a calm and comfortable environment, reassuring the patients after testing. The numbers of questions and tests were kept at a minimum. For the qualitative interviews, patients seemed pleased to be visited and interviewed, expressing that they wanted to contribute to research and appreciated that their voice was being heard. Data were entered into a secure research

database at the hospital, and only a few members of the research team had access. All paper versions of questionnaires and tests were numbered and stored separately from personally identifying data. Patient identification linked to numbers was locked away in a separate cabinet where only ES had access.

Papers 2 and 3 have multiple co-authors to ensure interdisciplinary perspectives crucial to TAVI treatment, thus enhancing the likelihood of developing knowledge of clinical relevance and impact. None of the authors reported any conflict of interest, and none of the funders have influenced the thesis or papers in any way.

3.3 Study design and analysis, study 1

A qualitative design is recommended to investigate human experiences, motivation, interaction and thoughts, developing new knowledge that cannot be generated using quantitative methods [55, 56].

The qualitative study was conducted according to Kvale's principles for semi-structured individual interviews. These principles guided the interviews in terms of thematizing, designing, the interview situation, how to perform transcription, analysis, interpretation, verification and reporting of the results [57].

3.3.1 Data collection

Patients over 70 years were eligible for the study and were included before discharge from hospital, but after TAVI. We sought a purposive sample, emphasizing diversity in age, gender and complication rate. The only exclusion criteria was lack of fluency in Norwegian. Participants were approached face to face by the principal investigator on the ward, and all signed an informed consent.

The first interview was performed on 9 February 2014 and the last on 24 April 2015. All interviews were conducted by the same researcher 9 to 52 days after TAVI, most of them two to four weeks post-procedure. Two of the interviews (interviews 3 and 4) were conducted late after TAVI because the analysis process took more time than expected (patients were included during index hospital stay) and revision of the interview guide. Even though this delay might have caused recall bias, the patients involved were cognitively well-functioning and did not have any difficulty in recalling

the decision-making process. Interviews lasted from 30 minutes to one hour, and were terminated when all aspects of the interview guide had been covered. A semi-structured interview implies that the researcher does not rigorously follow the interview guide, but allows the conversation to develop around the main theme of the study. No interviews were ended due to interruption. One patient was interviewed at the local hospital, two in a rehabilitation facility and the remainder in the patient's home. In one interview the patient's spouse was in the same room but did not participate in the interview. In the other interviews only the researcher and patient were present. All interviews were audiotaped and transcribed verbatim by the primary investigator and analysed manually (without software). We gave the patients fictitious names from the outset. Field notes were taken before and after the interviews. Thirteen patients were invited, twelve were included, one withdrew and one was unable to attend the interview. Ten patients were therefore interviewed. The interviews were conducted using an interview guide, see the Appendix. The questions in the interview guide were developed through discussions between MAS and ES (see list of authors in paper 1). The questions explored why the patients wanted TAVI, how they experienced the information they received, difficulties in decision-making, risk of death, how they involved their family members, what hopes for the future were important to them and how they felt taken care of by health care professionals during the process. After the first two interviews, the guide was revised to add "What were your expectations?", "How much detail would you prefer in the information about risk before this intervention?" and "Could you tell me a bit about how you typically face challenges/hard times in life?" These questions were added in order to further explore motivation, communication preferences and coping strategies. Based on consecutive, stepwise analysis of the interviews, the aims of the study were readjusted to focus specifically on clinical ethics and experienced conditions for autonomous choice preceding TAVI, after initially mapping general patient perspectives and experiences of the decision-making process.

3.3.2 *Participants*

Ten patients were interviewed with an age span from 73 to 89 years, median age 83.5 years. Five lived alone and five lived with their spouse. Three scored 10 or more points on the Short Physical Performance Battery (SPPB), six scored between 7 and 9, and one had a score below 6 points, indicating physical frailty. The SPPB is a validated test for lower extremity function, including balance, walking speed and chair stand. It has a range from 0 to 12, where a higher score indicates better function [58]. Six had a Mini Mental Status Examination (MMSE) score [59] over 27 at baseline, while four had MMSE 25-27. The EuroSCORE [7] was 10-20 in seven patients, two had a score below 10, and one over 20. Three received a pacemaker and two had severe complications post-procedure. In this early TAVI era, the length of stay (LOS) was significantly longer than today. In 2018 median LOS after TAVI was three days at Haukeland University Hospital [54], while in the present study six patients stayed 6-7 days, one five days, one 10, one 11 and one 17 days. Five were discharged to home, one to the local hospital, three to rehabilitation and one to intermediate care in a nursing home. Eight were Christians, one was a member of the Norwegian Humanist Association, and one did not have a clearly defined religious belief. Their previous work was very varied, e.g. housewife, factory worker, musician, professor, carpenter, home-care attendant, entrepreneur and insurance agent.

3.3.3 *Analysis by systematic text condensation*

Qualitative analysis was performed by MAS and ES, using systematic text condensation (STC), as described by Malterud [60]. This is a cross-case, thematic analysis and a suitable method for developing new descriptions and concepts. One advantage of STC is the detailed description of the procedure, making it applicable for researchers without comprehensive theoretical training. We chose this procedure instead of other qualitative methods such as grounded theory because we had a well-defined research aim focusing on patients' experiences, rather than a desire to develop new classifications and theory [55]. The purpose is not to present a full range of phenomena, but vital examples from people's life-world experiences. A decision trail documented the choices made during the analytical process [61]. The analysis was

stepwise, with new interviews supplementing the previous ones, and de- and recontextualization of the audiotaped transcribed text. We chose an editing analysis style, described by Crabtree and Miller [62], where categories develop from the empirical data instead of being predefined. However, theory of shared decision-making [63] and autonomy [64, 65] inspired the analysis, and the different categories reflected this theoretical framework. Systematic text condensation consists of four stages [60].

1) *From chaos to themes, total impression*

The first step consists of reading the material to get a sense of the whole, looking for preliminary themes, bracketing previous preconceptions. We started by reading the first two interviews, identifying themes that gained our attention. ES found eight themes and MAS found four. After discussion and negotiation we agreed on four themes, medically necessary, mobilization of power, information dilemma and fear and death. The categories represented empirical findings and were not identified in advance.

2) *From themes to codes, identifying and sorting meaning units*

We searched for elements of the text (“meaning units”) that addressed the experience of the decision-making process. This is a systematic line by line evaluation. “Meaning unit” is defined as a text fragment focusing on phenomena being investigated, not limited to sentences or comments, but including all parts of the text addressing the phenomenon, here the experience of the decision-making process. Then we started coding, where we identified, categorized and sorted meaning units related to the themes. This is called decontextualization, since fragments of the text are collected to be read together with similar text elements. During coding the code groups are elaborated from the themes from the first step of the analysis. This is a dynamic process and code groups develop during the analysis. We did this manually, by cutting the sections out of the manuscript and joining the parts addressing similar subjects.

3) *From code to meaning - condensation*

We sorted the material in each code group into subgroups and reduced the content of each subgroup to a condensate. This is an artificial quotation in which patients' own words from the meaning units are used to create a summary of the findings. Specifically for STC, the condensate incorporates all text from the meaning units and prevents the researcher from favouring meaning units supporting her preconceptions. The purpose of the artificial quotation is to translate the content in the subgroups to a more generalized version, rooted in the data, being a working paper for the final summary. After the first five interviews, we discussed relevant theoretical aspects which would give the analysis more focus and depth. We then decided to shift the centre of our attention from general patient experiences to clinical ethics, using theory of autonomy and shared decision-making.

4) *Descriptions and concepts, synthesizing from condensation*

In the last step, all parts were put together and recontextualized. Synthesizing the content of the condensate, we elaborated descriptions and concepts, providing trustworthy stories that clarified the study question. Relevant quotations were selected for each theme, illustrating the results of descriptions and concepts reflecting the most important aspects of the experienced conditions for autonomous choice reported by the patients. The relevant themes revealed in step 1 were elaborated through the analytic process, by coding meaning units, condensation and recontextualization, resulting in the final categories: "Deliberately taking the chance", "Autonomous trust in their doctors" and "Fundamental self-determination based on personal identity".

3.4 Study design and analysis (studies 2 and 3)

3.4.1 Study period and data collection

One hundred and forty-seven TAVI patients were included, 82 patients ≥ 70 years from October 2013 to April 2015 and 65 patients ≥ 80 years, enrolled from February 2011 to September 2013 from a concomitant study on delirium [53]. Patients were included and baseline examinations were performed the day before the procedure.

3.4.2. Assessment tools

Mini Mental Status Examination (MMSE)

The Mini Mental Status Examination is widely used for screening of cognitive function, with a range from 0 to 30 points, higher scores indicating better cognition. It is a test of orientation, memory, attention, calculation, ability to name, to follow verbal and written commands, and to copy a polygon [59]. It should be interpreted with caution, and not be used as a diagnostic test of cognitive impairment or dementia. High age and low education might give a low score despite normal cognition, and the test might also be influenced by hearing loss, visual difficulties and physical illness [59]. MMSE was performed by LPE and ES at baseline (see author list in paper 2).

Nottingham Extended Activities of Daily Living (NEADL)

NEADL is a measure of independence in instrumental activities of daily living (I-ADL), beyond the basic ADL [66]. It assess mobility and kitchen, domestic and leisure activities. Each item is rated on a four-point scale from 0 to 3, (0=unable, 3=able) with higher scores representing higher independence. The maximum score is 66. NEADL was examined using a questionnaire at baseline (studies 2 and 3), and by telephone interviews at six months by ES in study 3 [66].

Study of osteoporotic fracture index (SOF index)

Physical frailty was assessed by the SOF index [67], consisting of three components: weight loss (using a modified version with patient reported weight loss, not measured as in the original index), incapacity to rise from a chair five times without using one's arms, and reduced energy level by answering "no" to the question "Do you feel full of energy?". Physical frailty is defined when two or more of these three components are present [67]. Chair stand was tested by LPE and ES (see author list in paper 2) and weight loss and energy were patient-reported (questionnaire). All measures were performed at baseline.

Hospital Anxiety and Depression Scale (HADS)

HADS [68] is a screening for mood disorders. It encompasses fourteen statements describing the patient's feelings and emotions, with seven items in each of the subscales anxiety and depression. Scoring ranges from 0 to 3 indicating probable absence, possible presence and probable presence of clinically meaningful degrees of the mood disorder. The response alternatives for each question have minor differences; however, a typical statement is: "I feel cheerful" with response options of "not at all=3", "not often=2", "sometimes=1" and "most of the time=0". The maximum score is 42, with a higher score representing probable/possible mood disorder. The HADS questionnaire was administered at baseline.

Charlson Comorbidity Index

The Charlson Comorbidity Index [69] is a commonly used index for assessing comorbidity. We searched the electronic medical records for previous diseases and thus did not consider comorbidity based on what was reported at this admission alone. The index consists of nineteen diseases, assigning different weighing depending on the severity of the disease, for instance one point for myocardial infarction, congestive heart failure, peripheral vascular disease and dementia, two points for hemiplegia, moderate or severe renal disease, three points for severe liver disease and six points for metastatic solid tumour and AIDS.

Nutrition

We assessed nutrition in two ways, calculating body mass index (BMI) and using the weight question from SOF [67], asking whether the person's weight had increased, decreased or been stable in the past year. In order to simplify the presentation, we only listed BMI under nutrition in the frailty score. In calculating BMI, weight was measured for all patients, height was measured in the first 65 patients and was patient-reported for the last 82 of the cohort.

New York Heart Association (NYHA)

We assessed the degree of symptoms of cardiac disease by NYHA classification [70], where NYHA class I represents no limitation of physical activity. Ordinary physical activity does not cause undue palpitation, fatigue dyspnoea, or angina pain. Class II: Slight limitation of physical activity, comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or angina pain. Class III: Marked limitation of physical activity, comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea, or angina pain. Class IV: Unable to carry on any physical activity without discomfort, symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases. NYHA at baseline was collected from the medical record and by telephone interview (ES) at six months.

European System for Cardiac Operative Risk Evaluation (EuroSCORE)

The logistic EuroSCORE [7, 71] is a scoring system estimating early mortality in heart surgery on the basis of objective risk factors. However, it overestimates 30-day mortality and ignores important risk factors like frailty, porcelain aorta and chest radiation therapy [1]. Low surgical risk by logistic EuroSCORE is defined with a score of <10%, intermediate risk 10-20%, and high surgical risk is defined as >20%. From 2012, it is recommended to replace this score with EuroSCORE II. However, when we planned the study it was still the preferred score in clinical practice, and we chose the logistic score for better comparison of our study with other TAVI studies [38, 72].

The logistic EuroSCORE covers age, gender (higher risk in females), chronic pulmonary disease, extracardiac arteriopathy (claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids), neurological dysfunction, previous cardiac surgery, creatinine > 200 $\mu\text{mol/L}$, active endocarditis, critical preoperative state, unstable angina, left ventricle function, recent myocardial infarction, pulmonary hypertension (systolic artery pressure >60 mmHg), emergency, other than isolated coronary artery bypass grafting, surgery on thoracic aorta and post-infarct septal rupture, giving different weight to the different domains. Neurological dysfunction is specified as disease severely affecting ambulation or day to day functioning.

3.4.3 *Developing a novel frailty scale*

To support the decision-making process we developed a frailty score based on geriatric assessment. Studies define frailty differently, but the specific aim of this study was to help identify frail patients, thus informing clinicians and patients as to whether TAVI might be futile. The concept of physical frailty (Fried model [35]) was considered too narrow, excluding important domains like cognitive function. The additional advantage of GA is that it closely resembles clinical work, using validated, well known assessment tools proven feasible in older adults. It is based on few parameters with a high degree of transparency regarding which domain is frail (cognition, nutrition, etc.), making it easier to understand and communicate to other members of the heart team. This is in contrast to the frailty index, where there are at least 30 recommended assessments, providing a score from 0 to 1, with a lower score indicating more severe frailty [73, 74]. The frailty score was inspired by the thesis of Siri Rostoft Kristjansson from 2011 [75] on surgery in patients with colorectal cancer, where frailty categorization based on comprehensive geriatric assessment predicted morbidity and mortality. When we planned the study, only one paper provided information on prediction of frailty in a TAVI population [47].

The statistical strategy is described by Harrell [76], where clinicians assign severity points to each condition and add the points to give a total score. Possible variables in the score were determined by the variables in the concomitant study on delirium [77], and the principal investigator (ES) sent e-mails to the geriatricians and the supervisors containing the different variables and explaining the principles from Harrell and asking them to provide a suggestion, and send it by return without copies to the others. The variables included assessment of cognition, instrumental activity of daily living, nutrition, physical frailty, comorbidity and psychological health. ES also provided a suggestion before reading the e-mails from the others. Independently, three geriatricians (AWS, AHR and ES, see author list paper 2) and one cardiologist (JEN, see author list paper 2) ranked the clinical severity of signs within each potential important domain. The different suggestions were sent to the first author who

developed a combined frailty score based on the different proposals, and returned this to the others. The researchers then agreed on the final score (Appendix).

Table 1: Geriatric assessment tools used in the novel frailty score and the corresponding scoring scheme

Domain	Cut-off	Points
Cognition	MMSE ≥ 27	0
	MMSE 20-26	1
	MMSE < 20	2
Instrumental activity of living	NEADL ≤ 43	1
Nutrition	BMI $< 20,5$	1
Energy level (SOF)	Low energy	1
Weight loss (SOF) ^a	Weight loss	1
Limb strength(SOF)	Chair stand (not able)	1
Comorbidity	Charlson Comorbidity Index ≥ 3	1
Psychological factors	HADS (total score) ≥ 15	1
Total	Maximum score	9

The total score is calculated by adding the different domain scores. BMI, Body Mass Index; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini Mental Status Examination; NEADL, Nottingham Extended Activities of Daily Living Scale; SOF, Study of Osteoporotic Fractures Index. ^a Modified from the original SOF, by self-reporting weight loss, not measured.

3.4.4 Statistics

All statistical analyses in the papers were performed by an experienced biostatistician (KOH, see author list in papers 2 and 3). We present the data as means and standard deviations, percentages and counts, or proportions and hazard ratios with 95% confidence intervals, as appropriate.

Paper 2:

To assess whether the new frailty score could predict mortality within two years, also when adjusted for other usual predictors, we fitted Cox regression models with Firth's correction. Firth's correction offers reduced bias when there are a small number of events (deaths) compared to the number of predictors. The regression models contained frailty score as a continuous predictor (unadjusted model and trend test), or

frailty score, gender, age and logistic EuroSCORE as predictors (adjusted model). We also fitted a similar adjusted model with frailty score as a dichotomized variable. Time to death stratified by frailty score (continuous or dichotomized) was demonstrated using Kaplan–Meier plots. Cut-off values for the dichotomized GA frailty score were found by examining the receiver operating characteristic (ROC) curve [78]. The area under the curve (AUC) was reported as a summary measure. We obtained two cut-off values with an estimated high sensitivity and specificity, and chose the one (≥ 4) that highlighted specificity over sensitivity. Confidence intervals for sensitivity and specificity were determined using the Wilson method [79].

We used IBM SPSS Statistics 24 and R version 3.5.0 for statistical analysis [80]. The ROC and AUC calculations were performed using the R ‘pROC’ package version [81], and the Cox regression with Firth’s correction was performed using the R ‘coxphf’ package version 1.13 [82].

Paper 3:

Changes from baseline to six months were analysed by paired *t*-tests. There were few missing data (< 6.1% for NEADL), and we therefore used complete case analysis and reported the number of observations each analysis was based on. We carried out statistical analysis in IBM SPSS Statistics 24 and R version 3.6.0 [80]. *P*-values <0.05 were considered significant.

3.4.5 Missing variables

Some patients had missing data for a few of the questions in the HADS and NEADL questionnaires. Where there was no ambiguity as to which side of the cut-off the total frailty score would fall on, we used the data for these patients. Otherwise, the patients were excluded from analysis. We lacked data for calculating the frailty score in five individuals. In one secondary analysis based on the mEFT frailty scale, there were additional missing data from three patients. In paper 3 there were few missing data, and for all analyses we reported the number of observations used.

4. Summary of results

Paper 1

Background and aims Patient autonomy is an important principle in bioethics and a basis for shared decision-making. This study explored conditions for autonomous choice as experienced by older adults who recently underwent TAVI.

Methods and results This was a qualitative study involving semi-structured interviews of a purposive sample of ten older adults (range 73-89, median 83.5 years) after TAVI (median 23 days). The study setting was a department of heart disease at a university hospital performing TAVI since 2010. Analysis was by systematic text condensation. Even when choice seemed difficult or lacking, TAVI patients deliberately took the chance offered them by taking into account risk assessment, ambivalence and fate. They regarded declining the treatment as worse than accepting the risk related to the procedure. The experience of being carefully advised by their doctor formed the basis of autonomous trust. The trust they felt for the doctors' recommendations mitigated ambivalence about the procedure and risks. TAVI patients expressed feelings consistent with self-empowerment and claimed that it had to be their decision. Despite this, choosing the intervention as an obligation to their family or passively accepting it were also reported.

Conclusions Older TAVI patients' experience of an autonomous decision may encompass a frank trade-off, deliberate dependency on the doctor as well as a resilient self-view. Doctors should be especially aware of how older adults' cognitive ability subtly declines and how the inclination to preserve their identity can influence decision-making when obtaining informed consent. Cardiologists and other providers may also use these insights to develop new strategies that better respond to such inherent complexities.

Paper 2

Background and aims: Established surgical scores have limitations in determining risk among candidates for transcatheter aortic valve implantation (TAVI). Assessment of frailty might help to estimate the mortality risk and identify patients likely to benefit from treatment. The aim of this study was to develop a frailty score to guide the decision for TAVI.

Methods and results: We conducted a prospective observational study in patients ≥ 70 years referred for TAVI during 2011-2015. A heart team had refused the patients for open heart surgery due to high risk but accepted them for TAVI. Prior to the procedure, a geriatric assessment (GA) was performed. Based on this, an eight-element frailty score with a 0-9 (least frail to most frail) scale was developed. A total of 142 patients, 54% women, mean age 83 (SD 4) years, with severe and symptomatic aortic stenosis were assessed. All-cause two-year mortality was 11%. The novel GA frailty score predicted two-year mortality in Cox analysis, also when adjusted for age, gender and logistic EuroSCORE (HR 1.75, 95% CI: 1.28-2.42, $p < 0.001$). A ROC curve analysis indicated that a GA frailty cut-off score of ≥ 4 predicted two-year mortality with a specificity of 80% (95% CI: 73%-86%) and a sensitivity of 60% (95% CI: 36%-80%). The area under the curve was 0.81 (CI 0.71-0.90).

Conclusion: A novel eight-element GA frailty score identified gradations of survival in patients refused for open heart surgery. Patients with higher GA frailty scores had significantly higher two-year mortality after TAVI.

Paper 3

Background and aims: Decision-making in frail older adults is challenging, where treating a single disease may have limited benefit due to other chronic conditions or functional decline. For older persons who are seriously ill, risk of losing independence might be more feared than death itself. The objective of this study was to examine baseline frailty status, including cognitive deficits and important clinical outcomes, to inform shared decision-making in older adults receiving Transcatheter Aortic valve Implantation (TAVI).

Methods and results: We conducted a prospective, observational study of 82 TAVI patients, recruited from 2013 to 2015, with two-year follow-up. Mean age was 83 years (SD 4.7). Eighteen percent of the patients were frail, as assessed with an eight-item frailty scale. Fifteen patients (18%) had a Mini Mental Status Examination (MMSE) score below 24 points at baseline, indicating cognitive impairment or dementia, while five patients had an MMSE below 20 points. Mean New York Heart Association (NYHA) class at baseline and six months was 2.5 (SD 0.6) and 1.4 (SD 0.6) ($P<0.001$). There was no change in the mean scores on the Nottingham Extended Activities of Daily Living (NEADL) scale between baseline and six months, at 54.2 (SD 11.5) and 54.5 (SD 10.3) points respectively, mean difference 0.3 ($p=0.7$). At two years, six patients (7%) had died, four (5%, $n=79$) lived in a nursing home, four (5%) had had a disabling stroke and six (7%) had contracted infective endocarditis.

Conclusion: TAVI patients had symptom improvement and could maintain activities of daily living at six months. They had low mortality and most patients lived in their own home two years after TAVI. Complications such as death, stroke and endocarditis occurred. Some patients had cognitive impairment before the procedure which might have influenced decision-making. Our findings may be used to develop pre-TAVI decision aids.

5. Discussion

5.1 Methodological aspects (study 1)

A qualitative design is suited to exploring patients' perspectives, experiences or views in order to provide complex and detailed descriptions of a phenomena, generating new knowledge not possible to obtain from predefined questionnaires [55, 56]. Have we used the best methods to shed light on our research question? The qualitative research interview is a relevant method when we aim to explore the meaning of social phenomena as experienced by the people themselves, although there are limitations to this design [56].

