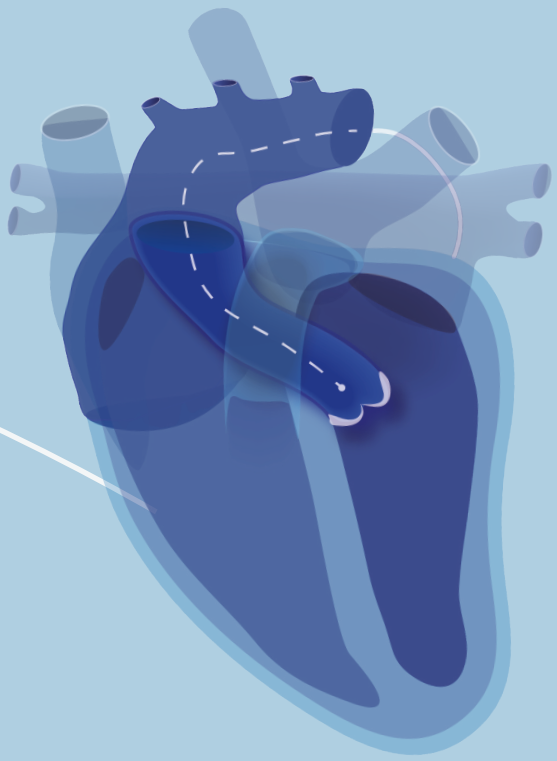
Transcatheter Aortic Valve Implantation;

From an academic pioneering project to a multidisciplinary patient-centered clinical and scientific program



Maria Josephina Agnes Gerarda de Ronde-Tillmans

Transcatheter Aortic Valve Implantation;

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Marjo de Ronde-Tillmans

Erasmus University Medical Center

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Transkatheter aortaklepimplantatie;
Van een academisch baanbrekend project tot een multidisciplinair patiëntgericht klinisch en wetenschappelijk programma

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General introduction

GENERAL INTRODUCTION

Aortic Stenosis (AS) is a degenerative Valvular Heart Disease (VHD) in adults of which its prevalence increases with age, varying from 3%-9% (1). If left untreated, the two-year mortality rate is approximately 50% (2). Surgical Aortic Valve Replacement of the native valve (SAVR) has been the standard of care and is now being challenged by Transcatheter Aortic Valve Implantation (TAVI) that was first performed in 2002 (3-5). Since then, TAVI has become an alternative, initially in patients at high-surgical risk and at present also in the so-called surgical candidates (4-7). In the Netherlands, the first TAVI was performed in November 2005 in the Erasmus Medical Center, Rotterdam (8). At that time the first patients were treated under general anesthesia, with surgical access of the femoral artery and circulatory support using a heart-lung machine (9). Clinical practice has rapidly changed as a result of improvements and miniaturization of catheter- and valve technology, an improved experience that has led to the implemetation of a truly percutaneous procedure and subsequently to a minimalistic approach using local anesthesia, a minimal percutaneous incision, avoidance of invasive lines and a percutaneous closure technique (PCI-like procedure). This in combination with randomised comparisons (SAVR vs TAVI) has led to the expansion of TAVI to low risk patients (10-12).

The combination of the developments described above have significantly improved procedural success and outcomes in all patient- or risk-categories (5, 13-15) which have led to a revision and update of the guidelines on the management of patients with valvular heart disease (ESC, EACTS) in combination with more emphasis on a patient-tailored treatment selection and decision-making via a multidisciplinary Heart Team meeting (16).The role of such a multi-disciplinary Heart Team, as advocated in these guidelines, is crucial and encompasses the combined expertise of interventional cardiologists, cardio-thoracic surgeons, imaging-cardiologists, cardiac anesthetists, geriatricians and dedicated nursing staff, all with expertise in the care of patients with VHD (17).