5.1.1 Internal validity

Contemporary qualitative studies belong to the tradition of postmodernism and social constructivism, in which the researcher is an active participant in the development of knowledge, and investigators are prepared to achieve partial understanding and to identify new questions about their research topic, rather than definite answers [56]. Internal validity asks whether the study investigates what it is meant to [55] or describes the phenomena that it was intended to describe, theorize or explain [62]. Among patients eligible for the study, we sought a sample with explicit variation, and the interviews contained rich and varied descriptions of the conditions for autonomy in the decision-making process [83]. Despite this, the questions in the interview guide might have been insufficient and different questions or another interviewer might have revealed other aspects [55]. Participants in studies differ in how personal they want to be, and some of the interviews were richer than others. During the interviews, patients disclosed both positive and negative aspects of the process they had been through, doctors they had seen and their own responses, suggesting that they answered honestly [57]. We aimed to achieve a quiet and calm atmosphere during the interviews, also when they were conducted in an institution [57]. The power asymmetry that normally exists in doctor-patient relationships may have been reduced by the interviewer not wearing a hospital uniform and being younger than the patients [84], yet there is an inherent imbalance between the researcher and the researched in qualitative health

research [85]. The interviewer was familiar with and fond of talking to older adults, and conscious of creating a secure environment for answers and thoughts. On the other hand, this background might have led to fear of making the interviewee uncomfortable, and hesitation in asking excessively personal questions. Although the interviewer was inexperienced, her self-confidence grew during the interviews [57], but the first interviews probably had lower quality than the later ones. One of the patients had reduced cognition and the interviewer tried to compensate by asking follow-up questions to clarify the patient's experience. This interview was less rich with fewer descriptions, and the patient's cognitive impairment probably influenced the answers. None of the patients in this study had a MMSE below 25. For all patients, more exploratory questions were asked if the interviewer doubted whether the patient had understood the question. We considered this validation during the interviews to be sufficient and did not perform member checks (return transcriptions to participants to provide feedback on the findings) or repeated interviews, which would have risked burdening patients without necessarily increasing validity [86]. However, we might have missed the opportunity for an even more nuanced description from the patients' point of view [62]. Research conducted in one's own practice raises some concerns, and the interviewer working in the cardiology unit and being a colleague of the interventional cardiologists might have led to less exploration of patients' negative experiences of the decision-making process [87]. We did not use the words trust or autonomy in the interview guide, yet experiences of trust and of being autonomous were frequently reported and thus further interpreted. The interview guide being in plain language might have reduced deeper reflexions on autonomy and trust. However, our aim was for all the patients to understand the questions, and we received varied descriptions. After the first two interviews we expanded the interview guide to obtain more precise descriptions of why the patients wanted the procedure, how they preferred to receive risk information and how they faced challenges. This flexible approach with stepwise analysis during data collection and modification of the interview guide is recommended in qualitative research in order to sharpen one's focus and aim [60]. The planning of the study and the data collection and analysis were performed by doctors not trained in philosophy, and this affected the process, aiming

for clinical implications of the results rather than in-depth philosophical analysis. We were inspired by O'Neill [64] and Dodds [65] in our focus on trust and autonomy, including relational aspects. Validation of the analysis and presentation was strengthened by several of the research team not being involved in the TAVI treatment, bringing external perspectives to the data collection and findings.

5.1.2 External validity

External validity is defined by asking in what context the findings can be applied [55]. Qualitative research aims for transferability, i.e. to outline the situations in which the findings might provide valid information, as opposed to generalization in quantitative research [55]. We included a purposive sample of patients as described under sample size in order to increase transferability [55]. However, our sample contained elective TAVI patients from a single hospital, and the majority were intermediate or robust on a physical frailty score and other patterns may have been revealed in a frailer group. We interviewed patients who were accepted for TAVI, and the results are probably not transferable to decision-making in older patients in general, and we might have obtained different descriptions had we interviewed the patients before the procedure or before the decision was made. The interventional cardiologists assess patients' lease on life before offering treatment, and TAVI patients might be psychologically more robust than their peers. However, since there are strict selection criteria for TAVI and the majority of candidates are older than 70 years, our findings may be relevant to patients accepted for TAVI in other countries [1].

Hospital treatment in Norway is provided through the public health care system and there are no financial incentives for cardiologists to perform TAVI. Studies have revealed that in the Nordic countries people trust public authorities [88]. There were only white participants in our study, and most were Christians. The results may consequently not be transferable to diverse cultural and religious contexts.

5.1.3 Sample size

The sample size was guided by the concept of information power, i.e. "the more information the sample holds, relevant for the actual study, the lower amount of

participants is needed” [83]. The study aim narrowed from the more general “patient perspective and decision-making prior to TAVI” to a focus on the “conditions for an autonomous choice”. All patients in the interview study had already been included in the quantitative study, meaning that the baseline characteristics were known to the researcher. The investigator introducing herself as a researcher and a geriatrician probably increased the likelihood of patients accepting the invitation, and also the fact that they were offered home interviews when it suited them increased participation. We included TAVI patients over 70 years with variations in complications, age, gender and level of physical frailty, ensuring strong specificity. At the outset we did not have a strong theoretical framework; however, during the interviews and analysis process we applied the theory of “shared decision-making” and “autonomy”. Most interviews were rich, where patients elaborated on the questions in the interview guide. We focused on in-depth analysis from a few selected patients and did not seek to cover the whole area of decision-making before TAVI. We do not exclude that interviewing more patients would have provided even greater knowledge. However, after four rounds of stepwise, cross-case analysis, adding two or three interviews at a time, the data were assessed as sufficient to answer the research question when we had included ten patients.

5.1.4 Reflexivity

The question is not if but how the researcher will influence the qualitative research process, in relation to transparency [55]. Objectivity in qualitative research means recognizing that knowledge is partial and situated, accounting adequately for the effect of the researcher, and realizing that subjectivity will occur when the effect of the researcher is ignored [55]. For a geriatrician in the Department of Heart Disease, it became a challenge to deal with the oldest patients and decision-making before procedures in general. The balance between overtreating and undertreating was of concern, and TAVI being a new treatment aroused curiosity about the decision-making process preceding the intervention. The vulnerability of cognitively impaired patients in decision-making became clear after working with patients with moderate to severe dementia for some years in a nursing home and an old age psychiatric hospital, as well

as seeing patients with dementia at the local hospital as part of the programme in geriatric medicine.

The supervisory team included a former interventional cardiologist, a geriatrician and a junior doctor specializing in cardiology and thoracic medicine. Before starting this study, we were uncertain as to whether patients felt they had a choice or just passively accepted the offer of TAVI. Several issues could compromise decision-making: a busy department with little time for complex information, junior doctors with limited experience with TAVI assessing the patients, and the fact that diagnosing a severe valve disease will often make clinicians keen to “do something”, rather than focusing on patient choice. We were uncertain whether the patients were informed of rare, but severe complications of TAVI, such as stroke and death. There was no written information for patients prior to TAVI at the time of this study. The wish to illuminate these issues was the driving force and motivation for conducting the studies included in this thesis.

5.2 Methodological aspects (studies 2 and 3)

5.2.1 Study design

We chose a single-centre prospective observational cohort study design for papers 2 and 3 and will discuss potential weaknesses of this design in the following [89].

All patients in the study underwent TAVI, and the procedure was described in the patient record. For paper 2 the primary outcome was two-year all-cause mortality. All deaths are automatically registered in the patient’s medical record and no patients were lost to follow-up for the primary outcome, reducing risk of information bias. For paper 3, accuracy regarding death was as in paper 2. As for the NYHA classification, previous studies have shown low inter-rater reliability and results must be interpreted with caution [90]; however, our results are in line with other TAVI studies demonstrating significant symptom improvement [91, 92].

We did adjust for confounding factors based on literature in developing the frailty score, and adjusted for age, gender and logistic EuroSCORE, but hidden confounders

might have been present. We found a satisfactory internal consistency for NEADL in study 3, with Cronbach's alpha of 0.87 at baseline and 0.86 at six months.

Selection bias refers to the study population failing to mirror the target population of interest. Our studies were performed in the early era of TAVI, when more robust older adults may typically have been referred, but this is unknown. Patients in long-term nursing home care or patients with advanced dementia have not been offered TAVI in Norway, so the frailest group of patients with aortic stenosis is not included. The most robust older adults with aortic stenosis were offered SAVR at the time of this study [1].

Among 166 patients qualified for inclusion in study 2, ten refused to participate, seven were not included due to logistical reasons and two cases were not elective treatment. The patients not included for logistical reasons were probably missing completely at random. For the ten patients who refused to participate and for the two treated acutely, this might not have been the case. The patients who refused were not asked to give a reason, but some said they were too tired to complete the tests, and they might have been frailer than the included patients. We conclude that there is a risk of missing not at random in the study, and we are aware that the population does not include all patients ≥ 70 years with severe, aortic stenosis; however, there was a high inclusion rate, at 89% of eligible patients, and we consider the study to have good external validity. We collected a large number of variables and had comprehensive information on the patients, which increased internal validity.

5.2.2 Power calculations

Estimation of sample size was based on the PARTNER cohort B study [3] reporting one-year mortality of 30.7% in the TAVI group, and a high rate of complications, estimated at 40%. We expected a lower rate of complications among fit patients (20%) and a higher rate among frail patients (55%), based on previous studies in different patient populations [45, 93]. With power of 80% and a 5% level of significance, we needed 35 patients in each of the fit and frail groups. Most patients are intermediate.

With 25% of patients in each of the fit and frail groups, and 50% in the intermediate group, we needed 140 patients. We expected only a few drop-outs because the baseline examinations were not too challenging, and follow-up telephone interviews were at six months. Based on this we included 5% more, thus a total number of 147 patients. In our material, we found a significantly lower event rate than expected from the PARTNER cohort B study, and the basis for our power calculation may thus have been weakened. We therefore did not perform a power calculation for paper 3, which is a limitation of this study, and consequently we may have overlooked potential positive relations. Subgroup analysis to examine whether frail patients had more complications, as expected from other studies [94], showed overlapping confidence intervals, supposedly due to lack of power.

5.2.3 The cost of dichotomizing continuous variables

We chose to present the frailty score as a dichotomized variable. This is common in clinical research, since it is helpful to label individuals as having or not having a quality and it simplifies the analysis and makes it easier to interpret and present the results [95]. However, it comes at a cost of loss of information and reduces the statistical power to detect a relationship between the variable and patient outcome. It also increases the risk of a positive result being a false positive and there might be extensive variability within each group. Individuals close to, but on opposite sides of, the cut-off point are categorized as being very different rather than very similar [95]. The frailty score is therefore also presented as a continuous variable.

5.2.4 Cut-offs for variables in the novel frailty score

When developing the frailty score, we also dichotomized the different variables in the score (except for MMSE, where we used three categories), risking loss of information as mentioned above. However, by using cut-offs from previous research we diminished the risk of a data-driven analysis and increased power.

In order to separate better, we chose to have three categories for MMSE. The cut-off of <20 was chosen because this might distinguish between mild and moderate dementia [31, 96], and it has also been predictive of decision-making capacity [31].

We chose a high cut-off for normal cognition of ≥ 27 , because this was used in a previous TAVI study [47], and because we assumed that some of the patients would have a high level of education, and we wanted to reduce the risk of false positive results [97]. MMSE is affected by age and educational level and the results must therefore be assessed with caution [98].

We measured instrumental activities of daily living with the Nottingham Extended Activities of Daily Living scale (NEADL) [99]. Based on clinical experience, we postulated that most patients accepted for TAVI would be independent in basic activities of daily living, and chose a scale measuring activities beyond basic self-care skills, in order to distinguish better between patients. The four subsections, mobility, kitchen, domestic and leisure may be added to an overall score [66]. To simplify implementation in clinical practice we chose a cut-off for NEADL of a score below 44 indicating dependence in at least one instrumental activity of daily living. The 22 items are scored on a four-point scale ranging from 0=not at all, 1=with help, 2=on your own with difficulty, 3=on your own, and a summary score (range 0-66) is generated.

Previous research has used a cut-off of >43 for classifying a patient as fit [45, 100]. Reduced cognition might affect how patients recalled their performance of different activities and NEADL must therefore be interpreted with some caution due to recall bias. A lower cut-off for NEADL would probably be preferable to increase the sensitivity of the novel frailty score, but no such cut-off has been described, and we chose not to examine the dataset to find the best cut-off, risking a data-driven analysis. One study of stroke patients reported a valid and reliable change if the NEADL improved or deteriorated by 4.9 points or more, and clinically important if the mean change score was in the range from 2.4 to 6.1 points after treatment [101].

Body Mass Index (BMI) is frequently used as a screening for malnutrition. There are different cut-offs of BMI to identify risk of malnutrition. We chose a cut-off at BMI $<20.5 \text{ kg/m}^2$ from Nutritional Risk Screening 2002 (NRS 2002), because it is a validated score [102], and mandatory at Haukeland University Hospital, where it is included in the patient's electronic record, thus increasing the feasibility of implementing a frailty score in clinical practice [103]. For 82 patients we only have self-reported height, but a Swedish longitudinal study has revealed only a small

misclassification bias between self-reported and measured height in older adults [104], and due to small cultural differences between Norway and Sweden, we would expect similar findings in Norway. Nutrition was also assessed by responses to the question “Have you lost weight during the past year?” This is a modification of the original Study of Osteoporotic Fracture (SOF) frailty index; in the original index they stated that weight loss of $\geq 5\%$ between the third and fourth examinations (mean 2.0 (SD 0.3) years between examinations) was significant. Since we only had baseline data, we used self-reported weight loss, as this has been used in other studies [105]. We assigned one point for each of the three dimensions in SOF to arrive at the score [67]; however, we did not use the cut-off in the original paper (≥ 2 points=frail) since we used it as part of the total score.

For the Charlson Comorbidity Index, we chose the cut-off of ≥ 3 as recommended when the mortality of the disease under study is high [106]. We chose the Charlson Comorbidity Index because it is less time-consuming than other comorbidity scores, such as the Cumulative Illness Rating Scale [107], thus increasing applicability in clinical practice.

5.3 Discussion of main results

The European Society of Cardiology recommends a thorough selection of patients and an objective assessment of frailty before TAVI. However, there are no clear cut-offs or agreement about when the procedure might be futile. The aim of this thesis was to provide data to inform the decision-making process when choosing between TAVI and conservative treatment, by assessing patients’ experience of autonomy, the predictive value of a frailty score and examining baseline frailty including cognition and outcomes of importance.

5.3.1 Benefit and risk

Natural course of aortic stenosis – difficult to prognosticate

Severe, symptomatic aortic stenosis has a poor prognosis without valve intervention. However, few studies focus on the natural course of AS, and most of them are small, retrospective studies [4, 108, 109]. The classic study of Braunwald and Ross from

1968 was an autopsy study based mainly on studies before 1955 (before echocardiography was used in diagnosis), and the number of patients included in the study is not accounted for [110]. Different studies find different survival rates, and the 2012 ESC guidelines state: “As soon as symptoms occur, the prognosis of severe AS is dismal, with survival rates of only 15-50% at 5 years” [111]. In one of the papers referred to, the author states that severe aortic stenosis with no or mild symptoms (NYHA I and II) has a better long-term prognosis with a five-year survival of 76% [4]. The guideline recommends valve implantation when symptoms occur, irrespective of severity [1].

Selective survival after TAVI?

In the PARTNER study cohort B, 358 inoperable, symptomatic patients with severe aortic stenosis were randomized to TAVI or “standard care”, which often included balloon aortic valvuloplasty. At two-year follow-up, 43% in the TAVI group and 68% in the “standard therapy” group had died, while 83% of survivors in the TAVI cohort and 43% in the standard therapy cohort were asymptomatic or had mild symptoms (NYHA I or II) [91]. The authors suggest that the mortality benefit after TAVI may be limited to patients who do not have extensive coexisting conditions. A systematic review of long-term follow-up after TAVI including 13 857 patients, mean age 81.5 (+/- 7 years), found survival at 1, 2, 3, 5 and 7 years to be 83%, 75%, 65%, 48% and 28% respectively, and lower than the actuarial survival of 82-year-olds [112], as shown in Figure 3:

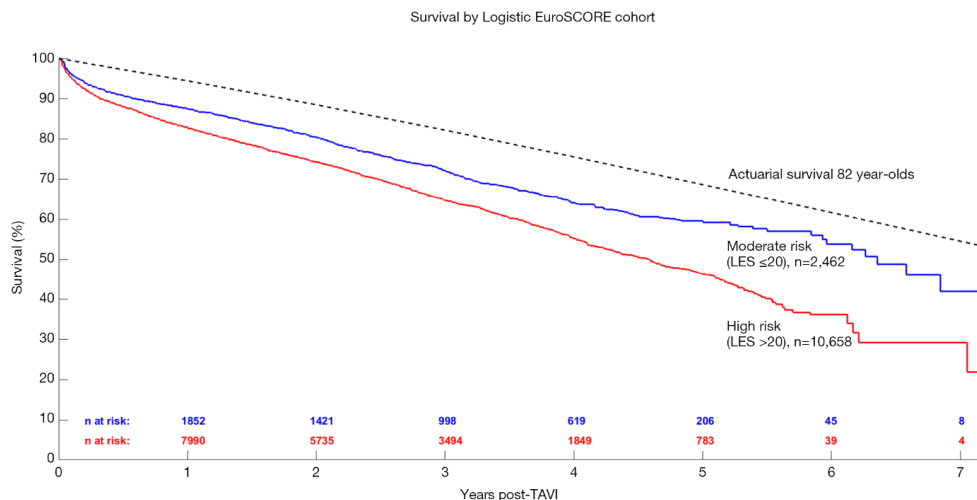


Figure 3: Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of five-year survival and beyond, Vol 6, No 5 (September 2017), permission conveyed through Copyright Clearance Center, Inc. Used with permission of AME Publishing Company, from *Annals of Cardiothoracic Surgery* [112].

The Norwegian Registry of Interventional Cardiology report from 2018 states that three-year mortality after TAVI is 20% in Norway [54]. Another systematic review [113] found only two studies on the comparison of TAVI with medical therapy. One of them was the previously mentioned PARTNER cohort B. The other was a retrospective propensity-matched study of 270 patients, with 135 patients in each group. At two-year follow-up, 30% in the TAVI group and 59% in the medical group had died. It is well-documented that TAVI provides survival benefit and improvement of symptoms, as our study confirms. However, uncertainty remains as to whether patients with mild symptoms have the same poor prognosis as those with more severe symptoms. This could be of importance for frail patients with mild symptoms when there is doubt about the benefit. The favourable survival rate after TAVI appears not to be valid for all patients.

Endocarditis

We found a higher frequency of infective endocarditis (IE) than expected. In a recent meta-analysis with a mean follow-up at 3.4 years, the overall incidence of IE in TAVI was 2.0% [114]. In paper three, five of six patients with IE had a pacemaker or an

implantable cardioverter defibrillator, which might be linked to an increased risk of IE [115]. Several single-centre studies finding higher incidences suggest that IE is underreported in large studies and registries [116, 117]. Diagnosing endocarditis is challenging, and the presentation might be atypical since the patients are old with comorbidities [114]. As endocarditis can occur later on, longer follow-up than one year seems significant. Antibiotic prophylaxis during the TAVI procedure was administered to all patients. At discharge, the patients and their general practitioners were informed routinely about the risk of endocarditis and indications for prophylaxis. Pacemaker implantation was higher in this early period of TAVI treatment, where 39% of the patients received a new pacemaker during the hospital stay. The Norwegian Registry of Interventional Cardiology [54] reported 18% pacemaker implantation after TAVI at Haukeland University Hospital in 2018.

Symptom improvement and maintenance of extended activities of daily living

We found a substantial improvement in NYHA class from baseline to six months. Based on the improvement of symptoms we expected to find an improvement in NEADL. However we found no change in mean NEADL. There was variation on an individual level. Some patients improved in independence and others deteriorated, although for most patients, the change in NEADL was minor. This was not due to a floor or ceiling effect, since only a few patients had the maximum score, and none had the lowest score. Other factors such as frailty and dementia probably have more impact on level of independence than the aortic stenosis per se and six months follow-up is probably too short to establish deterioration due to other causes [118]. In a study of patients before and after hip replacement, the NEADL was insensitive to change with poor effect sizes compared with other scales of health status. Being designed to assess the wide range of disabilities seen after a stroke, the NEADL has quite large distances between each of the points on its scale, making it more difficult to register improvement [119]. There was no difference between the frail and robust patients regarding change in NEADL from baseline to six months. Given its previously mentioned limitations, the present study suggests that patients should be informed that

most patients are likely to maintain their functioning in activities of daily living six months after TAVI.

Frailty assessment and suggestions for cut-off values

As presented in the introduction, frailty adds information to risk assessment in older TAVI patients, where frail patients have a higher risk of morbidity and mortality [38, 52]. Data from the UK TAVI registry indicated that frailty was associated with lower observed survival following TAVI as shown in Figure 4:

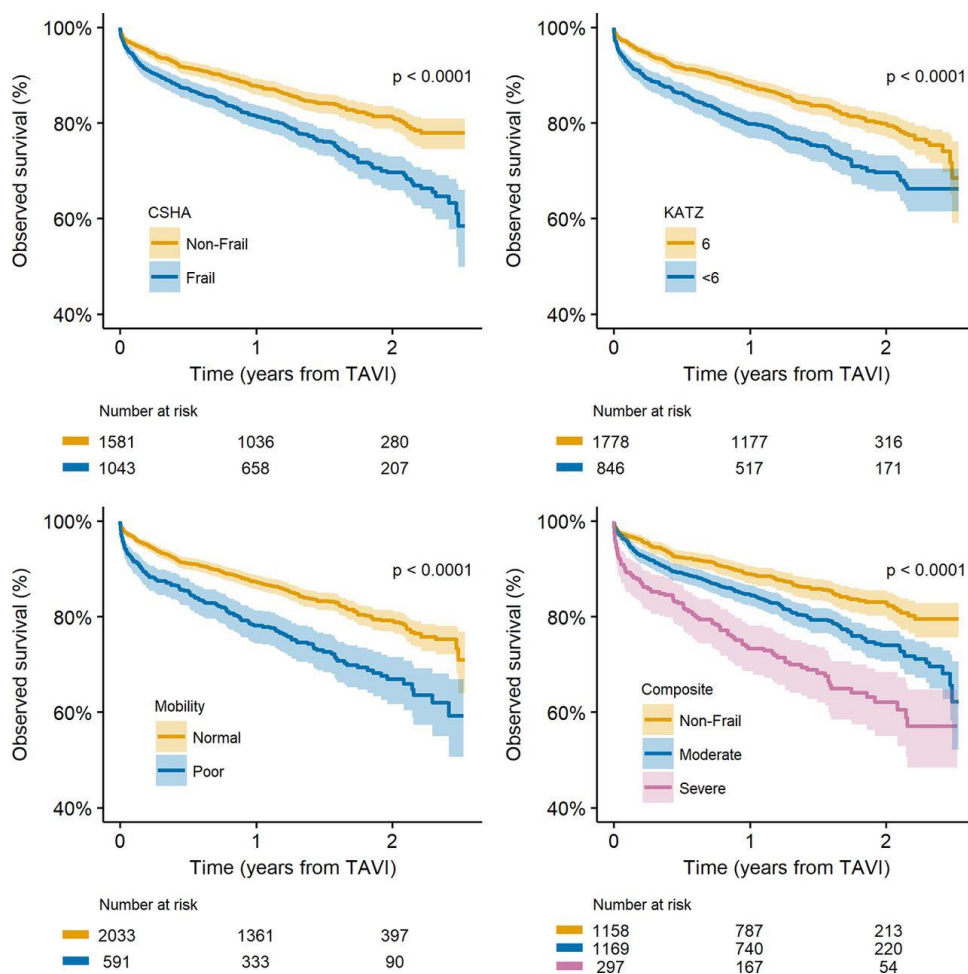


Figure 4: Kaplan-Meier plots across Canadian Study of Health and Ageing (CSHA) estimated frailty (top left), KATZ activities of daily living dependency (top right), physician-estimated poor mobility (bottom left) and the composite frailty score (bottom right) [120].