The role of a multidisciplinary heart team meeting should not be underestimated. As mentioned above, aortic stenosis is an age-associated degenerative cardiac disorder. As such, it is not surprising that - despite the fact that TAVI is now available for patients at low-surgical risk - the age of patients who are referred for TAVI remains relatively stable and high (18). Age in itself is an important determinant of peri-operative complications and, hence, in-hospital but also long-term clinical outcomes including treatment effects (i.e. symptom reduction, quality of life). Age is also associated with frailty, defined by a decrease of the physiologic reserve and an increased vulnerability to stressors, and therefore increased risk of perioperative complications and mortality after both SAVR and TAVI (19-21). Consequently, care of elderly patients requires a more critical and

"holistic" approach entailing the standard principle of a risk/benefit assessment. However, with respect to risk, this encompasses more than just the eventual occurrence of cardiovascular complications but also includes the risk of postoperative neuro-cognitive decline and delirium, in addition to other less devastating complications such as infections associated with prolonged hospital stay. Frail patients are at a particular risk of such postoperative complications and poor outcomes as they often suffer from a combination of impaired somatic and neurocognitive reserve in addition to co-morbid conditions such as diabetes, renal insufficiency, peripheral vascular disease, and/or coronary artery disease (22, 23) and, consequently need extra care and attention.

It may be clear that all these factors combined *(age with or without signs of frailty or loss of physiologic reserve, antecedents , comorbidity*) render treatment decision making more complex. Cardiac and non-cardiac complications affect immediate and long-term outcomes and may impede the desired treatment effect(s). With respect to the latter, symptom reduction and improvement of quality of life are often the treatment effect of choice by both the patient and the family, above longevity. The recognition of the above has been the stimulus for the creation of the Rotterdam TAVI Care and Cure Program of which the first patient was enrolled in November 2013. In this program, all patients referred for TAVI are subjected to a protocol-defined cardiologic and geriatric pre- and post-operative assessment and follow-up that includes functional & cognitive status, frailty and quality of life (24). Pre-operative assessment is followed by a multidisciplinary Heart Team meeting. The objective of this program is to improve outcomes by better treatment-decision making and offering TAVI (or SAVR) to those who are expected to benefit the most from the treatment (utility vs futility).

Of note, the TAVI Care and Cure programm started in late 2013, eight years after the first TAVI procedure in the Netherlands (*November 15, 2005, patient #16 in the world treated with the self-expanding Corevalve, Chaper 1 of this thesis)* (25) This period of eight years reflects the experimental nature of TAVI via the retrograde transfemoral approach upon its introduction *(first TAVI performed by A Cribier et al via the antegrade transseptal approach in April 2002, Rouen, France)* (6) followed by progressive refinements in the execution of the procedure thanks to increased operator experience in conjunction with improvements in delivery catheter, miniaturisation in particular, and valve technology.

As mentioned above, the first series of patients (n=4) who received TAVI in the Erasmus MC underwent TAVI under general anethesia, surgical cut-down of the femoral artery and circulatory support (ECMO system). The latter was used as a safety measure in the absence of insight and experience of how the cardiovascular system would react to the intervention. In the quest to simplify the procedure, the ECMO system was replaced

by the TandemHeart, a circulatory support system already used in complex PCI cases and inserted via a percutaneous approach. Circulatory support can be obtained up to 3-4 l/min depending on patient- and catheter-related facors *(circulating volume, heart function, catheter dimensions)*. Manipulating the RPM *(reducing output by reducing RPM)* taught the implanting team that TAVI was technically possible without circulatory support. This, in combination with relaunching catheter-based closure systems of the femoral artery, (introduced in the 1990's during percutaneous directional atherectomy, *(Prostar system)*, and echo-guided access instructed by dr. Lukas van Dijk (radiologist, Erasmus MC) and dr Marc van Sambeek (vascular surgeon, Erasmus MC) who used this during percutaneous endovascular procedures of the abdominal aorta, lead to the first true percutaneous TAVI on October 12, 2006. This, in combination with increasing familiarity with TAVI, led to the expansion of indications, e.g. TAVI for failed aortic bio-prosthesis, TAVI in combination with PCI, TAVI via the subclavian and later axillary artery *(first percutaneous TAVI via axillary on September 09, 2013)* and ultimately TAVI under local anesthesia which has become the default choice since November 2015. The use of local anaesthesia allowed the development of an early discharge programm (11, 12, 26). TAVI combined with Endo Vascular Aortic Repair (EVAR) under local anesthesia also became a possibility and was performed by a team of cardiologists and vascular surgeons.

During this intense period in which time, effort and attention was mostly spent on technical refinements and improvements (i.e. Cure), it became more and more clear that another essential pillar of medicine also needed to be addressed, namely Care and more specifically improvements in outcome via more refined patient selection *(i.e. utility vs futility)*, advoidance of postoperative complications, and more specifically non-cardiovascular complications such as delirium. This formed the impetus of the TAVI Care and Cure program that was initiated with the department of Geriatrics (Prof.dr. F.U.S.Mattace-Raso, drs. J.A. Goudzwaard), and which became the basis of the thesis.

The scope of this thesis is to:

1) Provide a structured insight in the clinical application, findings and historical markers of TAVI as performed in the Erasmus MC,
2) Emphasize the added value of integrating the geriatrician and standardized geriatric assessments to the pre- and postoperative care of TAVI patients,
3) Evaluate short-and long-term outcomes of TAVI aiming at improving procedures,
4) Further explore clinical driven innovation such as local anesthesia and an early discharge strategy without compromising patient-safety, and
5) How to further improve care for patients with aortic stenosis by setting up a benchmark for quality of care.

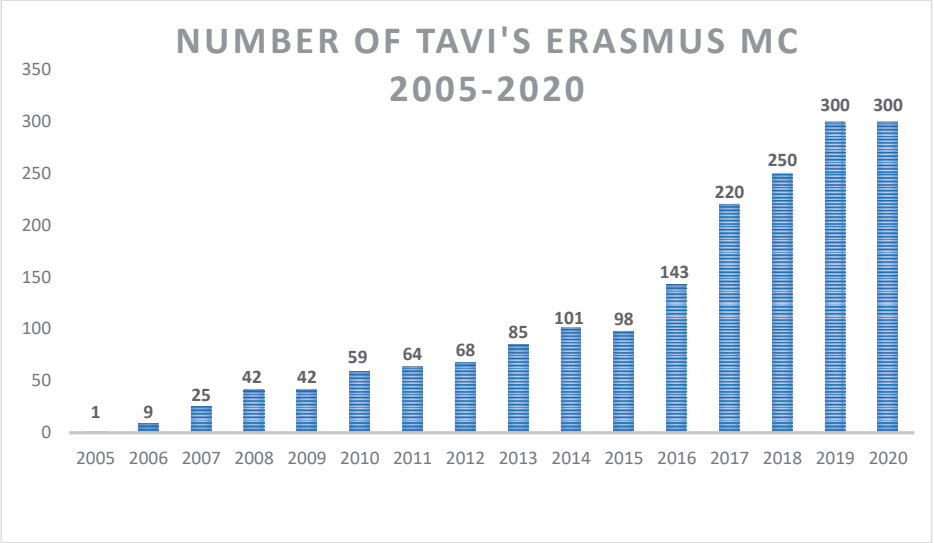

Figure 1

OUTLINE OF THE THESIS

This thesis encompasses 10 chapters that are ordered as follows:

Chapter 2 Describes the history of TAVI and the role of the Erasmus MC leading to the first true percutaneous transfemoral TAVI, which became the global default technique,

Chapter 3 Is a summary of the protocol of the TAVI Care and Cure program,

Chapter 4 Concerns a first retrospective reflection on results and outcomes of the EMC-TAVI program,

Chapters 5-7 Report outcomes assessed in the framework of the TAVI Care and Cure program and, more specifically, the incidence of delirium (chapter 5) and quality of life during longer follow-up (chapter 6, 7),

Chapters 8-9 Describe further refinements in the execution of TAVI at the Erasmus MC,

Chapter 10 Is a reflection of the changes in demographics and baseline risk profiles of patients treated with TAVI at the Erasmus MC between 2005 and 2020,

Chapter 11 Concludes this thesis by sharing insights in how to further improve the program via a benchmark assessment of quality of care.