In a recent single-centre prospective observational study ($n=246$) by Kim et al. [94], preoperative geriatric assessment was performed before intervention for severe aortic stenosis. The authors identified five trajectories based on a frailty index, suggesting that functional decline or lack of improvement is common in older adults with severe frailty undergoing TAVI or SAVR. In our study, patients characterized as frail had a significantly higher all-cause mortality after two years compared with robust patients. Despite this, we were not able to identify different trajectories in the surviving patients based on frailty score, and there was no difference in mean NEADL at baseline and six months. There is no agreement on cut-off values for frailty in TAVI. A recent position statement from the Canadian Cardiovascular Society (CCS) describes severe frailty and states that the following are risk factors for futility: A - advanced dementia, B - bedbound, not mobile, C - cachexia or severe sarcopaenia, D - disability for all/most ADLs, E - end stage renal, liver, lung or malignant disease [121]. Patients with severe frailty (A-D) as described in the CCS statement will have a life expectancy < 1 year. The implication of this statement in regard to futility is of uncertain clinical relevance, since these patients are indisputably too frail for TAVI and would not be offered this treatment in the first place. In contrast, the 2017 ACC Expert Consensus Decision Pathway for TAVI describes patients where benefit/risk in TAVI is uncertain. They recommend a functional assessment including frailty and a more detailed investigation with regards to futility if gait speed is <0.5 m/s or <0.83 m/s with disability/cognitive impairment, BMI < 21 kg/m², albumin <3.5 mg/dl, <10 pounds weight loss in past year, mini nutritional assessment \leq 11, 6 min walk <50 m or unable to walk, dependent in \geq 1 activities, MMSE<24, depression history or positive screen, < 1 year life expectancy or survival with benefit <25% at two years [20].

In a recent qualitative review on patients' experiences of TAVI, the authors found that patients with slow or no symptom improvement and/or long hospital stays after TAVI had difficulty in reconciling their expectations with their actual experience. The impact of comorbidities on their health and lives became clearer after TAVI amongst those whose expectations were not met [122]. In study 2, >70% of the patients regarded as frail survived for two years, and in study 3 most patients had symptom improvement

after six months. We therefore cannot argue for a strict cut-off for when it should be recommended not to offer TAVI based on the frailty score alone. However, the frailty score will identify patients where TAVI might be futile, and discussing the scoring may enhance shared decision-making by displaying increased risk of worse outcome.

Quality of life

In this thesis we chose to focus on functional status measured by NYHA class and have not assessed quality of life in a broader perspective. Previous studies have addressed this topic. A systematic review on functional status and quality of life after TAVI [123] found substantially improvement of NYHA class and other disease-specific measures. Despite this, overall quality of life improved to a lesser degree and the change was not always regarded as clinically important. This has later been confirmed in another systematic review [124].

5.3.2 Shared decision-making, autonomy and trust

Shared decision-making

In situations where doubt prevails regarding benefit, shared decision-making and exploring patient preferences are even more important. A systematic review on patient values and preferences regarding AS valve replacement was published in 2016 [125]. The authors found two studies eligible for review. The first revealed that patients were willing to tolerate high mortality risk in order to achieve full health [126]. The second study found that patients' decision-making involved several concerns, including symptom burden, a trusting relationship with their doctor and obligations to family and caregivers [127].

A qualitative study examined patient-defined goals in older adults facing treatment decisions for severe aortic stenosis [128]. This study found that patients emphasized the ability to perform a specific activity and maintaining independence as the most important goals of treatment.

Another qualitative study examined patterns in patients' decision-making process and found variation in that some patients left the decision to others, some were unsure if

they wanted the procedure, while others had reached a point where they were certain that they wanted the procedure [129].

For patients receiving medical treatment, a study from 2017 [130] found that doctors reported patient preference as the most common reason for medical AS treatment.

However, patients felt that their heart valve doctor involved them to a lesser extent in treatment decisions than patients accepted for SAVR or TAVR. The authors conclude that there is “a potential gap in care that may benefit from additional efforts to enhance communications between patients and doctors”.

The 2017 ACC Expert Consensus Decision Pathway for TAVI [20] emphasized shared decision-making, and that patient expectations and goals should be established early in the process in the context of a discussion on life expectancy, expected improvement in symptoms or survival, and end-of-life constructs. The authors argued that this enabled an exchange about the promise of TAVI as well as the realities of advanced age, alternatives to intervention and palliative care options. The statement from the Canadian Cardiovascular Society also highlights shared decision-making through incorporation of patients and their preferences, and suggests the implementation of shared decision-making tools, such as the American College of Cardiology Aortic Stenosis Choice [121]. A recent summary from the American Geriatrics Society provides a framework for care of older adults with multiple chronic conditions. They recommend recognizing the limitations of the evidence base and identifying patients’ health priorities and incorporating these into decision-making [131], especially where there is uncertainty as to whether disease-specific guidelines are applicable. This is illustrated in Figure 5:

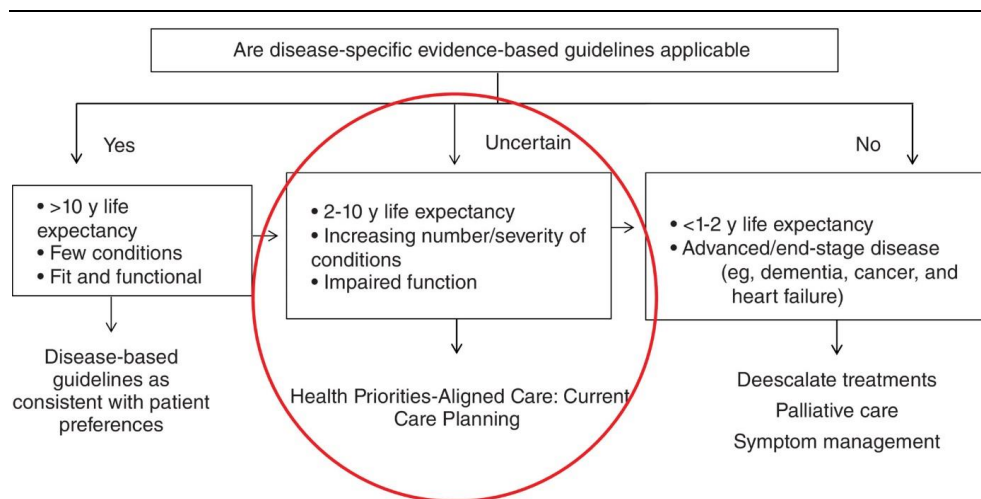


Figure 5: Decision-making and care of older adults with multiple chronic conditions. The Multiple Chronic Conditions Action Steps facilitate decision-making in the face of uncertainty of disease guideline-driven decision-making for the large segment of older adults with increasing numbers of chronic conditions and functional limitations. Reproduced with permission from the *Journal of the American Geriatric Society*. © 2018. The American Geriatrics Society [132].

Autonomy

A core element of shared decision-making is respecting patients' autonomy. Beauchamp and Childress' seminal book "Principles of Biomedical Ethics" [26] presents the four principles of bioethics: *autonomy*, *non-maleficence*, *beneficence* and *justice*. In order to behave autonomously, one must act with intention, understanding and absence of controlling influences [26]. Critics have argued that the concept of autonomy used in bioethics is too narrow [64, 65]. It overlooks the social settings and power relations that affect the context of a choice. It is difficult to choose autonomously in the limited (rationalistic and individualistic) version of the concept when one is ill and vulnerable. A relational understanding of autonomy recognizes that decisions do not take place in isolation or full independence, and patients trusting their doctor might still make an autonomous choice, as our findings indicate [65]. Shared decision-making might conceal the power asymmetry, with an illusion that it supports a dialogue between equals, but underestimate the fact that doctors' medical knowledge gives them power [84]. In a complex clinical setting, it is important to identify and respect the patient's degree of autonomy and to be aware of paternalistic attitudes

among health care professionals when providing care in the best interest of the patient [25]. Physicians should enhance patients' autonomous capacity by understanding their experience and emotions in a broader way, being aware of power, trust, scientific uncertainty, vulnerability, agency and responsibility [133], as shown in Figure 6:

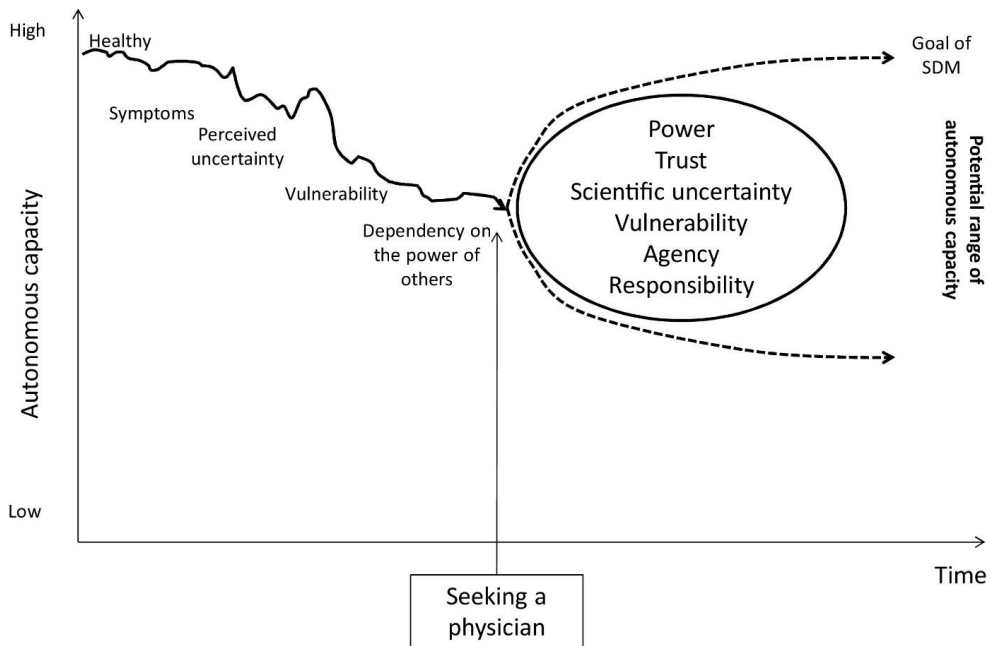


Fig. 6. Illness and shared decision-making as an existential journey. Illness may (temporarily) reduce the healthy person's autonomous capacity (solid arrow). Shared decision-making, depending on its quality, has the potential to restore this autonomous capacity (the goal) (upper dotted arrow) but also to further reduce it (lower dotted arrow). The ellipse depicts the consultation. We have not provided arrows to suggest whether power, trust, etc. will restore or reduce the patient's autonomous capacity, because we think this could vary with the situation, people involved, and how shared decision-making is performed. Studies are needed to explore these proposed effects [133]. Reprinted with permission of Copyright Clearance Center. All rights reserved

In our study, TAVI patients expressed self-empowerment and claimed it had to be their decision. Yet some chose the intervention as an obligation to their family or passively accepted it. This substantiates the importance of illuminating all aspects of the patient's motivation.

Trust

Patient involvement and doctors' respect for patients' values and beliefs are vital to medical decisions, but the concept of shared decision-making has limitations [64]. For instance, to list all imaginable side effects may disturb a patient who definitely wants to be treated and understands that there are risks associated with accomplishing that goal [65]. Our study reveals ambivalence towards knowing the most feared complications and at the same time needing to feel safe. O'Neill argues that a strong focus on autonomy might fail to secure trust: "Trust belongs with relationship and (mutual) obligations; individual autonomy with rights and adversarial claims" [64]. We found that trusting doctors is a core element of decision-making, and this puts patients at the mercy of doctors' power [84]. However, in the present study, patients did not blindly trust their doctors and wanted a second opinion if not reassured. Skirbekk describes this as mandates of trust, where patients consider appropriate restrictions to the doctors' judgement [134]. Not all patients desire to participate in the decision-making process to the same degree [135-137], and shared decision-making emphasizes including "the patient in the decision-making to the extent that they desire" [138]. Safeguarding patients' rights might therefore be in opposition to shared decision-making. A Norwegian study of doctor-patient conversations prior to high-risk cardiac procedures revealed a deep confidence in the doctors' ability to get them through the treatment they were facing, yet the obligation to make the decision was mutual in an asymmetrical power relationship [139].

5.3.3 Vulnerable autonomy and the impact of cognitive impairment and dementia

For patients with cognitive impairment, the concepts of autonomy and shared decision-making are even more challenging. In the qualitative study, only one patient presented signs of cognitive impairment that might have affected the decision-making process. In study 3, 15 patients (18%) had an MMSE below 24, indicating possible dementia. The prevalence of dementia in Western Europe rises exponentially with age, from 4.3% among 70 to 74-year-olds to 43.1% in the 90+ population [30, 140], although more recent studies find a lower age-specific incidence [141]. In the Swedish TAVI

registry, the average age for TAVI patients is about 82 years [142]. Dementia will eventually diminish a patient's ability to make an informed choice. It is recommended to assess cognition with standardized methods before TAVI, to have a baseline measure in case of procedure-related deterioration and to weigh risk, benefit and cost-effectiveness carefully [23]. Since TAVI is a procedure with a risk of complications, family wishes alone should not be sufficient for performing the intervention. Curing aortic stenosis in order for patients to survive to end-stage dementia raises ethical questions, and even if this is what the family wishes, it might not be what the patient would want if he or she could act autonomously. These are difficult issues to discuss with patients with dementia and their families, both due to patients' anosognosia (a physiological damage to the brain, where patients have no awareness of their disease) [143] and health care professionals' fear of patients losing hope when focusing on the deterioration and increased dependence expected after a diagnosis of dementia [144]. Cognitive decline leaves the patient more reliant on, and less capable of questioning, doctors' advice. Beyond the challenges of patient autonomy, dementia decreases expected survival. In a recent study of >50 000 patients with dementia, mean survival time was 5.1 years in a cohort with mean age 81.1 years and mean MMSE 21 at diagnosis of dementia. Mean (interquartile range) survival time was related to MMSE score, with lower MMSE scores indicating lower survival. The lowest expected survival in patients with MMSE 0-17 points was 3.0 years (1.5-5.1) in men and 3.7 years (1.9-6.2) in women. The average 80-year-old in Sweden has a life expectancy of nine years, including a significant proportion of people with dementia. Survival for those who do not develop dementia is expected to be even longer [145]. Other studies have confirmed variety in progression of the disease, and demonstrate that in patients with Alzheimer's disease about half of the patients have a slow progression [146]. Novel treatment opportunities raise new ethical dilemmas that we should discuss thoroughly to ensure that we do no harm. Advance care planning is recommended in order to provide high-quality care for patients with dementia. This is a dynamic, continuous process, in which early dialogue and reflection on patient preferences, including end-of-life care, are sought [147]. Starting the process at an early stage,

preferably before the diagnosis of dementia, may facilitate the transition to palliative care.

5.3.4 Geriatric cardiology facilitating comprehensive decision-making

Geriatricians are specialists in care for frail older adults and are able to evaluate coexisting geriatric syndromes and comorbidity, which makes them essential partners in the decision-making process prior to TAVI. End-of life planning and acceptance of the inevitability of death as part of the normal human life trajectory rather than an enemy to be avoided at all times can help relocate care decisions away from options that may no longer be useful or relevant [148]. A focus on patient preferences is not a specific task for geriatricians, but geriatricians are aware that care goals may change as people age. Thus, geriatricians' approach to treatment dilemmas consists of seeking information about what matters most to the individual patient, being aware that guidelines are often based on younger patients with fewer comorbidities. Several publications recommend integration of geriatric assessment prior to TAVI, and the inclusion of geriatricians in the heart valve team [19, 23]. As demonstrated in this thesis, geriatricians can provide an objective assessment of frailty and also incorporate patient preferences in a situation of vulnerable autonomy, facilitating a tailor-made treatment strategy.

6. Conclusions

1. The study confirms the value of self-determination and autonomy in medical decisions, and adds to previous knowledge by providing empirically-based descriptions of what constitutes the conditions for TAVI patients' autonomy as experienced in the decision-making process.
2. We found that a frailty scale based on geriatric assessment predicted two-year mortality in TAVI patients beyond the established risk score.
3. Patients had symptom improvement and could maintain activities of daily living six months after TAVI, and had low mortality after two years. Rarely, severe complications occurred, such as stroke and endocarditis. Some patients had cognitive impairment or dementia at baseline which might have influenced the decision-making process.

This thesis provides support to identify patients with higher risk and lower expected benefit after TAVI, and circumstances under which the procedure might be futile. The decision to offer TAVI should be based on an analysis of benefit versus risk, taking into account symptom burden, patient perspectives, comorbidity and frailty.

7. Implications and suggestions

7.1 Clinical practice

Frailty screening should be performed in older adults before TAVI, and if the screening reveals possible obstacles to TAVI, a more thorough geriatric assessment should be performed.

Doctors should be aware that older adults might have vulnerable autonomy, and the concept of shared decision-making could conceal the power asymmetry, where patients with cognitive decline and/or dementia are particularly vulnerable.

In older adults with comorbid conditions, patients should be informed that TAVI might not solve all their health problems.

7.2 Future research

Further studies are recommended on risk versus benefit in patients where TAVI might be futile, and pre-TAVI decision aids should be developed to inform these patients and their families.

Is frailty reversible in some patients after TAVI, and what are the characteristics of patients with dynamic frailty?

Further studies are recommended on benefit versus risk in providing TAVI for patients with dementia. Complementary qualitative studies should be conducted involving health care personnel and older adults (including patients with dementia and their relatives) to explore attitudes to TAVI for patients with established dementia.

Might geriatric assessment contribute to a sustainable health care system, by informing treatment decisions in the oldest population, not overtreating frail patients and not undertreating robust patients? What is the impact of a geriatrician in the heart valve team?

8. References

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017 Sep 21;38(36):2739-91.
2. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. The Tromso study. *Heart*. 2013 Mar;99(6):396-400.
3. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010 Oct 21;363(17):1597-607.
4. Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. *Eur Heart J*. 1987 May;8(5):471-83.
5. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J*. 2005 Dec;26(24):2714-20.
6. Clark RE. The STS Cardiac Surgery National Database: an update. *Ann Thorac Surg*. 1995 Jun;59(6):1376-80; discussion 80-1.
7. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999 Jul;16(1):9-13.
8. Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ*. 2016 Sep 28;354:i5085.
9. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation*. 2002 Dec 10;106(24):3006-8.
10. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011 Jun 9;364(23):2187-98.
11. Vipparthy SC, Ravi V, Avula S, et al. Meta-Analysis of Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Patients With Low Surgical Risk. *Am J Cardiol*. 2019 Nov 8;125(3):459-68.
12. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol*. 2014 Mar 4;63(8):747-62.
13. Lauck SB, Gibson JA, Baumbusch J, et al. Transition to palliative care when transcatheter aortic valve implantation is not an option: opportunities and recommendations. *Curr Opin Support Palliat Care*. 2016 Mar;10(1):18-23.
14. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016 Jul 14;37(27):2129-200.
15. Palliative Care. World Health Organization; [cited 2019 Nov 25]; Available from: <https://www.who.int/cancer/palliative/definition/en/>.
16. Slawnych M. New Dimensions in Palliative Care Cardiology. *Can J Cardiol*. 2018 Jul;34(7):914-24.
17. McIlvennan CK, Allen LA. Palliative care in patients with heart failure. *BMJ*. 2016 Apr 14;353:i1010.
18. Sobanski PZ, Alt-Epping B, Currow DC, et al. Palliative Care for people living with heart failure - European Association for Palliative Care Task Force expert position statement. *Cardiovasc Res*. 2019 Aug 6;116(1):12-27.
19. Kappetein AP, Windecker S. The heart team in acute cardiac care. Oxford University press; Available from: http://resource.heartonline.cn/20150827/0_9Cp8F4y.pdf.
20. Otto CM, Kumbhani DJ, Alexander KP, et al. 2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis:

-
- A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2017 Mar 14;69(10):1313-46.
21. Puri R, lung B, Cohen DJ, Rodes-Cabau J. TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J*. 2016 Jul 21;37(28):2217-25.
 22. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012 Apr;41(4):734-44; discussion 44-5.
 23. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg*. 2012 Nov;42(5):S45-60.
 24. Brock D. *Life and Death*. New York: Cambridge University Press; 1993,1-78.
 25. Fernandez-Ballesteros R, Sanchez-Izquierdo M, Olmos R, Huici C, Ribera Casado JM, Cruz Jentoft A. Paternalism vs. Autonomy: Are They Alternative Types of Formal Care? *Front Psychol*. 2019;10:1460.
 26. Beauchamp T, Childress J. *Principles of Biomedical Ethics: 7th Edition*; Oxford University Press: New York, USA, 2013; 104-105.
 27. Principles for priority setting in health care. Summary of a white paper on priority setting in the Norwegian health care sector. Norwegian Ministry of Health and Care Services; 2017; Available from: <https://www.regjeringen.no/contentassets/439a420e01914a18b21f351143ccc6af/en-gb/pdfs/stm201520160034000engpdfs.pdf>.
 28. Helse-og-omsorgsdepartementet. Lov om pasient-og brukerrettigheter. 1999 [cited 2019 Oct 8.]; Available from: https://lovdata.no/dokument/NL/lov/1999-07-02-63/#KAPITTEL_4.
 29. Coulter A, Collins A. Making shared decision-making a reality. No decision about me, without me. The Kings Fund; 2011 [cited 2019 Nov16]; Available from: https://www.kingsfund.org.uk/sites/default/files/Making-shared-decision-making-a-reality-paper-Angela-Coulter-Alf-Collins-July-2011_0.pdf.
 30. World Health Organization and Alzheimer's Disease International. Dementia: a public health priority. 2012 [cited 2019 Sep 25]; 112]. Available from: https://apps.who.int/iris/bitstream/handle/10665/75263/9789241564458_eng.pdf.
 31. Sessums LL, Zembrzuska H, Jackson JL. Does this patient have medical decision-making capacity? *JAMA*. 2011 Jul 27;306(4):420-7.
 32. Appelbaum PS, Grisso T. Assessing patients' capacities to consent to treatment. *N Engl J Med*. 1988 Dec 22;319(25):1635-8.
 33. Lanken P, Ahlheit B, Crawford S, et al. Withholding and Withdrawing Life-Sustaining Therapy. *Am Rev Respir Dis*. 1991;144(3):726-31.
 34. Lindman BR, Alexander KP, O'Gara PT, Afalalo J. Futility, benefit, and transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2014 Jul;7(7):707-16.
 35. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. [Research Support, U.S. Gov't, P.H.S.]. 2001 Mar;56(3):M146-56.
 36. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013 Mar 2;381(9868):752-62.
 37. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc*. 2012 Aug;60(8):1487-92.
 38. Anand A, Harley C, Visvanathan A, et al. The relationship between preoperative frailty and outcomes following transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes*. 2017 Apr 1;3(2):123-32.
 39. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013 Jun;14(6):392-7.
 40. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007 Jul;62(7):722-7.
 41. Petronio AS, Giannini C. Frailty in patients undergoing TAVI: how can we measure it? *EuroIntervention*. 2019 Oct 20;15(8):652-5.

42. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019 Jul 1;48(4):601.
43. Kleczynski P, Tokarek T, Dziejewicz A, et al. Usefulness of Psoas Muscle Area and Volume and Frailty Scoring to Predict Outcomes After Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2018 Jul 1;122(1):135-40.
44. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist*. 2000;5(3):224-37.
45. Kristjansson SR, Nesbakken A, Jordhoy MS, et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. *Crit Rev Oncol Hematol*. 2010 Dec;76(3):208-17.
46. WHO Clinical Consortium on Healthy Ageing. Topic focus: frailty and intrinsic capacity. Report of consortium meeting 1-2 December 2016 in Geneva, Switzerland. Geneva:World Health Organization; 2017. [cited 2020 Jan 4th]; Available from: <https://apps.who.int/iris/bitstream/handle/10665/272437/WHO-FWC-ALC-17.2-eng.pdf>.
47. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. [Research Support, Non-U.S. Gov't]. 2012 May;5(5):489-96.
48. Shinall MC, Jr., Arya S, Youk A, et al. Association of Preoperative Patient Frailty and Operative Stress With Postoperative Mortality. *JAMA Surg*. 2019 Nov 13:e194620.
49. Ellis G, Whitehead MA, O'Neill D, Langhorne P, Robinson D. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev*. 2011 Jul 6(7):CD006211.
50. Ommundsen N, Wyller TB, Nesbakken A, et al. Preoperative geriatric assessment and tailored interventions in frail older patients with colorectal cancer: a randomized controlled trial. *Colorectal Dis*. 2018 Jan;20(1):16-25.
51. Hosler QP, Maltagliati AJ, Shi SM, et al. A Practical Two-Stage Frailty Assessment for Older Adults Undergoing Aortic Valve Replacement. *J Am Geriatr Soc*. 2019 Jun 18;67(10):2031-7.
52. Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. *J Am Coll Cardiol*. 2017 Aug 8;70(6):689-700.
53. Eide LS, Ranhoff AH, Fridlund B, et al. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *Am J Cardiol*. 2015 Mar 15;115(6):802-9.
54. Hovland S, Nygaard E, Løland K, Rotevatn S. Norsk register for invasiv kardiologi (NORIC). 2018 [cited 2019 Dec 12th]; Available from: <https://www.kvalitetsregistre.no/registers/484/resultater/1047>.
55. Malterud K. Qualitative research: standards, challenges, and guidelines. *Lancet*. 2001 Aug 11;358(9280):483-8.
56. Malterud K. The art and science of clinical knowledge: evidence beyond measures and numbers. *Lancet*. 2001 Aug 4;358(9279):397-400.
57. Kvale S. *InterViews, an introduction to qualitative research interviewing*: Thousand Oaks, CA: Sage; 1996; 14,125, 146-147.
58. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994 Mar;49(2):M85-94.
59. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975 Nov;12(3):189-98.
60. Malterud K. Systematic text condensation: a strategy for qualitative analysis. *Scand J Public Health*. 2012 Dec;40(8):795-805.
61. Whitehead L. Enhancing the quality of hermeneutic research: decision trail. *J Adv Nurs*. 2004 Mar;45(5):512-8.

-
62. Crabtree B, Miller W. *Doing qualitative research: 2nd Edition*; Thousand Oaks, CA: Sage;1999; 21-23, 81,193.
 63. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). *Soc Sci Med*. 1997 Mar;44(5):681-92.
 64. O'Neill O. *Autonomy and trust in bioethics*: New York: Cambridge University Press; 2002, 1-48.
 65. Mackenzie C, Stoljar N, Dodds S. *Relational autonomy*: New York: Oxford University Press; 2000; 213-235.
 66. Lincoln NB, Gladman JR. The Extended Activities of Daily Living scale: a further validation. *Disabil Rehabil*. 1992 Jan-Mar;14(1):41-3.
 67. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med*. 2008 Feb 25;168(4):382-9.
 68. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983 Jun;67(6):361-70.
 69. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83.
 70. The Criteria Committee for the New York Heart Association. *Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels*. Boston, MA: Little Brown; 1964.
 71. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *Eur Heart J*. 2003 May;24(9):881-2.
 72. Singh K, Bhalla AS, Qutub MA, Carson K, Labinaz M. Systematic review and meta-analysis to compare outcomes between intermediate- and high-risk patients undergoing transcatheter aortic valve implantation. *Eur Heart J Qual Care Clin Outcomes*. 2017 Oct 1;3(4):289-95.
 73. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal*. 2001 Aug 8;1:323-36.
 74. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008 Sep 30;8:24.
 75. Kristjansson SR. *The role of geriatric assessment and frailty measurements in predicting surgical risk and survival in elderly patients with colorectal cancer*. PhD thesis. Faculty of Medicine: University of Oslo; 2011.
 76. Harrell FE. *Regression Modeling Strategies, With Applications to linear Models, Logistic and Ordinal Regression, and Survival Analysis*. 2nd edition. Switzerland: Springer International Publishing; 2015; 79-80, 330-333.
 77. Eide LS, Ranhoff AH, Fridlund B, et al. Delirium as a Predictor of Physical and Cognitive Function in Individuals Aged 80 and Older After Transcatheter Aortic Valve Implantation or Surgical Aortic Valve Replacement. *J Am Geriatr Soc*. 2016 Jun;64(6):1178-86.
 78. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982 Apr;143(1):29-36.
 79. Wilson E. Probable interference, the Law of Succession, and Statistical Interference. *J Am Stat Assoc*. 1927;22(158):209-212.
 80. R Core Team (2019). Vienna, Austria [cited 2019]; R: A language and environment for statistical computing]. Available from: <https://www.r-project.org/>.
 81. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011 Mar 17;12:77.
 82. Heinze G, Plo M. Cox Regression with Firth's Penalized Likelihood. R. 2018; Available from: <https://CRAN.R-project.org/package=coxphf>.
 83. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qual Health Res*. 2015 Nov 27;26(13):1753-60.
 84. Grimen H. Power, trust, and risk: some reflections on an absent issue. *Med Anthropol Q*. 2009 Mar;23(1):16-33.

-
85. Raheim M, Magnussen LH, Sekse RJ, Lunde A, Jacobsen T, Blystad A. Researcher-researched relationship in qualitative research: Shifts in positions and researcher vulnerability. *Int J Qual Stud Health Well-being*. 2016;11:30996.
 86. Goldblatt H, Karnieli-Miller O, Neumann M. Sharing qualitative research findings with participants: study experiences of methodological and ethical dilemmas. *Patient Educ Couns*. 2011 Mar;82(3):389-95.
 87. Aase M. Interviewing colleagues-Ethical and methodological challenges. 2006 [cited 2019 Dec 31]; Available from: https://www.psy.au.dk/fileadmin/site_files/filer_psykologi/dokumenter/CKM/NB41/aase.pdf.
 88. Bergh A, Bjornskov C. Historical Trust Levels Predict the Current Size of the Welfare State. *Kyklos*. 2011 Feb;64(1):1-19.
 89. Boyko EJ. Observational research-opportunities and limitations. *J Diabetes Complications*. 2013 Nov-Dec;27(6):642-8.
 90. Raphael C, Briscoe C, Davies J, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart*. 2007 Apr;93(4):476-82.
 91. Makkar RR, Fontana GP, Jilalawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med*. 2012 May 3;366(18):1696-704.
 92. Liu Z, Kidney E, Bem D, et al. Transcatheter aortic valve implantation for aortic stenosis in high surgical risk patients: A systematic review and meta-analysis. *PLoS One*. 2018;13(5):e0196877.
 93. Ekerstad N, Swahn E, Janzon M, et al. Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. *Circulation*. 2011 Nov 29;124(22):2397-404.
 94. Kim DH, Afilalo J, Shi SM, et al. Evaluation of Changes in Functional Status in the Year After Aortic Valve Replacement. *JAMA Intern Med*. 2019 Feb 4;179(3):383-91.
 95. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ*. 2006 May 6;332(7549):1080.
 96. Pernecky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am J Geriatr Psychiatry*. 2006 Feb;14(2):139-44.
 97. O'Bryant SE, Humphreys JD, Smith GE, et al. Detecting dementia with the mini-mental state examination in highly educated individuals. *Arch Neurol*. 2008 Jul;65(7):963-7.
 98. Dufouil C, Clayton D, Brayne C, et al. Population norms for the MMSE in the very old: estimates based on longitudinal data. *Mini-Mental State Examination*. *Neurology*. 2000 Dec 12;55(11):1609-13.
 99. Nouri F, Lincoln NB. An extended activities of daily living scale for stroke patients. *Clin Rehabil*. 1987;1:301-5.
 100. Ommundsen N, Wyller TB, Nesbakken A, et al. Frailty is an independent predictor of survival in older patients with colorectal cancer. *Oncologist*. 2014 Dec;19(12):1268-75.
 101. Wu CY, Chuang LL, Lin KC, Lee SD, Hong WH. Responsiveness, minimal detectable change, and minimal clinically important difference of the Nottingham Extended Activities of Daily Living Scale in patients with improved performance after stroke rehabilitation. *Arch Phys Med Rehabil*. 2011 Aug;92(8):1281-7.
 102. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc EWG. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003 Jun;22(3):321-36.
 103. Tangvik RJ, Tell GS, Guttormsen AB, et al. Nutritional risk profile in a university hospital population. *Clin Nutr*. 2015 Aug;34(4):705-11.

-
104. Dahl AK, Hassing LB, Fransson EI, Pedersen NL. Agreement between self-reported and measured height, weight and body mass index in old age—a longitudinal study with 20 years of follow-up. *Age Ageing*. 2010 Jul;39(4):445-51.
 105. Kiely DK, Cupples LA, Lipsitz LA. Validation and comparison of two frailty indexes: The MOBILIZE Boston Study. *J Am Geriatr Soc*. 2009 Sep;57(9):1532-9.
 106. Charlson ME, Pompei P, Ales KL, MacKenzie C. A new Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. *J Chron Dis*. 1987;40(No 5):373-83.
 107. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc*. 1968 May;16(5):622-6.
 108. Chizner MA, Pearle DL, deLeon AC, Jr. The natural history of aortic stenosis in adults. *Am Heart J*. 1980 Apr;99(4):419-24.
 109. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J*. 1988 Apr;9 Suppl E:57-64.
 110. Ross J, Jr., Braunwald E. Aortic stenosis. *Circulation*. 1968 Jul;38(1 Suppl):61-7.
 111. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg*. 2012 Oct;42(4):S1-44.
 112. Chakos A, Wilson-Smith A, Arora S, et al. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. *Ann Cardiothorac Surg*. 2017 Sep;6(5):432-43.
 113. Wagner G, Steiner S, Gartlehner G, et al. Comparison of transcatheter aortic valve implantation with other approaches to treat aortic valve stenosis: a systematic review and meta-analysis. *Syst Rev*. 2019 Feb 5;8(1):44.
 114. Ando T, Ashraf S, Villablanca PA, et al. Meta-Analysis Comparing the Incidence of Infective Endocarditis Following Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement. *Am J Cardiol*. 2019 Mar 1;123(5):827-32.
 115. Kolte D, Goldsweig A, Kennedy KF, et al. Comparison of Incidence, Predictors, and Outcomes of Early Infective Endocarditis after Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in the United States. *Am J Cardiol*. 2018 Dec 15;122(12):2112-9.
 116. Rodriguez-Vidigal FF, Nogales-Asensio JM, Calvo-Cano A, et al. Infective endocarditis after transcatheter aortic valve implantation: Contributions of a single-centre experience on incidence and associated factors. *Enferm Infecc Microbiol Clin*. 2018 Oct 30;37(7):428-34.
 117. Puls M, Eiffert H, Hunlich M, et al. Prosthetic valve endocarditis after transcatheter aortic valve implantation: the incidence in a single-centre cohort and reflections on clinical, echocardiographic and prognostic features. *EuroIntervention*. 2013 Apr 22;8(12):1407-18.
 118. Schoenenberger AW, Stortecky S, Neumann S, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur Heart J*. 2013 Mar;34(9):684-92.
 119. Harwood RH, Ebrahim S. A comparison of the responsiveness of the Nottingham extended activities of daily living scale, London handicap scale and SF-36. *Disabil Rehabil*. 2000 Nov 20;22(17):786-93.
 120. Martin GP, Sperrin M, Ludman PF, et al. Do frailty measures improve prediction of mortality and morbidity following transcatheter aortic valve implantation? An analysis of the UK TAVI registry. *BMJ Open*. 2018 Jun 30;8(6):e022543.
 121. Asgar AW, Ouzounian M, Adams C, et al. 2019 Canadian Cardiovascular Society Position Statement for Transcatheter Aortic Valve Implantation. *Can J Cardiol*. 2019 Nov;35(11):1437-48.
 122. Smith A, Argaez C. Ottawa (ON)2019 [cited 2019 Dec]; Available from: <https://www.ncbi.nlm.nih.gov/pubmed/31721546>.

-
123. Kim CA, Rasania SP, Afilalo J, Popma JJ, Lipsitz LA, Kim DH. Functional status and quality of life after transcatheter aortic valve replacement: a systematic review. *Ann Intern Med.* 2014 Feb 18;160(4):243-54.
 124. Straiton N, Jin K, Bhindi R, Gallagher R. Functional capacity and health-related quality of life outcomes post transcatheter aortic valve replacement: a systematic review and meta-analysis. *Age Ageing.* 2018 May 1;47(3):478-82.
 125. Lytvyn L, Guyatt GH, Manja V, et al. Patient values and preferences on transcatheter or surgical aortic valve replacement therapy for aortic stenosis: a systematic review. *BMJ Open.* 2016 Sep 29;6(9):e014327.
 126. Hussain AI, Garratt AM, Brunborg C, Aakhus S, Gullestad L, Pettersen KI. Eliciting Patient Risk Willingness in Clinical Consultations as a Means of Improving Decision-Making of Aortic Valve Replacement. *J Am Heart Assoc.* 2016 Mar 18;5(3):e002828.
 127. Lauck SB, Baumbusch J, Achtem L, et al. Factors influencing the decision of older adults to be assessed for transcatheter aortic valve implantation: An exploratory study. *Eur J Cardiovasc Nurs.* 2016 Dec;15(7):486-94.
 128. Coylewright M, Palmer R, O'Neill ES, Robb JF, Fried TR. Patient-defined goals for the treatment of severe aortic stenosis: a qualitative analysis. *Health Expect.* 2016 Oct;19(5):1036-43.
 129. Olsson K, Naslund U, Nilsson J, Hornsten A. Patients' Decision Making About Undergoing Transcatheter Aortic Valve Implantation for Severe Aortic Stenosis. *J Cardiovasc Nurs.* 2016 Nov/Dec;31(6):523-8.
 130. Dharmarajan K, Foster J, Coylewright M, et al. The medically managed patient with severe symptomatic aortic stenosis in the TAVR era: Patient characteristics, reasons for medical management, and quality of shared decision making at heart valve treatment centers. *PLoS One.* 2017;12(4):e0175926.
 131. Boyd C, Smith CD, Masoudi FA, et al. Decision Making for Older Adults With Multiple Chronic Conditions: Executive Summary for the American Geriatrics Society Guiding Principles on the Care of Older Adults With Multimorbidity. *J Am Geriatr Soc.* 2019 Apr;67(4):665-73.
 132. Blaum CS, Rosen J, Naik AD, et al. Feasibility of Implementing Patient Priorities Care for Older Adults with Multiple Chronic Conditions. *J Am Geriatr Soc.* 2018 Oct;66(10):2009-16.
 133. Gulbrandsen P, Clayman ML, Beach MC, et al. Shared decision-making as an existential journey: Aiming for restored autonomous capacity. *Patient Educ Couns.* 2016 Sep;99(9):1505-10.
 134. Skirbekk H, Middelthon AL, Hjortdahl P, Finset A. Mandates of trust in the doctor-patient relationship. *Qual Health Res.* 2011 Sep;21(9):1182-90.
 135. Chewning B, Bylund CL, Shah B, Arora NK, Gueguen JA, Makoul G. Patient preferences for shared decisions: a systematic review. *Patient Educ Couns.* 2012 Jan;86(1):9-18.
 136. Levinson W, Kao A, Kuby A, Thisted RA. Not all patients want to participate in decision making. A national study of public preferences. *J Gen Intern Med.* 2005 Jun;20(6):531-5.
 137. Price EL, Berecknye S, Kuby A, Levinson W, Braddock CH, 3rd. New elements for informed decision making: a qualitative study of older adults' views. *Patient Educ Couns.* 2012 Mar;86(3):335-41.
 138. Edwards A, Elwyn G. Inside the black box of shared decision making: distinguishing between the process of involvement and who makes the decision. *Health Expect.* 2006 Dec;9(4):307-20.
 139. Schaufel MA, Nordrehaug JE, Malterud K. "So you think I'll survive?": a qualitative study about doctor-patient dialogues preceding high-risk cardiac surgery or intervention. *Heart.* [Research Support, Non-U.S. Gov't]. 2009 Aug;95(15):1245-9.
 140. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* 2013 Jan;9(1):63-75 e2.

-
141. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. *N Engl J Med*. 2016 Feb 11;374(6):523-32.
 142. SWEDEHEART. Issued in 2015- Percutaneous Valve Registry. [cited 2015 Aug 14]; Available from: <http://www.ucr.uu.se/swedeheart/67-swedeheart/english/169-swedeheart-annual-report-in-english>
 143. Salmon E, Perani D, Herholz K, et al. Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Hum Brain Mapp*. 2006 Jul;27(7):588-97.
 144. Marzanski M. On telling the truth to patients with dementia. *West J Med*. 2000 Nov;173(5):318-23.
 145. Haaksma ML, Eriksson M, Rizzuto D, et al. Survival time tool to guide care planning in people with dementia. *Neurology*. 2019 Dec 16.
 146. Eldholm RS, Barca ML, Persson K, et al. Progression of Alzheimer's Disease: A Longitudinal Study in Norwegian Memory Clinics. *J Alzheimers Dis*. 2018;61(3):1221-32.
 147. Piers R, Albers G, Gilissen J, et al. Advance care planning in dementia: recommendations for healthcare professionals. *BMC Palliat Care*. 2018 Jun 21;17(1):88.
 148. Forman DE, Rich MW, Alexander KP, et al. Cardiac care for older adults. Time for a new paradigm. *J Am Coll Cardiol*. 2011 May 3;57(18):1801-10.



Conditions for autonomous choice: a qualitative study of older adults' experience of decision-making in TAVR

Elisabeth Skaar,^{1,2,3} Anette Høyen Ranhoff,^{2,3} Jan Erik Nordrehaug,² Daniel E Forman,⁴ Margrethe Aase Schaufel^{5,6}

¹Department of Heart Disease, Haukeland University Hospital, Bergen, Norway

²Department of Clinical Science, University of Bergen, Bergen, Norway

³Kavli Research Centre for Geriatrics and Dementia, Haralds plass Deaconess Hospital, Bergen, Norway

⁴University of Pittsburgh Medical Center, VA Pittsburgh Healthcare System, Pittsburgh, USA

⁵Research Unit for General Practice, Uni Research Health, Bergen, Norway

⁶Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

Abstract

Background Patient autonomy is a leading principle in bioethics and a basis for shared decision making. This study explores conditions for an autonomous choice experienced by older adults who recently underwent trans-catheter aortic valve replacement (TAVR). **Methods** Qualitative study entailing semi-structured interviews of a purposive sample of ten older (range 73–89, median 83.5 years) adults after TAVR (median 23 days). The study setting was a cardiac department at a university hospital performing TAVR since 2010. Analysis was by systematic text condensation. **Results** Even when choice seemed hard or absent, TAVR-patients deliberately took the chance offered them by processing risk assessment, ambivalence and fate. They regarded declining the treatment to be worse than accepting the risk related to the procedure. The experience of being thoroughly advised by their physician formed the basis of an autonomous trust. The trust they felt for the physicians' recommendations mitigated ambivalence about the procedure and risks. TAVR patients expressed feelings consistent with self-empowerment and claimed that it had to be their decision. Even so, choosing the intervention as an obligation to their family or passively accepting it was also reported. **Conclusions** Older TAVR patients' experience of an autonomous decision may encompass frank tradeoff; deliberate physician dependency as well as a resilient self-view. Physicians should be especially aware of how older adults' subtle cognitive declines and inclinations to preserve their identities which can influence their medical decision making when obtaining informed consent. Cardiologists and other providers may also use these insights to develop new strategies that better respond to such inherent complexities.

J Geriatr Cardiol 2017; 14: 42–48. doi:10.11909/j.issn.1671-5411.2017.01.007

Keywords: Aortic stenosis; Older adults; Patient-centered care; Shared decision-making; Trans-catheter aortic valve replacement

1 Introduction

From 2002, trans-catheter aortic valve replacement (TAVR) has been an option for patients with severe and symptomatic aortic stenosis and too high risk of open heart surgery. Typical TAVR patients are old and have significant comorbidities. While TAVR in general is better tolerated than surgery, it is still associated with complications,^[1,2] and it is important that the patient understands risk and benefit for the procedure.