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2

The history of Transcatheter Aortic Valve Implantation. The role and contribution of an early believer and adapter, The Netherlands

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ABSTRACT

This paper describes the history of transcatheter aortic valve implantation (TAVI) from its preclinical phase during which visionary pioneers developed its concept and prototype valves against strong head wind to first application in clinical practice (2002) and scientific role of an early believer and adopter, the Netherlands (2005).

Keywords: Aortic stenosis · TAVI

INTRODUCTION

2020 is the year that The Netherlands was to host the annual meeting of the European Society of Cardiology (ESC) whose mission is to reduce the burden of cardiovascular disease through education, congresses, surveys and publishing [1]. We as medical professionals as well as those who are directly or indirectly involved in the deterrence of illness or ailment and/or the delivering of care *(e.g. health care authorities such as governments, controlling & advisory bodies, insurance companies, medical industry, etc),* should in addition to that statement also be inspired by the US Food and Drug Administration (FDA) that has taken the role and responsibility of ensuring the timely availability of innovative, safe and effective products to the American people [2].

Transcatheter Aortic Valve Implantation (TAVI) is an example of such a technology that has proven to reduce disease burden by improving quality of life and survival in patients with aortic stenosis [3-9]. Because of its minimally invasive nature *(local anesthesia, minimal incision, beating heart procedure, no cardiopulmonary bypass, …)* and its undeniable efficacy as it reduces valve stenosis it has been embraced by physicians, patients and relatives. This enthusiasm is supported by the findings showing overall clinical equivalence between TAVI and surgical aortic valve replacement (SAVR) which necessitates general anesthesia, extensive surgical trauma, cardiac arrest and cardio-pulmonary bypass. TAVI is a disruptive technology and has caused a sea change in cardiovascular therapy similar to intracoronary stenting 40 years earlier [10].

At the cradle of TAVI are the visionary pioneers in Europe who came up with the idea and had the courage to introduce TAVI in clinical practice notwithstanding endless pessimism and even open opposition. Interestingly, the discussion of added clinical value and, thus, appropriateness of reimbursement is still present notwithstanding the consistent findings of the various randomised controlled trials and numerous multicentre surveys. This contrasts with the position of the FDA that has granted approval of TAVI in patients with aortic stenosis at low risk (August 2019). It also contrasts with the respected position of the Netherlands, which ranks fourth on the Global Innovation Index 2019 (after USA, Switzerland and Sweden) and has been in the top ten of all countries in the world since many years [11]. It also ranks very highly in matters of social-, economic- and political stability, infrastructure and organisation and belongs to the elected group of high-income countries.

The early 1990s – Henning Andersen, Aarhus, Denmark

The TAVI story started in February 1989 when Henning Andersen – inspired by a lecture of Julio Palmaz on the development of coronary stents – thought of inserting a biologi-

cal valve inside a large stent and to implant this using a balloon-expandable technique similar to the stent-technique described by Palmaz. Andersen manufactured himself a stent with a diameter of 30 mm using metal wires that he bought in a hardware store in which he mounted a porcine aortic valve that was crimped onto a second-hand 30 mm balloon catheter pioneered by Cribier in the 1980s. The assembly was then inserted into a 41 Fr. introducer sheath (Fig. 1).

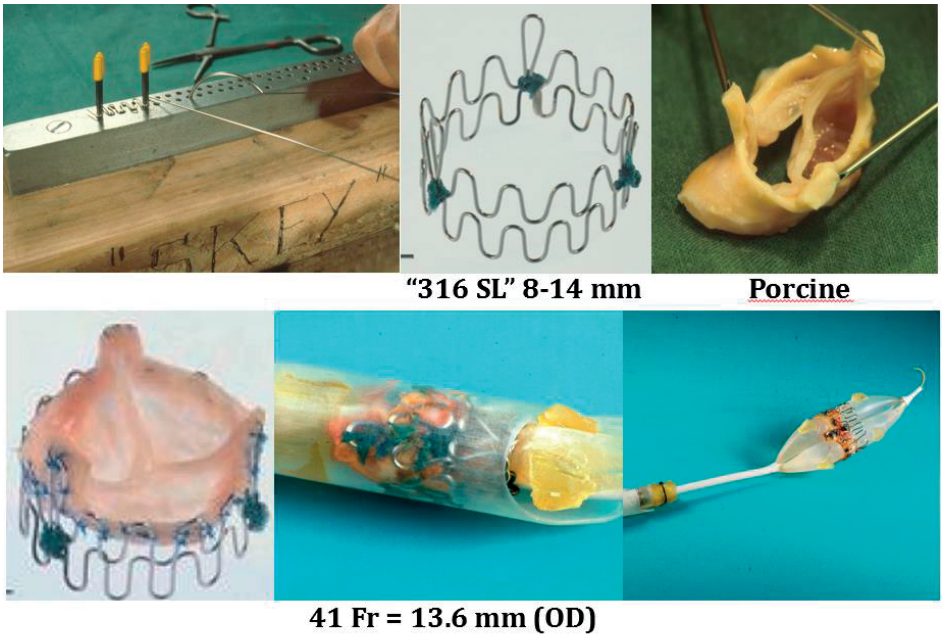

Figure 1 Henning Andersen's prototype percutaneous aortic valve technology

The first implantation on 1 May 1989 in an 80 kg pig was uneventful. Yet, during subsequent experiments coronary occlusion and valve embolization occasionally occurred. He also found that arresting blood flow prevented balloon migration for which he developed a custom-made balloon-tipped catheter inflated in the common pulmonary trunk.

He presented his work on 19 May, 1990 at the Danish Society of Cardiology (Odense, Denmark) but the abstract submitted to the 12th Congress of the ESC in 1990 (Stockholm, Sweden) was rejected. This also held for the paper submitted to the Journal of American College of Cardiology (1990) and Circulation (1991). Both journals considered *"it too low a priority for publication".* The paper was ultimately accepted by European Heart Journal in 1992 (impact factor 1.6) followed by another publication in 1993 [12, 13]. Posters at the ESC and AHA meeting in 1992 received little attention.

Andersen realized that after 41 implantations and the submission of a patent (1993) he needed support from industry, engineering and funding to move forward. Yet, none showed interest as their medical advisers predominantly consisting of cardio-thoracic surgeons provided numerous reasons why this could not work. As he could no longer afford the patent-related costs, he sought and received support from Stanford Surgical Technologies (SST), a small company founded by cardio-thoracic surgeons in San Francisco, which licensed his patent with the promise to develop the technology. Yet, nothing happened. SST became Heartport and concentrated on the development of a less invasive SAVR (port access) while holding the exclusive license agreement. On 21 January, 2001, Heartport was acquired by Johnson&Johnson-IS (JJ-IS) but three days earlier (18 January, 2001) Heartport had sold the exclusive license agreement to Percutaneous Valve Technologies (PVT).

The balloon-expandable valve story – Alain Cribier, Martin Leon, Stan Rabinovich, Stanton Rowe (PVT)

In the mid-1990s Alain Cribier pioneered aortic balloon valvuloplasty (1985) but confronted with the high restenosis rate, he presented a similar idea to a number of companies (Fig. 2). He knew that a balloon was capable of disrupting a stenotic aortic valve and decided to take advantage of the calcification for frame-anchoring. The first cadaver experiment was performed in 1994. The stent was conceptualised together with the cardiac surgeon (Dr Bessou) in such a way that in its crimped configuration (8 mm) it would be possible to deliver it via the femoral artery. Analogous to Andersen's experience, companies were not interested as it was considered: *"ridiculous, impossible and unnecessary"*. Yet, Stanton Rowe championed the concept at JJ-IS, which licensed Cribier's ideas and agreed to develop the percutaneous valve. Unfortunately, JJ-IS was at that time (1996) in the midst of acquiring Cordis and nothing happened. Cribier returned to Stanton Rowe and Stan Rabinovich who both had left JJ-IS. They brought Cribier's idea back to Martin Leon which resulted in the creation of PVT (21 July, 1999). In search of venture capital, they came into contact with an Israeli company ARAN R&D (June 1999, Jerusalem) who were interested in investing money but also in the development of the valve. Yet, the development of the percutaneous valve necessitated Andersen's patents licensed to SST as they contained the fundamentals around a collapsible and expandable valve for which the PVT series A financing was used (December 2000). Despite negative advice of cardio-thoracic surgeons, Medtronic and Boston Scientific subsequently became the main investors. A meeting between PVT and Edwards Lifesciences (TCT, September 2003) led to the acquisition of PVT (12 December, 2003) after consent from Medtronic and Boston Scientific [14].