Autonomy is a core element of shared decision making

(SDM), the preferred model for health care treatment decisions. The purpose of SDM is to decrease the asymmetrical power between physicians and patients, by increasing patients' information, sense of autonomy, and that treatment choices should reflect patient's values and preferences.^[3] In medical ethics, autonomy is understood as a "capacity for independent decisions and action".^[4] Beauchamp and Childress state three conditions for autonomy: intentionality, understanding and noncontrol, meaning intentionally as opposed to accidental and noncontrol as voluntariness free of both external and internal (for instance mental illness) control.^[5] However, relational understanding challenges this definition of autonomy by stating "it ignores the social circumstances and power relations that affect choice contexts".^[6] In the elderly population, where medical decisions are more complex due to comorbidity and frailty, some stu-

Correspondence to: Elisabeth Skaar, Department of Heart Disease, Haukeland University Hospital, PO Box 1400, Bergen 5020, Norway. E-mail: elisabeth.skaar@helse-bergen.no

Received: October 9, 2016 **Revised:** January 12, 2017

Accepted: January 19, 2017 **Published online:** January 28, 2017

studies emphasize the importance of a trusting relationship with the physician.^[7,8] As cognitive decline and dementia increase substantially with age, some patients have difficulties giving informed consent.

Patients' decision to undergo TAVR assessment is multifaceted, and understanding their reasons for wanting to be treated and asking them to define their goals can enhance shared decision making.^[9,10] Three patterns in TAVR patients' decision making have been identified: the ambivalent, obedient and reconciled patient, highlighting that health care professionals should give tailored information based on patients' values.^[11] Patients' need to discuss risks and benefits of the treatment has also been emphasized. TAVR-programs have been developed to improve communication and provide decision support, including transition to palliative care.^[12] Still, little is known about how patients experience autonomy preceding TAVR.

As clinicians and researchers with extensive experience within geriatrics and cardiology, we wanted to address the special challenges for older TAVR patients examining their motivation for the procedure, risk perception, understanding of the procedure and ability of making an independent choice. The combination of advanced age and a busy hospital environment might challenge patient autonomy, and our preconception was that patients passively accepted the offered treatment. Thus, our study explores conditions for an autonomous choice experienced by older adults who recently underwent TAVR, with a special focus on relational and cognitive aspects.

2 Methods

We conducted a qualitative study based on semi-structured, individual interviews of TAVR patients.^[13] This design is suitable to explore perspectives of human experiences, motives, feelings, thoughts and values of major clinical relevance.^[13]

2.1 Study setting

Participants in the study were enrolled post-procedure from a large university hospital in Norway with 860 somatic beds. The hospital has advanced interventional and surgical expertise, and has performed TAVR procedures since 2010. All patients were discussed in a heart team before the decision of offering TAVR treatment. Patients received information from different physicians on the ward during the preprocedural hospital stay and from interventional cardiologists performing TAVR the day before the procedure. Some patients also got information from their private consultant cardiologists. There was no written information pro-

vided to the patient preceding TAVR at the time of this study.

2.2 Data collection

Interviews were conducted between February 2014 and April 2015. We searched for a purposive sample aiming for diversity regarding age, gender and complication rate. The inclusion criteria were patients over 70 years who underwent TAVR; the only exclusion criterion was not speaking Norwegian. Inclusion was stepwise according to analytical strategy. The interviews lasted from 30 to 60 min and were conducted 2 to 4 weeks after TAVR, except for three patients who were interviewed after 9, 41 and 52 days due to either practical reasons or the analytical process. All interviews were audiotaped and transcribed verbatim by Skaar. Sample size was determined by the concept of information power and thus continuously evaluated as enrolment proceeded.^[14] We had a narrow aim, dense specificity, applied theory and a strong dialogue. After four stepwise analyses adding two and three interviews at a time, the material was assessed sufficient to answer our research question according to the mentioned criteria of information power when ten participants had been recruited. This does not imply that other phenomena could not have been discovered by further enrolment, but that the developed categories at that point were large and rich enough for thorough description of the experiences investigated.

2.3 Participants

Ten patients over 70 years were recruited, six were women. The characteristics of participants were list in Table 1. All underwent elective TAVR due to severe symptomatic aortic stenosis and high risk for complications to SAVR, but time to procedure varied from a few weeks after activity-induced syncope to several months with less dramatic symptoms. Logistic EuroSCORE varied between 8 and 28. One patient had mean pressure gradient of 39 mmHg, maximum jet velocity of 3.9 m/s and indexed aortic valve area for body surface area (BSA) 0.4 cm²/m², the others fulfilled the echo cardiac criteria of severe aortic stenosis with mean pressure gradient over 40 mmHg, maximum jet velocity over 4.0 m/s and indexed aortic valve area for BSA below 0.6 cm²/m². All ten patients had symptoms related to their AS. One of the patients had severe complications with cardiac arrest and stroke during the procedure; another had TAVR with direct aortic approach and was re-operated with open heart surgery two days after the procedure due to profound bleeding.

Table 1. Characteristics of participants.

Men/Women	4/6
Age	
70–79 yrs	3
80–89 yrs	7
Symptoms	
[†] NYHA I–II	1
[†] NYHA II	7
[†] NYHA III	2
Syncope	1
Angina	2
[#] Logistic EuroSCORE	
< 10	2
10–20	7
> 20	1
Social status	
Live alone	5
Comorbidities	
Coronary artery disease	3
Chronic obstructive lung disease	2
Diabetes	1
Stroke or transitory ischemic attack	1
Bypass graft surgery	2
Peripheral vascular disease	1
Renal failure	0
Pulmonary hypertension	1
Low ejection fraction (below 35%)	1
Concomitant valve disease	3
Education level	
Primary school	3
High school	4
College and/or university	3
Cognition (prior to intervention)	
[†] MMSE NR > 27	6
[†] MMSE NR 25–27	4
Physical frailty	
[§] SPPB fit	3
[§] SPPB intermediate	6
[§] SPPB frail	1
Post procedure pacemaker	3
Severe complications	2
Length of stay	
5 days	1
6 or 7 days	6
10 and 11 days	2
17 days	1
Discharged to	
Home	5
Other hospital	1
Rehabilitation	3
Intermediate care	1

[†]NYHA classification of the stages of heart failure, range from I–IV, most severe dyspnea at IV; [#]Logistic Euro SCORE is a model of predicting mortality in high risk cardiac surgical patients; [†]MMSE-NR measures cognitive impairment, range from 0–30, higher score means better cognition; [§]SPPB measures physical frailty, higher scores better function. NYHA: New York Heart Association; MMSE-NR: Mini Mental Status Examination, Norwegian Revision; SPPB: short physical performance battery.

2.4 Ethical statement

This study was approved from the Regional Committee for Medical Research Ethics 04.09.13, 2013/1310 REK. Informed consent was obtained from all participants.

2.5 Analysis

Qualitative analysis was performed in collaboration by Skaar and Schauffel following systematic text condensation,^[15] proceeding through the following stages: (1) reading all the material to obtain an overall impression, bracketing previous preconceptions; (2) identifying units of meaning, representing different aspects of the patients' experiences and coding for these; (3) condensing and abstracting the meaning within each of the coded groups; and (4) summarizing the contents of each code group to generalized descriptions and concepts reflecting the most important elements of autonomy reported. The interview guide consisted of questions addressing how patients experienced the process preceding TAVR, focusing why they wanted the treatment, how they coped with risk information and the challenge of making a choice. We used an editing analysis style where categories were developed from the empirical data, not in a theory-driven template analysis style from predefined theoretical concepts.^[16] Still, the analysis was informed by theory of patient autonomy.^[17] Analysis was done stepwise with new interviews supplementing the sample. A decision trail documented the choices during the analytical process.^[18]

3 Results

Even when choice seemed hard or absent, TAVR-patients deliberately took the chance offered them by processing risk assessment, ambivalence and fate. They experienced lack of a real sense of choice based on their condition's severity and the risks presented to them, but regarded declining the treatment to be worse than accepting the risk related to the procedure. The experience of being truthfully and thoroughly advised by their physician formed the basis of an autonomous trust. The trust they felt for the physicians' recommendations and the copious information provided mitigated ambivalence about the procedure and risks. TAVR-patients' striking self-determination comprised extensive mobilization of hope, lease of life and a robust sense of self. They expressed feelings consistent with self-empowerment and claimed that it had to be their decision. Even so, choosing the intervention as an obligation to their family or passively accepting it was also reported.

3.1 Deliberately taking the chance

Participants regarded declining the treatment to be worse

than accepting the risk related to the procedure. Based on information about symptoms gradually increasing and no hope for recovery without the procedure, the patient perceived making a decision. None of them reported this as a difficult choice. Facing serious complications, they expressed that they could and had to deal with risk, since this to some extent is inherent in all medical procedures, and distanced themselves partly by thinking that "it happens to all others, but not me." They regarded the intervention as routine, despite being aware of complications, and let fate decide. *"It was not difficult at all to decide. I reckoned that if I said no, I wouldn't live much longer."* (Mark).

The majority experienced receiving good and well-adjusted amount of risk information, describing it as detailed and first-class. Even so, participants disclosed ambivalence regarding how much they wanted to know about complications. The importance of knowing the most dreaded complications was highlighted, but simultaneously relief was expressed not being aware of these. One patient had denied risk information prior to an earlier procedure and still preferred it this way. Too much information regarding complications could induce anxiety and unnecessary worry, making decision-making more difficult. One patient expressed fear ending up as a "vegetable" in a nursing home and become dependent upon others. She worried life then would have little meaning. However, the participants imparted they were prepared to die, viewing death as a natural part of life and expressing an acceptance of fate. *"I thought, I am 88 years old and I will not live for a long time anyway. I am also a Christian, so I thought come what may, and then I didn't ponder anymore."* (Molly).

Some were afraid they would regret it if they declined and later on experienced more symptoms. They were aware that TAVR might not be an option later if they declined now. During the investigation period they realized that something had to be done, like a virtue of necessity. Thus, they barely experienced being in a situation where they should make a choice, and reported little doubt or anguish. One of the patients, who admitted to hospital after an exercise-triggered syncope, outlined how he did not specifically want the procedure, but was convinced he needed it. Another patient who had been physically active his whole life and now experienced fatigue and declining physical performance, expressed it like this: *"In a way, you might say that I had a choice, however, I was rather determined to go through with the attempt to improve the situation with the operation. So it was not a difficult decision. (...)You're in a situation where you can make little difference, and you just have to resign and accept. (...) You never know when "fate strikes", as we say."* (Colin).

3.2 Autonomous trust in their doctors

Our participants chose to follow the physicians' treatment recommendation seeking symptom relief and trusting the physicians with whom they were interacting. The participants wished the physician to be honest and optimistic, still not concealing risk. Physicians spending time informing about the procedure and letting the patients take time to think it through, were cherished, as well as physicians recommending the procedure despite the risks. Patients expressed a general and strong confidence in GPs, private consultant cardiologists and hospital physicians. Even when the physicians described risks before surgery, it could not disturb the confidence and trust they also grounded in personal qualities of the physician. One patient expressed it like this: *"I had confidence in the physicians because I noticed how they were as people. I have never been a fan of titles; I am much more reassured by people themselves, not their degrees or titles."* (Jennifer).

The patients experienced lack of medical competence. When physicians recommended the treatment, patients trusted that the benefit outweigh the risk. This was illustrated by a female patient who explained how she would not have complained about the decision if she was denied TAVR, because she then reckoned that there was a good medical reason for not recommending her the treatment. Even when the procedure was thoroughly explained, they found it hard to understand and they trusted their physicians' medical competence: *"Then I accept the treatment boldly, I trust the physicians, because medicine is so advanced now, that you don't need to worry."* (Alice).

However, the patients did not have blind trust in their physicians, the physicians had to act trustworthy or else the patients seek a second opinion. One patient was told by a physician that her heart was exhausted and there was nothing more one could do. Immediately she went to her GP and asked him to send her to a cardiologist who referred her for TAVR. Another patient described that it was difficult making a decision about TAVR following extensive risk information where she felt the physician advised against the procedure, and said that it all resolved when she chose to rely on her private consultant cardiologist. This physician had spent time thoroughly explaining why he recommended the procedure, and she trusted him more than the risk information of severe complications that she received at the hospital. *So I went home and thought: "Should I do this or not, am I an idiot about to ruin my life?", but then I considered all the others (physicians on the ward) who had said "go through with it" and my own physician recommending it."* (Anna).

3.3 Fundamental self-determination based on personal identity

The participants in this study explicitly outlined how they made the decision on their own, and that this was important to them. This was expressed by a fundamental go-ahead spirit and strong lease of life when TAVR treatment was to be decided. They had a positive attitude towards themselves as robust and relatively strong, still acknowledging they were older and that their strength had declined. In general, TAVR candidates described themselves as feeling independent and coping well. They did not want to be a burden to their relatives. Most did not involve the family in the decision, but informed them of their choice afterwards. A man expressed his independence in the decision making like this: *"I told my wife that I had made the decision" ... "After the decision was made, I didn't reconsider, I slept well and didn't worry.*

The TAVR-patients had a clear future goal of living longer and did not want to sit down waiting to die from aortic stenosis when it could be cured by an operation. They aimed for improved body function, better health and quality of life. Describing lifelong patterns of an active life and having many interests, they wished to adapt to the adversities of aging like disease and poorer functioning as well as possible. The participants were not anxious, and universally expressed convictions to make the best of the situation: *"I'm the kind of person who—when I have to do something—think that I just have to deal with it, and set my heart on it."* (Edna).

Even if they considered the decision to be theirs, several highlighted that they felt an obligation to their relatives to accept a treatment that was recommended. One patient expressed how she did not want to let her children down if she died suddenly one day and they knew she could have had an intervention done to avoid it. Another patient took a more passive position during the decision-making process, possibly due to mild cognitive impairment and depressive symptoms. She explained that she accepted TAVR mostly because her daughter wanted her to, and that she didn't care too much herself: *"We did not discuss it too much the physician and I either. (...) He just asked if I wanted (the treatment) and I accepted. (...) I did it for the others' sake as well."* (Rachel).

4 Discussion

Interviewing patients about the TAVR decision-making process, we found that despite being in a situation with limited choice, they claimed the decision to be their own. Trust in their physicians and their medical expertise was an important element for the decision. Below, we discuss the

strengths and limitations of this study, and the impact of our findings.

4.1 TAVR patients' paradoxical autonomy

This study confirms the value of self-determination and autonomy in medical decisions,^[3,5,19] and adds to previous knowledge by providing empirically based descriptions of what constitutes conditions for TAVR patients' autonomy experienced in the decision-making process. Older TAVR patients claim to make an autonomous decision, despite admitting profound trust in their physicians and revealing lack of medical competence. Cognitive decline leaves the patient more dependent and less capable to question physicians advice. In the following, we will discuss the implications of our findings.

Arguments that the strong focus on autonomy might have underestimated the significance of trust have been made, claiming it's not true that *"doctors offer patients a smorgasbord of possible treatments and interventions, a varied menu of care and cure"*. By demanding informed consent, we make it possible to make an autonomous choice, but there is no guarantee.^[4] Being ill and vulnerable makes it hard to choose autonomously. Some argue that focus on free choice, patient autonomy and informed consent might conceal the power asymmetry, with an illusion that it facilitates a discussion between equals, but underestimate that the physicians' medical expertise gives him/her power.^[20] Our findings show that trusting physicians is a core element of decision making, exposing patients to physicians' power. However, this is no blind trust and these patients may seek a second opinion if they are not reassured by physicians' advice.

The philosopher Harald Grimen has outlined how difficult it is for the patient to challenge the authority of the physician, and *"patients may be forced to trust what they get"*.^[20] This does not mean a return to paternalism. Patients being involved and physicians' respect for patients' views are essential to medical decisions, but the concepts of informed consent and shared decision-making have limitations.^[4] A relational understanding of autonomy recognizes social circumstances and power relations. Autonomous decisions do not happen in isolation or fully independence,^[6,21] and patients trusting their physician might still make an autonomous choice, as our findings indicate. It is highlighted that in cases with a serious condition, no support in the decision-making may impede the patients' capacity of making a decision. *"A full listing of all possible side effects, for example, may well do nothing but agitate a patient who is clear that she desires to be treated and understands that there are risks associated with achieving that goal"*.^[6]

There are cultural differences influencing decision-

making. In the USA where physician-patient interactions are regulated in detail by law, courts have ruled that for invasive interventions physicians “*need to discuss rare but serious risks, such as death and stroke*”.^[19] This secures patient rights, but might come at the cost of reduced trust in the physician-patient relationship. Not all patients want to participate to the same extent,^[22–24] and shared decision-making emphasize to involve “*the patient in the decision-making to the extent that they desire*”.^[25] Securing patients' rights might therefore be in conflict with shared decision-making. Our study illuminates the way ambivalence of knowing the most dreadful complications balances the need to feel secure. A Norwegian study of physician-patient dialogues preceding high-risk cardiac treatment demonstrated a profound confidence in the physicians' ability to get them through the intervention or surgery they were facing, yet the responsibility making the decision was shared in an asymmetrical power relation.^[26]

In our study, only one patient revealed signs of cognitive impairment that might have influenced the decision-making process. Executive cognitive impairment is subtle and prevalent among cardiac patients, and particularly impactful on the ability of the patients to make medical decisions like TAVR.^[27,28] The prevalence of dementia in Western Europe increases exponentially with age, from 4.3% among 70–74 years old to 43.1% in the 90+ population,^[29] even if new studies find a lower age specific incidents.^[30] In a Swedish registry, the average age for TAVR patients are about 82 years.^[31] Dementia will eventually diminish a patients capability of making an informed choice. TAVI frequently being provided to patients at high age ideally requires a cognitive assessment,^[32] in order identify patients not capable of making an autonomous decision. TAVR being a procedure with risk of complications, family wishes alone are not sufficient for performing the intervention. Curing aortic stenosis in order for patients to survive to end stage dementia also raises ethical questions, and even if this is what the family wants, it might not be what the patient would want acting autonomously. New treatment opportunities thus initiate new ethical challenges and we need to discuss implications thoroughly in order to do no harm.

4.2 Validity and transferability

A trained geriatrician, who is used to talk to and gather information from elderly patients, performed the interviews. The interviewer was a woman and younger than the patients, and most interviews were conducted in the patients' own home. This reduced the asymmetrical power relation. As one of the patients had a cognitive impairment possibly affecting her answers, the interviewer asked follow-up ques-

tions when in doubt. Disclosing both positive and negative aspects of the process they had been through, physicians they had met and their own reactions makes it likely they answered the questions in honest terms. On the other hand, the interviewer being employed at the department and knowing the interventional cardiologists, might have diminished exploring patients' negative experiences.

Our focus was not how the decision-making was performed, but how patients experienced it. We therefore chose not to record and study the actual conversations between physicians and patient, but conducted an interview study. The analysis of trust focused on the participants' general experience and did not discern differences regarding interventional cardiologists, private consultant or primary care physicians. Thus, the variability of physician types and the variability of interactions with patients have not been explored in this study, nor the complexity implicit in seeking a procedure.

Our sample includes elective TAVR patients from one hospital, and the majority had an intermediate or fit frailty score. Other patterns may have been discovered in a frailer sample.

Since we only interviewed patients who were accepted for TAVR, the results may not be transferable to decision-making in older patients in general. The interventional cardiologists assess lease on life before offering treatment, and TAVR patients are probably more physiological robust. However, since there are strict selection criteria for TAVR the majority of candidates are older than 70 years, our findings may be applied to patients accepted for TAVR in other countries.

Hospital treatment in Norway is funded through the public health care system and provides no economic motives for cardiologists to perform TAVR. Studies have also shown that in the Nordic countries, people have a high level of trust towards authorities.^[33] There were only white participants in our study, and most were Christians or non-religious. The results may therefore not be transferable to a different cultural and religious setting.

4.3 Conclusions

Older TAVR patients' experience of an autonomous decision may encompass frank tradeoff; deliberate physician dependency as well as a resilient self-view. Physicians should be especially aware of how older adults' subtle cognitive declines and inclinations to preserve their identities can influence their medical decision making when obtaining informed consent. Cardiologists and other providers may also use these insights to develop new strategies that better respond to such inherent complexities.

Acknowledgements

We would like to thank the participants in this study, and professor Kirsti Malterud for valuable comments. This study was mainly supported by Grants from Grieg Foundation, Department of Heart Disease, Haukeland University Hospital and Kavli Research Centre for Geriatrics and Dementia, Haralds plass Deaconess Hospital, Bergen.

References

- Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010; 363: 1597–1607.
- Davies WR, Thomas MR. European experience and perspectives on transcatheter aortic valve replacement. *Prog Cardiovasc Dis* 2014; 56: 625–634.
- Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). *Soc Sci Med* 1997; 44: 681–692.
- O'Neill. In *Autonomy and trust in bioethics*; Cambridge University Press: New York, USA, 2002; 1–48.
- Beauchamp T, Childress J. In *Principles of Biomedical Ethics*; 7th Edition; Oxford University Press: New York, USA, 2013; 104–105.
- Mackenzie C, Stoljar N. In *Relational autonomy*; Dodds S, Ed; Oxford University Press: New York, USA, 2000; 213–235.
- Bastiaens H, Van Royen P, Pavlic DR, et al. Older people's preferences for involvement in their own care: a qualitative study in primary health care in 11 European countries. *Patient Educ Couns* 2007; 68: 33–42.
- Wrede-Sach J, Voigt I, Diederichs-Egidi H, et al. Decision-making of older patients in context of the doctor-patient relationship: a typology ranging from “self-determined” to “doctor-trusting” patients. *Int J Family Med* 2013; 2013: 478498.
- Lauck S, Baumbusch J, Achem L, et al. Factors influencing the decision of older adults to be assessed for transcatheter aortic valve implantation: An exploratory study. *Eur J Cardiovasc Nurs* 2015; 1–9.
- Coylewright M, Palmer R, O'Neill ES, et al. Patient-defined goals for the treatment of severe aortic stenosis: a qualitative analysis. *Health Expect* 2016; 19: 1036–1043.
- Olsson K, Naslund U, Nilsson J, Hornsten A. Patients' decision making about undergoing transcatheter aortic valve implantation for severe aortic stenosis. *J Cardiovasc Nurs* 2016; 31: 523–528.
- Lauck SB, Gibson JA, Baumbusch J, et al. Transition to palliative care when transcatheter aortic valve implantation is not an option: opportunities and recommendations. *Curr Opin Support Palliat Care* 2016; 10: 18–23.
- Kvale S. In *InterViews, an introduction to qualitative research interviewing*; SAGE: Thousands Oaks, London, UK, 1996.
- Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qual Health Res*. Published Online First: Nov 27, 2015. DOI: 10.1177/1049732315617444.
- Malterud K. Systematic text condensation: a strategy for qualitative analysis. *Scand J Public Health* 2012; 40: 795–805.
- Crabtree B, Miller W. Doing qualitative research; 2nd Edition; SAGE: London, UK, 1999.
- Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. *J Gen Intern Med* 2012; 27: 1361–1367.
- Whitehead L. Enhancing the quality of hermeneutic research: decision trail. *J Adv Nurs* 2004; 45: 512–518.
- Lo B. In *Resolving Ethical Dilemmas, a guide for clinicians*; Lippincott Williams and Wilkins: Philadelphia, USA, 2013.
- Grimen H. Power, trust, and risk: some reflections on an absent issue. *Med Anthropol Q* 2009; 23: 16–33.
- Entwistle VA, Carter SM, Cribb A, McCaffery K. Supporting patient autonomy: the importance of clinician-patient relationships. *J Gen Intern Med* 2010; 25: 741–745.
- Chewning B, Bylund CL, Shah B, et al. Patient preferences for shared decisions: a systematic review. *Patient Educ Couns* 2012; 86: 9–18.
- Levinson W, Kao A, Kuby A, Thisted RA. Not all patients want to participate in decision making. A national study of public preferences. *J Gen Intern Med* 2005; 20: 531–535.
- Price EL, Bereknyei S, Kuby A, et al. New elements for informed decision making: a qualitative study of older adults' views. *Patient Educ Couns* 2012; 86: 335–341.
- Edwards A, Elwyn G. Inside the black box of shared decision making: distinguishing between the process of involvement and who makes the decision. *Health Expect* 2006; 9: 307–320.
- Schaufel MA, Nordrehaug JE, Malterud K. “So you think I'll survive?": a qualitative study about doctor-patient dialogues preceding high-risk cardiac surgery or intervention. *Heart* 2009; 95: 1245–1249.
- Eggermont LH, de Boer K, Muller M, et al. Cardiac disease and cognitive impairment: a systematic review. *Heart* 2012; 98: 1334–1340.
- Dickson VV, Tkacs N, Riegel B. Cognitive influences on self-care decision making in persons with heart failure. *Am Heart J* 2007; 154: 424–431.
- Prince M, Bryce R, Albanese E, et al. The global prevalence of dementia: a systematic review and Meta analysis. *Alzheimers Dement* 2013; 9: 63–75.
- Satzabal CL, Beiser AS, Chouraki V, et al. Incidence of dementia over three decades in the Framingham heart study. *N Engl J Med* 2016; 374: 523–532.
- SWEDHEART. Percutaneous Valve Registry, 2015. <http://www.ucr.uu.se/swedheart/67-swedheart/english/169-swedeheart-annual-report-in-english> (accessed Aug 14, 2015).
- Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg* 2013; 145: 6–23.
- Bergh A, Bjornskov C. Historical trust levels predict the current size of the welfare state. *Kyklos* 2011; 64: 1–19.

II

A novel geriatric assessment frailty score predicts 2-year mortality after transcatheter aortic valve implantation

Elisabeth Skaar^{1,2,3*}, Leslie Sofia Pareja Eide⁴, Tone Merete Norekvål^{1,2}, Anette Hysten Ranhoff^{2,3}, Jan Erik Nordrehaug², Daniel Edward Forman^{5,6}, Andreas W. Schoenenberger^{7,8}, Karl Ove Hufthammer⁹, Karel Kier-Jan Kuiper¹, Øyvind Bleie¹, Erik Jerome Stene Packer¹, Jørund Langørgen¹, Rune Haaverstad^{1,2}, and Margrethe Aase Schaufel^{10,11}

¹Department of Heart Disease, Haukeland University Hospital, PO box 1400, 5021 Bergen, Norway; ²Department of Clinical Science, University of Bergen, Norway; ³Kavli Research Centre for Geriatrics and Dementia, Haraldsplass Deaconess Hospital, Bergen, Norway; ⁴Institute of Health and Social Science, Western Norway University of Applied Sciences, Bergen, Norway; ⁵Department of Medicine, Section of Geriatric Cardiology, Divisions of Geriatrics and the Heart and vascular Institute, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; ⁶Geriatric Research, Education, and Clinical Center, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA; ⁷Department of Geriatrics, Inselspital, Bern University Hospital, Bern, Switzerland; ⁸University of Bern, Bern, Switzerland; ⁹Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway; ¹⁰Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway; and ¹¹Research Unit for General Practice, Uni Research Health, Bergen, Norway

Received 22 June 2018; revised 13 September 2018; editorial decision 17 September 2018; accepted 20 September 2018

Aims

Established surgical scores have limitations in delineating risk among candidates for transcatheter aortic valve implantation (TAVI). Assessment of frailty might help to estimate the mortality risk and identify patients likely to benefit from treatment. The aim of the study was to develop a frailty score to guide the decision for TAVI.

Methods and results

We conducted a prospective observational study in patients ≥ 70 years referred for TAVI during 2011–15. A Heart Team had declined the patients for open heart surgery due to high risk but accepted them for TAVI. Prior to the procedure, a geriatric assessment (GA) was performed. Based on this, an 8-element frailty score with a 0–9 (least frail–most frail) scale was developed. A total of 142 patients, 54% women, mean age 83 (standard deviation 4) years, with severe and symptomatic aortic stenosis were assessed. All-cause 2 year mortality was 11%. The novel GA frailty score predicted 2-year mortality in Cox analyses, also when adjusted for age, gender, and logistic EuroSCORE [hazard ratio (HR) 1.75, 95% confidence interval (CI): 1.28–2.42, $P < 0.001$]. A receiver operating characteristic (ROC) curve analysis indicated that a GA frailty score cut-off at ≥ 4 predicted 2-year mortality with a specificity of 80% (95% CI: 73–86%) and a sensitivity of 60% (95% CI: 36–80%). The area under the curve was 0.81 (95% CI 0.71–0.90).

Conclusion

A novel 8-element GA frailty score identified gradations in survival in patients declined for open heart surgery. Patients with higher GA frailty scores had significantly higher 2-year mortality after TAVI.

Keywords

TAVI • Decision-making • Frailty • Ageing • Prognosis

* Corresponding author. Tel: 0047 99601832, Email: elisabeth.skaar@helse-bergen.no

© The Author(s) 2018. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Introduction

The population of older adults is growing, and intrinsic susceptibility to aortic stenosis is high with this new demographic scenery. Improved decision making is necessary for the expanding population of those eligible for transcatheter aortic valve implantation (TAVI).¹

Commonly used risk scores for mortality and morbidity in coronary heart surgery, like the Society of Thoracic Surgeons risk score (STS score) and European System for Cardiac Operative Risk Evaluation (EuroSCORE), are based on age and comorbidity.^{2,3} However, by omitting frailty, sensitivity of these scores to predict adverse events in the oldest population is limited.^{4–6} Frailty, a condition frequent in older adults, is defined as a state of impaired physiologic reserve and decreased resistance to stressors which increase the risk of an adverse outcome.^{7,8} Frailty status enhances prognostic sensitivity for patients with multiple heart conditions including acute coronary disease, stable angina, heart failure,^{9–11} and TAVI.^{12,13} A recent systematic review confirmed the relationship between frailty and mortality in the TAVI population, with a more than doubled risk [hazard ratio (HR) 2.35] of early (≤ 30 days) death in frail patients, and a 1.63 HR of later death.¹⁴ Although TAVI has been assessed to be cost-effective compared with medical treatment,¹⁵ this is undermined by early mortality after TAVI. As the population of older adults expands, it is important to select patients who will benefit most from the intervention to best justify its expense.¹⁶

Both US and European guidelines recommend the use of a Heart Team in decision making prior to treatment for severe, symptomatic aortic stenosis.^{17,18} In addition to the assessments by the interventional cardiologist, cardiac surgeons and imaging specialists, the guidelines recommend a frailty assessment to evaluate cognition and physical function using validated checklists.¹⁷ However, it is not described in detail who should perform and evaluate the frailty assessment and which tools to use.^{1,17,19} Recently, Afalalo et al.²⁰ demonstrated that the essential frailty toolset (EFT) outperformed other frailty scores in predicting 1-year mortality in TAVI patients. Nonetheless the authors emphasized that the EFT is primary a screen for frailty. Once patients are identified by the EFT, further geriatric assessment (GA) is recommended. This demands a more thorough clinical evaluation. We developed a novel frailty score that provides additional information, based on a comprehensive GA. In this study, we show the utility of this novel GA frailty score to predict 2-year mortality, showcasing its powerful prognostic value.

Methods

Study design

A prospective, observational cohort study with 2-year follow-up and inclusion of elective TAVI patients from 2011 to 2015. The study was approved by the Regional Committee for Medical Research Ethics (REK 2010/2936-6 and 2013/1310). All participants signed an informed consent before assessment.

Participants

Patients with severe and symptomatic aortic stenosis accepted for TAVI were recruited from a tertiary university hospital in Western Norway

servicing a population of 1.1 million. All patients were recruited the day before the procedure and were assessed by a Heart Team consisting of a cardiac surgeon, an interventional cardiologist and an imaging specialist. Based on the evaluation, patients were all turned down for open heart surgery due to comorbidity and/or high EuroSCORE. The recruitment period lasted from February 2011 to April 2015. From February 2011 to September 2013, 65 patients ≥ 80 years also participating in a concomitant study of delirium were included.²¹ From October 2013 to April 2015, 82 patients ≥ 70 years were included (Figure 1). Age was then adjusted to 70 years as frailty was assessed to be important also in this younger group. Exclusion criteria were declined consent or inability to understand and/or speak Norwegian.

Severe aortic stenosis was defined as maximal Doppler velocity across the aortic valve ≥ 4 m/s, a mean gradient ≥ 40 mmHg or an aortic valve area < 1 cm² (indexed area < 0.6 cm²/m²) and concomitant clinical symptoms indicating severe aortic stenosis.

Development of a novel frailty score

The GA frailty score was developed based on a comprehensive GA which includes cognition, instrumental activity of daily living, nutrition, physical frailty, comorbidity, and psychological health.^{22,23} The method for developing this score is described by Harrell.²⁴ In this method expert clinicians assign severity points to each condition and sum the points in a total score. Three geriatricians (A.W.S., A.H.R., and E.S.) and one cardiologist (J.E.N.) independently ranked the clinical severity of signs within each potentially important domain. The suggestions were sent to the first author who developed a combined frailty score based on the different proposals.²⁴ All cut-off values in this combined score were based on previous studies.^{13,22} The researchers then agreed on the GA frailty score, a 0–9 point numeric scale with 8 validated geriatric variables (Table 1). The score was finalized before the statistical analysis were performed.

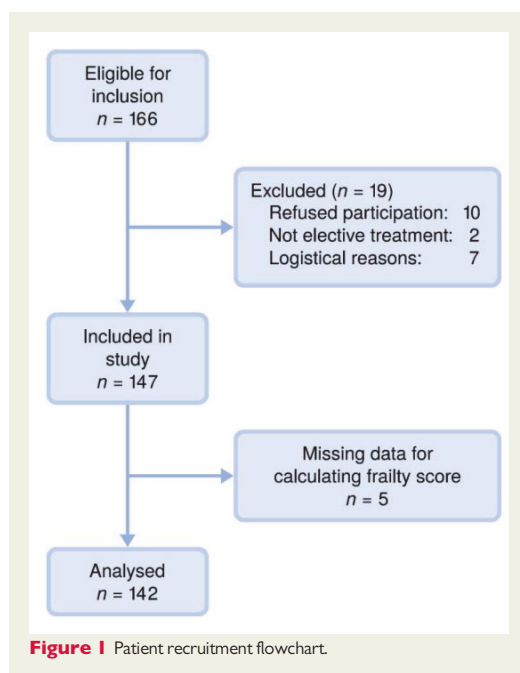


Figure 1 Patient recruitment flowchart.

Table 1 Geriatric assessment tools used in the novel frailty score, along with the corresponding scoring scheme

Domain	Cut-off	Points
Cognition	MMSE ≥ 27	0
	MMSE 20–26	1
	MMSE < 20	2
Instrumental activity of living	NEADL ≤ 43	1
Nutrition	BMI < 20.5	1
Energy level SOF index	Low energy	1
Weight loss SOF index ^a	Weight loss	1
Limb strength SOF index	Chair stand (not able)	1
Comorbidity	Charlson comorbidity index ≥ 3	1
Psychological factors	HADS (total score) ≥ 15	1
Total	Maximum score	9

The total score is calculated by adding the different domain scores. BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini Mental Status Examination; NEADL, Nottingham Extended Activity of Daily Living Scale; SOF Study of Osteoporotic Fractures index.
^aModified from the original SOF; see 'Measurements' section for details.

Measurements

Novel frailty score

Baseline data were collected by L.S.P.E. and E.S. All baseline examinations were performed the day before the procedure. Cognition was assessed by the Mini Mental Status Examination (MMSE).²⁵ It has a range from 0 to 30, with higher scores indicating better cognition. Different cut-offs are reported, and we chose a weighted score with one point for possible cognitive impairment/mild dementia and two points for probable dementia.^{13,26}

Instrumental activities of daily living was measured by Nottingham Extended Activities of Daily Living scale (NEADL),²⁷ a 22-item questionnaire assessing mobility, kitchen, domestic, and leisure activities. Each item has a score from 0 to 3, and the items are added to a total score from 0 to 66, with a higher score indicating better functioning. A cut-off ≤ 43 suggests that the patient is dependent, and studies have shown that this predicts complications and mortality after elective surgery in older patients.^{28,29}

Nutrition was assessed by the body mass index (BMI) and the weight question of modified Study of Osteoporotic Fractures index. The cut-off value for BMI was based on the nutritional risk screening 2002, a screening instrument for nutritional risk.³⁰

Physical frailty was assessed by a modified version (patients self-reported weight loss past year, not measured as in the original index) of the Study of Osteoporotic Fractures Index (mSOF index).³¹ This validated index has a maximum of three points: (i) One point if the patient has $>5\%$ weight loss the previous year (Since, we only had baseline characteristics, the patients were given one point if answering yes to the question 'have you lost weight during the past year'), (ii) one point if the patient is unable to rise from a chair without using their arms (This was tested by L.S.P.E./E.S., not reported by the patients.), and (iii) one point if the patient answers no to the question 'Do you feel full of energy?'

Comorbidity was assessed by Charlson comorbidity index. This is a weighted index based both on the numbers of diseases and the seriousness of each disease. A score of 1 is assigned for myocardial infarction, congestive heart failure, dementia, etc., while the highest score of 6 is

given to metastatic solid tumours and AIDS. In the original paper describing the index, Charlson et al.³² recommends a high cut-off of 2 or 3 if the mortality in the disease under study is high, and we chose a cut-off ≥ 3 .

Psychological health was assessed by the Hospital Anxiety and Depression Scale (HADS),³³ with seven questions on anxiety and seven on depression. Each question ranges from 0 to 3. Summing up the anxiety and depression subscales, we get total HADS, of which a cut-off ≥ 15 was used to identify symptoms of anxiety and/or depression.^{33,34}

The modified essential frailty toolset

The Essential Frailty Toolset (EFT) is a brief four-item (chair rise, cognition, haemoglobin, and serum albumin) frailty scale that predicts morbidity and mortality after TAVI.²⁰ Afילו recommends applying this scale as a screening tool.²⁰ In this study, we aimed to compare the GA frailty score to the EFT.

However, for the first 62 patients in our study, we only had information on success/failure of chair rise, not on the number of seconds it took to complete the chair rises. Therefore, when calculating the EFT for these patients, we assigned 0 points if they completed five sit-to-stand repetitions without using arms (chair rises) and 2 points if they failed to complete all five chair rises. We refer to this modified methodology for the EFT as the modified Essential Frailty Toolset (mEFT). This might give some patients one point lower total score (i.e. the patients who used ≥ 15 s to perform chair rise). For three patients, we missed serum albumin values, and the mEFT was thus calculated for 139 patients.

Follow-up measurements

Two-year all-cause mortality has been stated as a clinically relevant outcome for TAVI candidates and was the primary outcome of this study.¹ The Valve Academic Research Consortium-2 (VARC 2) consensus document⁶ recommends the use of composite endpoints after TAVI, and we report this for the first 6 months.

Power analysis

The initial power analysis was based on categorizing the patients into three groups, a fit group, an intermediate group and a frail group, with 25% in the frail group.^{22,35,36} To achieve a power of 80% with a 5% level of significance, power calculations showed that we needed a total of 140 patients. To account for dropouts, we included 5% more, a total of 147 patients. In order to make the frailty score more applicable in clinical practice, we ultimately dichotomized it into frail and non-frail (fit and intermediate). In addition, we analysed frailty as a continuous score, which increases the statistical power.

Statistical analyses

We present the data as means and standard deviations (SDs), counts and percentages, or proportions and Hazard Ratios (HRs) with 95% confidence intervals (CIs), as appropriate. To assess whether the new frailty score could predict mortality within 2 years, and also when adjusted for other common predictors, we fitted Cox regression models with Firth's correction. Firth's correction provides reduced bias when there are few events (deaths) compared with the number of predictors. The regression models included frailty score as a continuous predictor (unadjusted model/trend test), or frailty score, age, gender, and logistic EuroSCORE as predictors (adjusted model). We also fit a similar adjusted model with frailty score as a dichotomized variable. We present time to death stratified by frailty score (continuous or dichotomized) using Kaplan–Meier plots.

The Receiver Operating Characteristic (ROC) curve³⁷ was examined to find cut-off values for the dichotomized GA frailty score. We reported the Area Under the Curve (AUC) as a summary measure. We found two

cut-off values with an estimated high sensitivity and specificity, and chose the one (≥ 4) emphasizing specificity over sensitivity. Confidence intervals for the sensitivity and specificity were calculated using the Wilson (score) method.³⁸

Some patients had missing data for a few of the questions in the HADS and NEADL questionnaires. Where it was unambiguous on which side of the cut-off the total score would fall on, we used the data for these patients; otherwise, the patients were excluded. For one secondary analysis (based on the mEFT frailty scale), there were additional missing data. For all analyses, we report the number of observations used.

Statistical analyses were performed using IBM SPSS Statistics 24 and R version 3.5.0.³⁹ Cox regression with Firth's correction was performed using R 'coxph' package⁴⁰ version 1.13, and the ROC and AUC calculations were performed using the R 'pROC' package version 1.12.1.⁴¹

Results

Baseline data

General characteristics

A total of 147 patients with severe and symptomatic aortic stenosis were included. Of these, 142 patients had enough data so that the frailty score could be computed (Figure 1). Of the 142 patients, 54% were women, mean age was 83 years (SD 4), five patients were less than 75 years old and three patients were 90 years or older. The oldest patient in the study was 95 years old. More than half of the patients lived with their spouse.

Geriatric characteristics

More than half of the patients (56%) did not have significant cognitive disturbance, a MMSE of 27 or higher. The others (44%) had possible cognitive impairment, but for most of them (89%) probably mild cognitive impairment or mild dementia (MMSE 20–26). Most patients (82%) had a NEADL score above 43, suggesting they were independent in activities of daily living. Few patients (13%) had low BMI (below 20.5 kg/m²); however, 52 (37%) patients had a reported weight loss during the last year. Sixty-one (43%) of the patients had a high score of ≥ 3 on the Charlson comorbidity scale.

Cardiovascular characteristics

Almost all patients 127/135 (missing data on seven patients) had an indexed aortic valve area below 0.6 cm²/m². Logistic EuroSCORE was below 10 in 18% and over 20 in 30% of the patients. Half of the patients had New York Heart Association III or IV at the time of the procedure (Table 2).

Follow-up

No patients were lost to follow-up.

Mortality and morbidity

Fifteen patients (11%) had died within 2 years, 11 of cardiovascular causes and four of non-cardiovascular causes. There was a high degree of early device success, with 141/142 (99.3%) valves in the correct position with good valve function. Early (≤ 30 days) mortality was seen in four patients (2.8%). Moderate to severe prosthetic valve regurgitation and stroke occurred within 6 months in 12.7% and 4.8% of the patients, respectively (Table 3).

Table 2 Patient baseline characteristics (n = 142)

Characteristics	Mean or count	SD or (proportion)
Characteristics		
Age, years	83.4	4.0
Women	76	(54%)
Living alone	60	(42%)
Education		
Primary school	88	(62%)
High school	33	(23%)
University	21	(15%)
Geriatric characteristics		
Cognition		
MMSE	26.3	3.3
MMSE ≥ 27	80	(56%)
MMSE 20–26	55	(39%)
MMSE < 20	7	(5%)
Activities of daily living		
NEADL ≤ 43	121	(82%)
Nutrition		
BMI	25.0	3.9
BMI < 20.5	19	(13%)
SOF index		
Weight loss ^a	52	(37%)
Low energy	58	(41%)
Unable to chair stand	42	(30%)
Comorbidity		
Charlson comorbidity index	2.53	1.3
Charlson comorbidity index ≥ 3	61	(43%)
Psychological factors		
HADS ≥ 15	17	(12%)
Cardiovascular characteristics		
Logistic EuroSCORE	17	8.7
Aortic valve area index, cm ² /m ² ^b	0.4	0.12
Mean aortic valve gradient, mmHg ^c	47.6	14.4
Left ventricular ejection fraction	56.4	11
NYHA \geq III	67/134	(50%)
Previous myocardial infarction	34	(24%)
CABG	31	(22%)
Permanent pacemaker	12	(9%)
Atrial fibrillation	45	(32%)
Pulmonary hypertension	45/139	(32%)
Cerebral vascular disease	16	(11%)
Comorbidity		
COPD	31	(22%)
Kidney failure; creatinine > 177 μ mol/L ^d	5	(4%)

MMSE, Mini Mental Status Examination; NEADL, Nottingham Extended Activities of Daily Living Scale; BMI, Body Mass Index; SOF Index, Study of Osteoporotic Fractures Index; HADS, Hospital Anxiety and Depression Scale; NYHA, New York Heart Association Functional Classification of Heart Failure, Range From I-IV, Most Severe Symptoms at IV; CABG, Coronary Artery Bypass Grafting; COPD, Chronic Obstructive Pulmonary Disease.

^aModified from the original SOF index; see 'Measurements' section for details.

^bMissing data on seven patients.

^cMissing data on two patients.

^dAs reported in the PARTNER study; creatinine > 2 mg/dL (177 μ mol/L).¹

Table 3 Composite endpoints according to Valve Academic Research Consortium-2 consensus document^a criteria

	Total (N = 142)	Percent
Device success		
Absence of immediate procedural mortality ^b	142	100
Correct positioning	141	99.3
Intended performance of the prosthetic heart valve ^c	141	99.3
No moderate or severe prosthetic valve regurgitation ^d	135	95.1
Early safety(at 30 days)		
All-cause mortality	4	2.8
All stroke(disabling or non-disabling) in hospital ^e	4	2.8
Life-threatening or disabling bleeding	8	5.6
Acute kidney injury Stage 2 or 3 ^f	3	2.1
Coronary artery obstruction requiring intervention	1	0.7
Major vascular complication	6	4.2
Valve-related dysfunction requiring intervention	1	0.7
Clinical efficacy(30 days–6 months)		
All-cause mortality	6	4.2
All stroke(disabling or non-disabling)	3	2.1
Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure	15	10.6
NYHA class III or IV ^g	9/136	6.6
Time-related valve safety		
Structural valve deterioration		
Valve-related dysfunction (mean aortic valve gradient ≥ 20 mmHg) and/ or moderate or severe prosthetic valve regurgitation ^h	18/141	12.7
Requiring repeat procedure (TAVI or SAVR)	1	0.7
Prosthetic valve endocarditis	1	0.7
Trombo-embolic events (e.g. stroke)	7	4.8
VARC bleeding (life threatening/disabling bleeding or major bleeding) and unless clearly unrelated to valve therapy (e.g. trauma)	28	19.7

SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; NYHA New York Heart Association.

^aThe Valve Academic Research Consortium (VARC)-2 consensus document (see references).

^bImmediate or consequent death ≤ 72 h post-procedure.

^cNo prosthesis patient mismatch and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s.

^dAfter TAVI procedure at index hospitalization.

^eAssessment of stroke at index. All strokes verified by imaging (CT or MRI).

^fEvaluation of acute kidney injury is based on serum creatinine, we miss data on urine output.

^gNew York Heart Association (NYHA), missing data on six patients.

^hFollow-up at 6 months, missing data on one patient.

Frailty and mortality

The distribution of frailty scores and the corresponding 2-year mortality is shown in Table 5. Based on the dichotomized GA frailty score, 34 patients (24%) were characterized as frail (score ≥ 4).

The Cox analyses showed that the continuous GA frailty score predicted mortality within 2 years, with an estimated HR of 1.79 (95% CI: 1.34–2.36, $P < 0.001$), i.e. an estimated 79% increase in hazard for a unit increase in GA frailty score. This predictive power also remained (HR = 1.75, 95% CI: 1.28–2.42, $P < 0.001$) when adjusting for age, gender, and logistic EuroSCORE (Table 4). A test of the proportional hazard assumption did not find any problems with the model ($P = 0.77$).

The corresponding results for the dichotomous GA frailty score were HR = 5.35 (95% CI: 1.99–15.3, $P = 0.001$) (unadjusted) and HR = 4.91 (95% CI: 1.79–14.2, $P = 0.002$) (adjusted).

The ROC curve (Figure 2) illustrates that a frailty score cut-off at ≥ 4 predicts 2 year mortality with a specificity of 80% (95% CI:

73–86%) and a sensitivity of 60% (95% CI: 36–80%). The AUC was 0.81 (95% CI: 0.71–0.90).

None of the patients with a frailty score of 0 or 1 were dead after 2 years, and none of the patients had a frailty score of 8 or 9. In general, the higher the frailty score, the higher the risk of dying within 2 years (Table 5).

When adjusting for mEFT along with age, gender, and logistic EuroSCORE, the continuous GA frailty score were no longer a statistically significant predictor (HR = 1.36, 95% CI: 0.87–2.21, $P = 0.18$, $n = 139$), and neither were any of the other variables (including mEFT).

Discussion

In this prospective observational study, we found that a novel GA frailty score could predict 2-year all-cause mortality in TAVI

Table 4 Cox regression (with Firth's correction) (n = 142)

	Unadjusted			Adjusted		
	HR	95% CI	P-value	HR	95% CI	P-value
Age, years	1.16	1.00–1.37	0.04	1.16	1.01–1.37	0.04
Male gender	1.01	0.37–2.71	0.99	2.14	0.68–6.93	0.19
Logistic EuroSCORE	1.06	1.01–1.11	0.02	1.04	0.99–1.08	0.13
GA frailty score	1.79	1.34–2.36	0.001	1.75	1.28–2.42	<0.001

CI, confidence interval; HR, hazard ratio.

Hazard ratio estimates (with 95% confidence intervals) for death within 2 years of transcatheter aortic valve implantation. The hazard ratios show the increase in hazard for a unit increase in age (years), logistic EuroSCORE and/or GA frailty score, and for males compared with females.

Table 5 Distribution of geriatric assessment frailty score and mortality within each frailty score (n = 142)

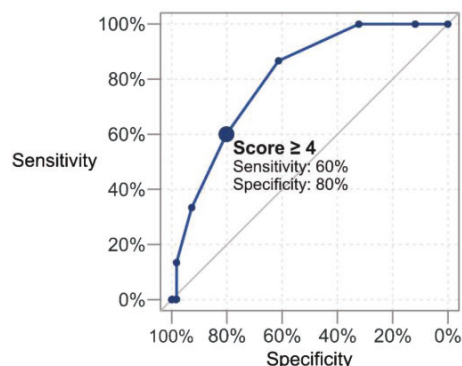
Frailty score	Count	Prop. (%)	Cum. prop. (%)	Deaths ^a	Mortality ^a (%)
0	15	11	11	0	0
1	26	18	29	0	0
2	39	27	56	2	5
3	28	20	76	4	14
4	20	14	90	4	20
5	10	7	97	3	30
6	2	1	99	2	100
7	2	1	100	0	0
8	0	0	100	—	—
9	0	0	100	—	—

Cum., cumulative; Prop., proportion.

^aDeaths within 2 years after TAVI.

patients declined for open heart surgery by a Heart Team. After 2 years, there were no deaths in the cohort with very low (0 or 1) frailty score.

Standard risk scores like EuroSCORE and STS score are insufficient for predicting adverse events in the older adult,^{11,13,42} and a frailty assessment adds information which increases predictability. There is an ongoing discussion regarding the definition of frailty and whether to include cognition, psychological factors, and comorbidity.⁴³ The GA frailty score was developed to provide information for a better decision making prior to TAVI. This study adds to previous work highlighting the need for a more thorough evaluation of the individual patient based on a comprehensive GA. This can provide significant decision-making support for the interventional cardiologist or surgeon. The purpose of the score is not to screen all TAVI candidates, as this will be too time-consuming. Rather it should be used in patients in whom a simpler screening⁴⁴ has revealed potential obstacles for TAVI. In this setting, an assessment solely on physical frailty would not be sufficient, in part due to decline in physical

**Figure 2** Receiver operator characteristics curve for geriatric assessment frailty score (0–9) and 2 year mortality (n = 142). The area under the curve is 0.81 (95% confidence interval: 0.71–0.90).

performance related to severe aortic stenosis. An approach with an initial basic screening for frailty and a selective thorough assessment by a geriatrician has been advocated.^{44,45}

Patients categorized as frail might still be eligible for TAVI. All patients should be involved in a shared decision process regarding their treatment, but for patients where there is doubt whether the procedure is beneficial, it is especially important. Previous studies have underlined the importance of exploring patients' perspectives.^{46,47} Asking the question "What do you hope to accomplish by having your valve repaired?" might capture what is most important to patients.⁴⁸ The decision to offer TAVI should in the end be made by the interventional cardiologist or cardiac surgeon performing TAVI, based on an analysis of benefit vs. risk, taking into account symptoms, comorbidity, patient perspective, procedural risk, and frailty. We suggest the geriatrician to be an important collaborator in this analysis. If TAVI is offered despite frailty, the treatment team should be prepared for a higher risk of complications, including delirium.²¹ Ideally, detecting frailty should lead to additional pre-, per-, and post-operative support.¹¹ The GA frailty score provides delineation of specific aspects of frailty that can be addressed (e.g. nutritional supply if undernourished, treatment for depression).^{49,50} We do not have enough evidence to recommend specific exercise before TAVI in order to improve frailty status.

This study confirms the clinical relevance of frailty assessment prior to TAVI.^{12,13,17} The GA frailty score evaluating cognition, independence in daily life, nutrition, physical frailty, comorbidity, and psychological health, give a thorough and comprehensive assessment of the patient. A high GA frailty score ≥ 4 indicates a reduced 2-year survival (Figure 3). However, we do not advocate a strict cut-off where TAVI is not offered. Knowledge of the (0–9 based) GA frailty score should lead to a careful final evaluation by the TAVI team, and should involve weighting frailty, technical challenges, exploring patient preferences, and symptom burden before offering TAVI. The geriatrician can contribute to the heart team as a frailty expert.

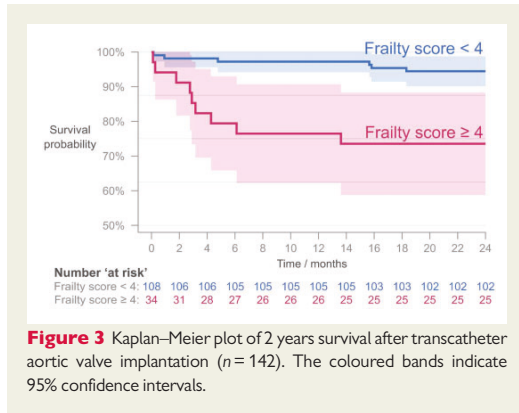


Figure 3 Kaplan–Meier plot of 2 years survival after transcatheter aortic valve implantation (n=142). The coloured bands indicate 95% confidence intervals.

Strengths of the study

This is a prospective study, with potentially fewer sources of bias and higher quality of data than a retrospective study would have. In Norway, deaths of all patients are automatically registered in the patients' electronic journal. Our primary outcome is therefore complete. We also have high completeness in the rest of our data, and importantly, no patients are lost to follow-up for the primary endpoint. The variables included in the GA frailty score were determined before the statistical analysis, eliminating the risks associated with a purely data-driven analysis. Finally, our risk score was reliable in patients already excluded from surgery due to comorbidity.

Limitations of the study

Survival with benefit after 2 years is advocated as a relevant clinical endpoint, and it would have strengthened the study if we also assessed quality of life in the patient 2 years after the procedure.¹ However, there are limitations to soft endpoints, and in order to simplify the interpretation of the frailty score, we chose to focus mainly on prediction of mortality. Some items were self-reported and not performance based, introducing some subjectivity to the index; however, previous studies have showed for all the selected self-report items to be markers of frailty.^{7,31} This is a single-centre study, and the results might not be transferable to any other centre, although they are probably comparable to other European centres of the same size. The study population changed during the study. Initially, inclusion consisted of patients ≥ 80 years, but was later expanded to include all patients ≥ 70 years. This was partly due to a shift in the general TAVI population, but also a growing awareness that frailty is a complex phenomenon where age is only one contributing factor.⁷ The partial lack of data used in calculating the EFT score reduces the precision of the score somewhat. And finally, the small sample size (especially the few number of deaths) is a limitation, particularly for calculating the sensitivity of the dichotomized frailty score in predicting 2-year mortality. Before recommending the GA frailty scale, it needs to be validated in an independent population.

Conclusions

In patients declined for open heart surgery, an 8-element frailty score based upon GA can identify patients less likely to benefit from TAVI. Patients with a frailty score ≥ 4 had significantly higher 2-year mortality. We believe the novel GA frailty score has clinical relevance and may be a useful tool for heart teams in decision making for TAVI.

Acknowledgements

We would like to thank the participants in this study.

Funding

Grants were received from Grieg Foundation, Department of Heart Disease, Haukeland University Hospital, Kavli Research Centre for Geriatrics and Dementia, Haraldsplass Deaconess Hospital, and from the Western Norway Regional Health Authority.

Conflict of interest: none declared.

References

- Otto CM, Kumbhani DJ, Alexander KP, Calhoun JH, Desai MY, Kaul S *et al.* 2017 ACC expert consensus decision pathway for transcatheter aortic valve replacement in the management of adults with aortic stenosis: a report of the American College of Cardiology task force on clinical expert consensus documents. *J Am Coll Cardiol* 2017;**69**:1313–1346.
- Clark RE. The STS cardiac surgery national database: an update. *Ann Thorac Surg* 1995;**59**:1376–1380; discussion 1380–1.
- Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;**16**:9–13.
- Mack M. Frailty and aortic valve disease. *J Thorac Cardiovasc Surg* 2013;**145**:S7–S10.
- Forman DE, Rich MW, Alexander KP, Zieman S, Maurer MS, Najjar SS *et al.* Cardiac care for older adults. Time for a new paradigm. *J Am Coll Cardiol* 2011;**57**:1801–1810.
- Kappetein AP, Head SJ, Genereux 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. *J Thorac Cardiovasc Surg* 2013;**145**:6–23.
- Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146–M156.
- Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;**381**:752–762.
- Rodriguez-Pascual C, Paredes-Galan E, Ferrero-Martinez AI, Gonzalez-Guerrero JL, Hornillos-Calvo M, Menendez-Colino R *et al.* The frailty syndrome is associated with adverse health outcomes in very old patients with stable heart failure: a prospective study in six Spanish hospitals. *Int J Cardiol* 2017;**236**:296–303.
- Ekerstad N, Swahn E, Janzon M, Alfredsson J, Lofmark R, Lindenberg M *et al.* Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. *Circulation* 2011;**124**:2397–2404.
- Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA *et al.* Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014;**63**:747–762.
- Sepehri A, Beggs T, Hassan A, Rigatto C, Shaw-Daigle C, Tangri N *et al.* The impact of frailty on outcomes after cardiac surgery: a systematic review. *J Thorac Cardiovasc Surg* 2014;**148**:3110–3117.
- Stortecky S, Schoenenberger AW, Moser A, Kalesan B, Juni P, Carrel T *et al.* Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2012;**5**:489–496.
- Anand A, Harley C, Visvanathan A, Shah ASV, Cowell J, MacLulich A *et al.* The relationship between preoperative frailty and outcomes following transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes* 2017;**3**:123–132.
- Watt M, Mealing S, Eaton J, Piazza N, Moat N, Brasseur P *et al.* Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement. *Heart* 2012;**98**:370–376.

III



Baseline frailty status and outcomes important for shared decision-making in older adults receiving transcatheter aortic valve implantation, a prospective observational study

Elisabeth Skaar^{1,2} · Anja Øksnes¹ · Leslie Sofia Pareja Eide³ · Tone Merete Norekvål^{1,2} · Anette Hylen Ranhoff² · Jan Erik Nordrehaug² · Daniel Edward Forman⁴ · Andreas W. Schoenenberger⁵ · Karl Ove Hufthammer⁶ · Karel Kier-Jan Kuiper¹ · Øyvind Bleie¹ · Erik Jerome Stene Packer^{1,2} · Jørund Langørgen¹ · Rune Haaverstad^{1,2} · Margrethe Aase Schaufel⁷

Received: 12 December 2019 / Accepted: 26 February 2020
© The Author(s) 2020

Abstract

Aims The objective of this study was to examine baseline frailty status (including cognitive deficits) and important clinical outcomes, to inform shared decision-making in older adults receiving transcatheter aortic valve implantation (TAVI).

Methods and results We conducted a prospective, observational study of 82 TAVI patients, recruited 2013 to 2015, with 2-year follow-up. Mean age was 83 years (standard deviation (SD) 4.7). Eighteen percent of the patients were frail, as assessed with an 8-item frailty scale. Fifteen patients (18%) had a Mini-Mental Status Examination (MMSE) score below 24 points at baseline, indicating cognitive impairment or dementia and five patients had an MMSE below 20 points. Mean New York Heart Association (NYHA) class at baseline and 6 months was 2.5 (SD 0.6) and 1.4 (SD 0.6), ($p < 0.001$). There was no change in mean Nottingham Extended Activities of Daily Living (NEADL) scale between baseline and 6 months, 54.2 (SD 11.5) and 54.5 (SD 10.3) points, respectively, mean difference 0.3 ($p = 0.7$). At 2 years, six patients (7%) had died, four (5%, $n = 79$) lived in a nursing home, four (5%) suffered from disabling stroke, and six (7%) contracted infective endocarditis.

Conclusions TAVI patients had improvement in symptoms and maintenance of activity of daily living at 6 months. They had low mortality and most patients lived in their own home 2 years after TAVI. Complications like death, stroke, and endocarditis occurred. Some patients had cognitive impairment before the procedure which might influence decision-making. Our findings may be used to develop pre-TAVI decision aids.

Keywords Aortic stenosis · TAVI · Activity of daily living · Shared decision making · Older adults

✉ Elisabeth Skaar
Elisabeth.skaar@helse-bergen.no

¹ Department of Heart Disease, Haukeland University Hospital, Postboks 1400, 5021 Bergen, Norway

² Department of Clinical Science, University of Bergen, Bergen, Norway

³ Institute of Health and Social Science, Western Norway University of Applied Sciences, Bergen, Norway

⁴ Section of Geriatric Cardiology, University of Pittsburgh, Medical Center, and Geriatric Research, Education, and Clinical Center, VA Pittsburgh Healthcare System, Pittsburgh, USA

⁵ Department of Geriatrics, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland

⁶ Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway

⁷ Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

Introduction

Transcatheter aortic valve implantation (TAVI) is an established treatment for severe and symptomatic aortic stenosis in patients not eligible for open heart surgery, and it improves symptoms and increase life expectancy [1, 2]. While indication for TAVI has expanded to also include younger and lower risk groups, the majority of TAVI patients are older and have significant comorbidity and frailty that contraindicated surgery. The Valve Academic Research Consortium-2 (VARC 2) consensus document recommends evaluation of independence in activity of daily living before the procedure as risk stratification [3]. However, few studies have focused on independence in activity of daily living as an outcome measure [4, 5].

Among older adults who are seriously ill, death might not be feared as the worse outcome. For many, reduced quality of life and functional or cognitive impairment [6, 7], are relatively greater concerns. Dementia is highly prevalent in older adults [8] and is the leading cause of dependency in older age [9]. Shared decision-making is the favoured model for health care decisions, enhancing treatment choices to reflect patients' values and preferences [10]. However, the context of cognitive impairment or dementia makes it more difficult for TAVI candidates to participate in the decision-making process [11].

Thus, the aim of this study was to examine baseline frailty status including cognition and outcomes important to decision-making prior to TAVI.

Methods

Study design

This is a single-centre prospective, observational cohort study of 82 elective TAVI patients, with 2-year follow-up. Ninety-four patients were eligible for inclusion, five refused to participate and seven were not included due to logistical reasons. The patients were recruited consecutively from 2013 to 2015.

Participants

Patients ≥ 70 years with symptomatic and severe aortic stenosis accepted for TAVI at Haukeland University Hospital in Western Norway were included. The hospital has a tertiary function for TAVI and serves a population of 1.1 million inhabitants. Severe aortic stenosis was defined by echocardiography according to the European Society of cardiology (ESC) guidelines [1]. Before accepting patients for TAVI, a heart team including interventional cardiologists, cardiac

surgeons and imaging specialists, had declined them for surgical aortic valve replacement due to high risk. At the time of the study, there was no screening for frailty preceding the intervention, and the frailty score of the study patients was not known to the treatment team. The number of patients selected for conservative treatment is not known but suspected to be small. Nursing home patients and patients with severe dementia are rarely referred for valve intervention in Norway. Exclusion criteria were inability to understand or speak Norwegian.

Procedural characteristics

TAVI was delivered by different routes, seventy five (92%) trans-femoral, five trans-subclavian and two with direct aortic access. Two different valves were used, the Medtronic Core Valve in 52 (63%) and Boston Scientific LOTUS Valve in 30 (37%) patients.

Measurements

Baseline

Mini-Mental Status Examination (MMSE) assesses cognition as a scale that ranges from 0 to 30, with higher scores indicating better cognition [12]. The cut-off for normal cognitive function is usually set at 24, with a sensitivity of 0.85 and a specificity of 0.90 for identifying anyone with dementia [13].

The research team developed an 8-item frailty scale [14]. The total score is calculated by adding different domain scores: cognition ($\text{MMSE} \geq 27 = 0$ points, $\text{MMSE} 20-26 = 1$ point, $\text{MMSE} \leq 19 = 2$ points), instrumental activity of daily living ($\text{NEADL} \leq 43 = 1$ point), nutrition ($\text{BMI} < 20.5 = 1$ point), modified SOF (low energy = 1 point, weight loss (reported, not measured weight loss; therefore, modified) = 1 point, chair stand, not able = 1 point) [15], Charlson Comorbidity Index ($\geq 3 = 1$ point) [16], and psychological factors ($\text{HADS} \geq 15 = 1$ point) [17]. The score range from 0 to 9, where 9 represents the frailest patients. Patients were classified frail if they scored ≥ 4 points. This cut-off had a specificity of 80% and sensitivity of 60% at predicting 2-year mortality for this population. In a receiver operating curve, the area under the curve was 0.81 (95% confidence interval 0.71–0.90) [14].

Baseline and 6 months:

Nottingham Extended Activity of Daily living scale (NEADL) is a scale originally developed to assess activities of daily living (ADL) for stroke patients discharged to home, yet frequently used in non-stroke populations [18, 19]. The scale measures extended activities of daily living using a 22-item questionnaire, evaluating four different sections: mobility, kitchen, domestic and leisure. Patients are asked whether they perform the different activities, and the response categories are 0 = not at all, 1 = with help, 2 = on my own with difficulty, 3 = on my own. The different scores sums into a total score of 0 to 66 points, with higher scores indicating greater independence. A score ≤ 43 indicates dependence [19]. One study of stroke patients reported a valid and reliable change if the NEADL improved or deteriorated by 4.9 points or more, and clinically important if the mean change score was in the range from 2.4 to 6.1 points after treatment [20].

The New York Heart Association (NYHA) classification describes patients' symptoms of heart failure [21] and has been applied to TAVI patients [3]. NYHA class I represents no symptoms of heart failure and no limitation of physical activity, while NYHA class IV represents symptoms of heart failure at rest. Despite limitations it's widely used both in research and clinical practice.

Follow-up measurements

Baseline NEADL and NYHA were assessed and then repeated at 6 months. Due to some patients living far from the hospital, we performed telephone interviews at 6 months, and MMSE and frailty testing were, therefore, not conducted. For the first 2 years, we recorded composite endpoints as recommended by the Valve Academic Research Consortium-2 (VARC-2) consensus document. We collected data of admission to long-term nursing homes for the first 2 years.

Statistical analyses

We present the data as means and standard deviations (SD), counts and percentages. Changes from baseline to 6 months are analysed using paired *t*-tests. There were little missing data so we have used complete case analysis and report the number of observations each analysis is based on. Statistical analysis was carried out in IBM SPSS Statistic 24 and R version 3.6.0 [22]. *p* values < 0.05 were considered statistically significant.

Results

Baseline data

General characteristics

We examined 82 patients with severe and symptomatic aortic stenosis, 39 (48%) women. Mean age was 83 years (SD 4.7), two patients were over 90 years, the oldest 95 years old, and there were six patients under 75 years. Most patients (62%) lived with their spouse. A majority (55%) had only primary school, while 20% had a university degree.

Geriatric characteristics

Fifteen patients (18%) had an MMSE score < 24 , suggesting they were cognitively impaired. One fifth of the patients had a low NEADL score (≤ 43), implying dependence in at least one instrumental activity of daily living. As expected, NEADL and MMSE was correlated (Spearman's $\rho = 0.47$, $p < 0.001$). Eleven patients had a low BMI, however, 27 (33%) reported weight loss last year. Charlson comorbidity index was ≥ 3 in 36 (44%) of the patients, demonstrating a high burden of comorbidity. Six (7%) patients had a score ≥ 15 on the Hospital Anxiety and Depression Scale; i.e., few patients had severe anxiety or depression. For 80 patients, baseline 8-item frailty scale was calculated, and 14 patients (18%) were defined as frail.

Cardiovascular characteristics

Logistic EuroSCORE [23] was below 10 (predicting low surgical risk) in 20 (24%) and over 20 (high surgical risk) in 19 (23%) of the patients. Almost half (48%) of the patients had NYHA ≥ 3 at baseline, indicating a significant burden of symptoms. Few patients (11%) had a pacemaker before TAVI, and 26 (32%) had atrial fibrillation at baseline (Table 1).

Follow-up

One patients was lost to follow-up at the telephone interview and three had died. For three patients, information was missing on whether they lived at home or in nursing home at 2-year follow-up. VARC 2 composite endpoint is presented in Table 2, and endocarditis is separately presented in Table 3 with complementary data.

Mortality and morbidity

Two patients (2%) died early (< 30 days), and one had a disabling stroke. At 1 year, four patients (5%) had died and

Table 1 Patient baseline characteristics ($n = 82$)

Characteristics	Mean or count	SD or (percent)
Characteristics		
Age, years	83	4.7
Women	39	(48)
Living alone	29	(35)
Education		
Primary School	45	(55)
High School	21	(26)
University	16	(20)
Geriatric characteristics		
Cognition		
MMSE	26.2	3.4
MMSE ≥ 24	67	(82)
MMSE 20–23	10	(12)
MMSE < 20	5	(6)
Activities of daily living		
NEADL ≤ 43	15/80	(19)
Nutrition		
BMI	24.8	3.6
BMI < 20.5	11	(13)
mSOF		
Weight loss ^a	27	(33)
Low energy	32	(39)
Unable to chair stand	10	(12)
Comorbidity		
Charlson Comorbidity Index	2.6	1.4
Charlson Comorbidity Index ≥ 3	36	(44)
Psychological factors		
HADS ≥ 15	6/81	(7)
Frailty ^b	14/80	(18)
Cardiovascular characteristics		
Logistic EuroSCORE	15	7.9
Aortic Valve Area Index, cm^2/m^2	0.4	0.12
Mean Aortic Valve gradient, mmHg	50	15
Left ventricular ejection fraction	57	12
NYHA \geq III	39	(48)
Previous myocardial infarction	15	(18)
CABG	15	(18)
Permanent pacemaker	9	(11)
Atrial fibrillation	26	(32)
Pulmonary hypertension	27	(33)
Cerebral Vascular Disease	12	(15)
Comorbidity		
COPD	19	(23)
Kidney failure; creatinine > 177 $\mu\text{mol/L}$ ^c	4	(5)

The total score is calculated by adding the different domain scores
MMSE mini-mental status examination, *NEADL* Nottingham extended activities of daily living scale, *BMI* body mass index, *SOF* study of osteoporotic fractures, *HADS* hospital anxiety and depression scale

Table 1 (continued)

^aModified from the original SOF, with patient-reported weight loss past year, not measured as in the original index (*mSOF* modified SOF)

^b8-item geriatric assessment frailty scale. Missing information to calculate the scale in two patients, NYHA, New York Heart Association functional classification of heart failure, range from I to IV, most severe symptoms at IV. *CABG* coronary artery bypass grafting, *COPD* chronic obstructive pulmonary disease

^cAs reported in the PARTNER study [2]; Creatinine > 2 mg/dl (177 $\mu\text{mol/L}$)

4 (5%) had a disabling stroke. After 2 years, 6 (7%) patients had died, five of cardiovascular and one of non-cardiovascular cause. Four patients lived in nursing homes. There were no new disabling stroke from one to 2 years. Six patients (7%) had endocarditis during the first 2 years. Thirty-two patients (39%) got a new pacemaker perioperative (during the hospital stay).

Patient-reported outcome measures at 6 months

NEADL

The NEADL score was available in 78 patients at 6 months. All patients were reached in person except for one, where the spouse provided information. For one patient, only NEADL at 6 months was available. There was no change in mean NEADL ($n = 77$) at baseline and 6 months with 54.2 (SD 11.5) and 54.5 (SD 10.3), respectively, mean difference 0.3 ($p = 0.7$). Even so, 13 patients (17%) improved 5 points or more at the NEADL from baseline to 6 months, and 14 patients (18%) deteriorated 5 points or more. We did not find an association between frailty status and deterioration in NEADL score. For example, the proportion of patients who deteriorated in NEADL score was similar in the frail and the non-frail group (42% and 55%, respectively, $p = 0.53$, Fisher's exact test).

NYHA class

After 6 months, the majority was in NYHA I (68%), about a quarter were in NYHA II (27%) and a few in NYHA III (5%). No patients were in NYHA IV. Mean NYHA ($n = 78$) at baseline and 6 months was 2.5 (SD 0.6) and 1.4 (SD 0.6), respectively, a significant improvement ($p < 0.001$). Four patients had missing NYHA class at 6 months (three dead, one lost to follow-up) (Fig. 1).

Table 2 Composite endpoints according to VARC 2^a criteria

	Total (n = 82)	Percent
<i>Device success</i>		
Absence of immediate procedural mortality ^b	82	100
Correct positioning	81	99
Intended performance of the prosthetic heart valve ^c	81	99
No moderate or severe prosthetic valve regurgitation ^d	78	95
<i>Early safety (at 30 days)</i>		
All-cause mortality	2	2
All stroke(disabling or non-disabling) in hospital ^e	1	1
Life-threatening or disabling bleeding	4	5
Acute kidney injury-stage 2 or 3 ^f	2	2
Coronary artery obstruction requiring intervention	1	1
Major vascular complication	5	6
Valve-related dysfunction requiring intervention	1	1
<i>Clinical efficacy (30 days–2 years)</i>		
All-cause mortality	4	5
All stroke(disabling or non-disabling)	5	6
Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure NYHA class III or IV ^g	13	16
NYHA class III or IV ^g	4	5
<i>Time-related valve safety</i>		
Structural valve deterioration		
Valve-related dysfunction (mean aortic valve gradient ≥ 20 mmHg) and/ or moderate or severe prosthetic valve regurgitation ^h	15/81	19
Requiring repeat procedure (TAVI or SAVR)	1	1
Prosthetic valve endocarditis ^f	6	7
Trombo-embolic events (eg stroke)	6	7
VARC bleeding (life threatening/disabling bleeding or major bleeding), unless clearly unrelated to valve therapy (e.g. trauma)	14	17

SAVR Surgical aortic valve replacement, TAVI transcatheter aortic valve implantation, NYHA New York Heart Association

^aThe Valve Academic Research Consortium (VARC)-2 consensus document (see references)

^bImmediate or consequent death ≤ 72 h post-procedure

^cNo prosthesis-patient mismatch. Mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s

^dAfter TAVI procedure at index hospitalization

^eAssessment of stroke at index. All strokes verified by CT/MRI

^fEvaluation of acute kidney injury is based on serum creatinine, we miss data on urine output

^gNYHA at 6 months

^hFour patients had new paravalvular leak or vegetation on the aortic valve

Discussion

This prospective observational study of 82 patients documents symptom improvement and maintenance of activities of daily living 6 months after TAVI. They had low mortality and most patients lived in their own home 2 years after TAVI. At baseline, 18% had an MMSE score, indicating cognitive impairment or dementia. We found a higher frequency of endocarditis than expected. According to the basic principles of shared decisions-making, balanced information regarding risks and benefits, and exploring patients' values and goals are important. Physicians should be aware that

patients' cognitive impairment or dementia might affect the ability to participate in the decision-making process and give an informed consent.

Mortality at one (5%) and 2 years (7%) after TAVI was low in this cohort, where mean age is over 80 years and there is a substantial burden of comorbidity and frailty. We found a substantial improvement in NYHA class from baseline to 6 months. Based on the improvement of symptoms we expected to find an improvement in NEADL. However, we found no change in mean NEADL. There was a variation on an individual level. Some patients improved their independence and others deteriorated, although for most patients, the

Table 3 Infective endocarditis first 2 years after TAVI

TAVI valve	Age at TAVI and gender ^a	Days after TAVI, positive blood culture	Bacteria (4/4 blood cultures)	Dukes criteria ^b	Outcome two year	TTE and TEE	Pacemaker device
Lotus 27 mm	86 y, F	49	<i>Stafylococcus aureus</i>	1 Major + 3 minor	Dead ^c	No vegetation or PVL	PM, 1 day after TAVI
Core valve 31 mm	77 y, M	190	<i>Streptococcus salvarius</i>	2 Major + 2 minor	Alive	Aortic valve vegetation	CRT-D, 3 months before TAVI
Core valve 31 mm	80 y, M	380	<i>Enterococcus faecalis</i>	1 Major + 3 minor	Alive	New aortic PVL	CRT-P, 2 months after TAVI
Core valve 29 mm	79 y, M	407	<i>Streptococcus sanguinis</i>	1 Major + 3 minor	Alive	New aortic PVL	No
Core valve 31 mm	77 y, M	448	<i>Stafylococcus aureus</i>	2 Major + 4 minor	Dead ^d	Aortic valve vegetation	CRT-P, 1 year before TAVI
Core valve 31 mm	80 y, M	528	<i>Streptococcus oralis</i>	1 Major + 1 minor	Alive	No vegetation or PVL	PM, 1 day after TAVI

TTE transthoracic echocardiography, TEE trans-oesophageal echocardiography, PVL para valvular leak, PM pacemaker, CRT-P/D coronary resynchronisation therapy with cardiac defibrillator (D) or pacemaker (P)

^ay years, M male, F female

^bAll meet criteria for definite infective endocarditis (IE) except the last patient who has a possible IE. All patients had trans-femoral access for TAVI

^cDied five months after diagnosed with IE

^dDied one month after diagnosed with IE

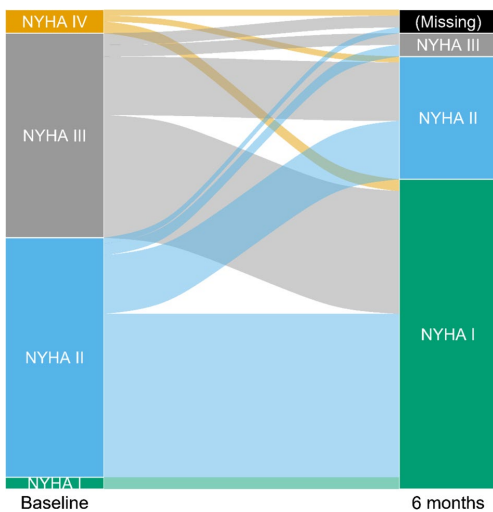


Fig. 1 Individual changes in NYHA class from baseline ($n=82$) to 6 months ($n=78$). The height of each bar is proportional to the number of patients with the corresponding NYHA class, and the width of the ends of each flow line is proportional to the number of patients with the given pattern of change of NYHA class

change in NEADL was minor. Other factors, like frailty and dementia, probably have more impact on the level of independence than the aortic stenosis per se [4], and 6 months

follow-up is probably too short to establish deterioration due to other causes. There was no difference between the frail and robust patients regarding change in NEADL from baseline to 6 months.

At baseline, 15 patients had an MMSE below 24, indicating possible cognitive impairment or dementia [13]. Five patients had an MMSE less than 20, which increases the probability of incapacity, and likely reduces their power of judgement during the decision-making processes before TAVI [11]. Several studies have suggested that a low MMSE score at baseline predicts poor outcomes after TAVI [4, 24]. However, there are also studies demonstrating cognitive improvement after TAVI when impairment is caused by the aortic stenosis itself [25]. For patients with established dementia, surviving to end stage dementia might not be what the patient would choose autonomously. These are difficult issues to discuss with patients with dementia and their families, both due to patients' anosognosia (a physiological damage to the brain, where patients have no awareness of their disease) [26], and also health care professionals' fear of patients losing hope when focusing on the deterioration and increased dependence expected after a diagnosis of dementia [27]. It is important to point out that an MMSE < 24 is not diagnostic of dementia, and sensitivity and specificity for MMSE cut-offs in a TAVI population, might be different than in the general population. Suspicion of dementia should, therefore, lead to further investigations.

We found a higher frequency of infective endocarditis (IE) than expected. In a recent meta-analysis with a mean follow-up at 3.4 years, the overall incidence of IE in TAVI was 2.0% [28]. In the present study, five of six patients with IE had a pacemaker or an ICD, which might be associated with an increased risk of IE [29]. Several single-centre studies finding higher incidences suggests that IE is underreported in large studies and registries [30, 31]. Diagnosing endocarditis is challenging, and the presentation might be uncharacteristic since the patients are old with comorbidities [28]. As endocarditis can occur later on, longer follow-up than 1 year seems important. Antibiotic prophylaxis during the TAVI procedure were administered to all patients. General practitioners were informed routinely on discharge about the risk of endocarditis and indications for prophylaxis.

Prior to TAVI, patients need to be informed of expected NYHA class improvement, survival benefit and maintenance of activities of daily living. Rare and severe complications, like death, stroke and infectious endocarditis, should also be part of the pre-TAVI discussion with the patient. Old patients with substantial comorbidity need to be informed that TAVI will not solve all their health problems. After the study period, written information about the procedure and risks and benefits was developed and administered to patients as part of the decision-making process. Our findings may be used when developing and improving decision aids for this treatment in older adults.

Strengths of the study

All hospitals in Western Norway use the same electronic medical records and VARC-2 endpoints are complete with no patients lost to follow-up. All deaths are automatically registered in the patients' electronic journal. The same investigator (ES) performed the assessment at baseline and 6 months, increasing reliability.

Limitations of the study

This is a single centre study performed in the early era of TAVI and some of the results might not be transferable due to improvement of equipment, better patient selection and training of the interventional cardiologists performing the procedure. Most patients were independent before TAVI, and minor (nevertheless important to patients) improvements might not be revealed by the NEADL questionnaire. Due to the small sample size, it was not possible to analyse whether specific subgroups improved or deteriorated in NEADL. We performed only telephone interviews at 6 months, preventing us from assessing MMSE and frailty at follow-up. We assume that living in their own home 2 years after TAVI reflects independence of activities of daily living, however,

we cannot exclude that some patients living at home were in need of extended care.

Conclusion

TAVI patients had symptom improvement and maintenance of activity of daily living at 6 months. They had low mortality, and most patients lived in their own home 2 years after TAVI. Severe complications, like death, stroke and endocarditis, occurred. Balanced information regarding these risks and benefits is needed to ensure informed consent prior to the procedure, and our findings may be used to develop and improve decision aids assisting this process. Clinicians should be aware that some patients have cognitive impairment before TAVI that might affect their power of judgement and decision-making.

Acknowledgements Open Access funding provided by University of Bergen. We would like to thank the participants of this study.

Funding This work was supported by Grieg Foundation; and the Department of Heart Disease, Haukeland University Hospital, Bergen, Norway. The funding sources had no influence on the study.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Human and animal rights statement All procedures performed in the study were in accordance with the ethical standards of the institution and the national research committee and with the 1964 Helsinki declaration and its later amendments. The regional Committee for medical research ethics approved the study (REK 2013/1310).

Informed consent Written, informed consent was obtained from all participants.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Baumgartner H, Falk V, Bax JJ et al (2017) 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 38: 2739–2791
2. Leon MB, Smith CR, Mack M et al (2010) Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 363: 1597–1607
3. Kappetein AP, Head SJ, Genereux P et al (2012) Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg* 42: S45–60
4. Schoenenberger AW, Stortecky S, Neumann S et al (2013) Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur Heart J* 34: 684–692
5. Eide LS, Ranhoff AH, Fridlund B et al (2016) Delirium as a predictor of physical and cognitive function in individuals aged 80 and older after transcatheter aortic valve implantation or surgical aortic valve replacement. *J Am Geriatr Soc* 64: 1178–1186
6. Fried TR, Bradley EH, Towle VR et al (2002) Understanding the treatment preferences of seriously ill patients. *N Engl J Med* 346: 1061–1066
7. Yellen SB, Cella DF, Leslie WT (1994) Age and clinical decision making in oncology patients. *J Natl Cancer Inst* 86: 1766–1770
8. Satizabal CL, Beiser AS, Chouraki V et al (2016) Incidence of dementia over three decades in the Framingham heart study. *N Engl J Med* 374: 523–532
9. World Health Organization and Alzheimer's Disease International. Dementia: a public health priority. 2012 [cited 2019 Sep 25]; 112]. https://apps.who.int/iris/bitstream/handle/10665/75263/9789241564458_eng.pdf.
10. Elwyn G, Frosch D, Thomson R et al (2012) Shared decision making: a model for clinical practice. *J Gen Intern Med* 27: 1361–1367
11. Sessums LL, Zembruska H, Jackson JL (2011) Does this patient have medical decision-making capacity? *JAMA* 306: 420–427
12. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189–198
13. Creavin ST, Wisniewski S, Noel-Storr AH et al (2016) Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database Syst Rev* 13: CD011145
14. Skaar E, Eide LSP, Norekval TM et al (2019) A novel geriatric assessment frailty score predicts 2-year mortality after transcatheter aortic valve implantation. *Eur Heart J Qual Care Clin Outcomes* 5: 153–160
15. Ensrud KE, Ewing SK, Taylor BC et al (2008) Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med* 168: 382–389
16. Charlson ME, Pompei P, Ales KL et al (1987) A new method of classifying prognostic co-morbidity in longitudinal-studies—development and validation. *J Chronic Dis* 40: 373–383
17. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67: 361–370
18. Lincoln NB, Gladman JR (1992) The extended activities of daily living scale: a further validation. *Disabil Rehabil. [Research Support, Non-U.S. Gov't]* 14: 41–43
19. Kristjansson SR, Nesbakken A, Jordhoy MS et al (2010) Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. *Crit Rev Oncol Hematol* 76: 208–217
20. Wu CY, Chuang LL, Lin KC et al (2011) Responsiveness, minimal detectable change, and minimal clinically important difference of the Nottingham Extended Activities of Daily Living Scale in patients with improved performance after stroke rehabilitation. *Arch Phys Med Rehabil* 92: 1281–1287
21. The Criteria Committee for the New York Heart Association (1964) Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels. Little Brown, Boston
22. R Core Team (2019) Vienna, Austria [cited 2019]. R: A language and environment for statistical computing]. <https://www.r-project.org/>
23. Roques F, Michel P, Goldstone AR et al (2003) The logistic EuroSCORE. *Eur Heart J* 24: 881–882
24. Kim DH, Afilalo J, Shi SM et al (2019) Evaluation of changes in functional status in the year after aortic valve replacement. *JAMA Intern Med* 179: 383–391
25. Schoenenberger AW, Zuber C, Moser A et al (2016) Evolution of cognitive function after transcatheter aortic valve implantation. *Circ Cardiovasc Interv* 9:e00359. <https://doi.org/10.1161/CIRCINTERVENTIONS.116.003590>
26. Salmon E, Perani D, Herholz K et al (2006) Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Hum Brain Mapp* 27: 588–597
27. Marzanski M (2000) On telling the truth to patients with dementia. *West J Med* 173: 318–323
28. Ando T, Ashraf S, Villablanca PA et al (2019) Meta-analysis comparing the incidence of infective endocarditis following transcatheter aortic valve implantation versus surgical aortic valve replacement. *Am J Cardiol* 123: 827–832
29. Kolte D, Goldswieg A, Kennedy KF et al (2018) Comparison of incidence, predictors, and outcomes of early infective endocarditis after transcatheter aortic valve implantation versus surgical aortic valve replacement in the United States. *Am J Cardiol* 122: 2112–2119
30. Puls M, Eiffert H, Hunlich M et al (2013) Prosthetic valve endocarditis after transcatheter aortic valve implantation: the incidence in a single-centre cohort and reflections on clinical, echocardiographic and prognostic features. *EuroIntervention* 8: 1407–1418
31. Rodriguez-Vidigal FF, Nogales-Asensio JM, Calvo-Cano A et al (2019) Infective endocarditis after transcatheter aortic valve implantation: contributions of a single-centre experience on incidence and associated factors. *Enferm Infecc Microbiol Clin* 37:428–434. <https://doi.org/10.1016/j.eimc.2018.09.009>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Appendix

Interview guide, TAVI decision-making process

The original questions were in Norwegian.

Background/Motivation

1. Could you tell me, please, why you wanted this procedure? **What were your expectations?**

The decision process

2. How did you find the information about the procedure?

3. Would you like to elaborate on what was most difficult in the decision-making?

4. What was the most crucial factor in deciding to undergo TAVI?

5. What did you think of the risk of complications? **How much detail would you prefer in the information about risk before this intervention?**

6. What did you think of the risk of death associated with the procedure?

7. How did you involve your family/relatives in the decision-making?

8. What hope for the future mattered the most to you in the process?

Closure

9. Do you have any thoughts on how doctors and other health care professionals could support you better in the decision to undergo TAVI?

10. Could you tell me a bit about how you typically face challenges/hard times in life?

11. Finally, are there any aspects of the decision-making process that we have not addressed yet? And if so, would you like to add a comment on them?

The interview guide was revised after two interviews, the questions marked in yellow being added. No questions were removed.

Developing the frailty score:

Frailty score	Suggestion 1	Suggestion 2	Suggestion 3	Suggestion 4	Fusion
Cognition	1 point if MMSE is under 24, 2 points if MMSE is under 20	MMSE	MMSE, cut-off < 24	MMSE ≥ 27 / < 27 = 0/1 point	MMSE ≥ 27 =0 points MMSE 20-26 =1 point MMSE < 20= 2 points
Independence in activities of daily living	NEADL	NEADL		NEADL, either walk around outside, climb stairs) 0 point if you manage alone, 1 point for every other answer (alone with help etc.) or the whole NEADL dichotomized (but it measures disability, a step further than frailty)	NEADL >43, independent=0 points, <= 43 = 1 point
Nutrition	BMI <20 1 point		BMI <20,5 (as in NRS 2002)	Weight loss according to Fried	BMI <20,5 (as in NRS 2002) 1 point
Limb strength, weight loss, energy level	SOF weight loss: 1 point Low energy: 1 point Chair stand (not able) 1 point	SOF	SOF	Chair stand test: Yes/no= 0/1 point Full of energy question: Yes/no=0/1 point	SOF weight loss: 1 point Low energy: 1 point Chair stand (not able) 1 point
Comorbidity	Charlson >3 , 1 point				Charlson > =3 , 1 point
Psychological factors	HADS (total score)>14, 1 point		Only the depression scale of HADS, cut-off >10 p	Total HADS dichotomized based on validated cut-off	HADS (total score)>14, 1 point

Errors

Paper 1

Page 43, Participants. The two patients recruited but not interviewed have not been accounted for. The correct statement is: 12 patients were recruited, one withdrew and one was unable to attend the interview due to hospital admission. Ten interviews were conducted.

Page 43, Participants. It should be phrased: participants are listed in table 1. Not *were list*.

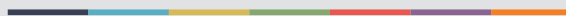
Page 47, find a lower age specific incidence, not *incidents*.

Paper 2

Table 2. Most patients (82%) were independent in instrumental ADL and the number (121 patients) reflects NEADL >43. (This is stated correctly in the accompanying text).



Graphic design: Communication Division, UIB / Print: Skjipes Kommunikasjon AS



uib.no

ISBN: 9788230862049 (print)
9788230842300 (PDF)