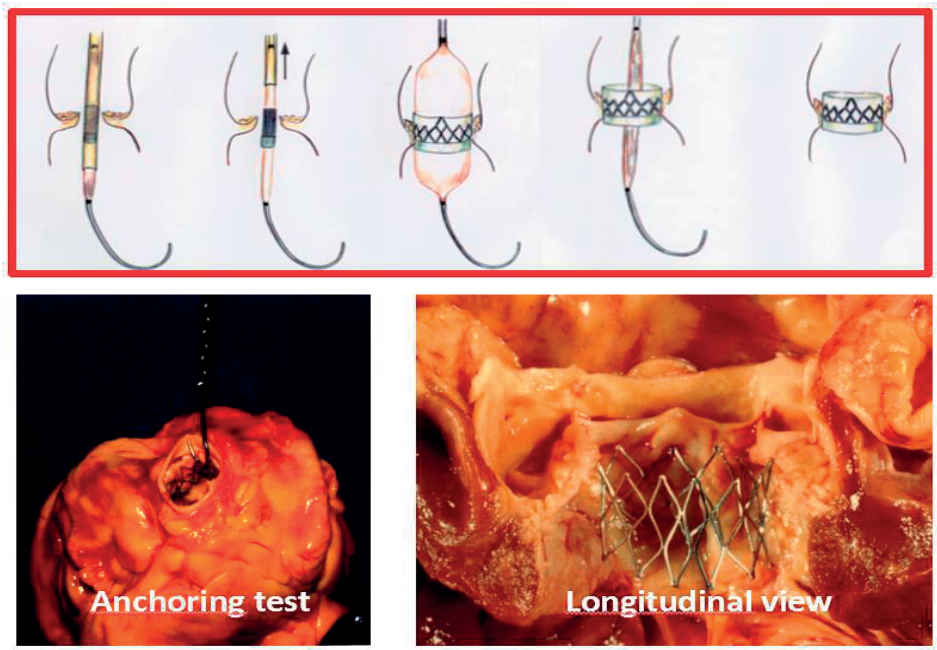

Figure 2 Alain Cribier's TAVI concept and cadaver experiment. Anchoring test concerns an in vitro test evaluating the stability of the valve that was deployed by balloon expansion within the aortic annulus by suspending the heart after valve implantation

The first animal (non-atherosclerotic) experiments were performed in August 2000 using polymeric valves but without success since there was no anchoring. The choice of healthy animals is understandable but surprising given Cribier's initial experiments with cadaver hearts. Noteworthy is the short time between the animal experiments and the first clinical TAVI (16 April, 2002). Cribier was faced with a 57-year-old man in heart failure and poor LVEF (10%). To complicate matters, the patient had a failed aorto-bifemoral graft precluding a transfemoral approach for which the valve system was designed. At the risk of jeopardizing all the work done, its future and the company the decision was taken to use the valve system via an "unplanned" antegrade-transseptal route given the patient's fate if nothing was done. In a subsequent feasibility study (36 patients, 2002-2005) the "success rate" was 75% but paravalvular aortic regurgitation frequently occurred since only one size (23mm) was available. During this study, the value of rapid ventricular pacing for valve delivery was recognized. Now, so many years after this pioneering work, Cribier says *"… it is moving to remember the fierce opposition of experts towards this "totally unrealistic and stupid idea" that "would never work".*

The self-expanding valve story - Georg Boertlein, Rob Michiels, Jacques Sequin (CoreValve)

CoreValve was founded by a cardio-thoracic surgeon J Seguin in Paris in 2001 together with a bio-medical engineer Georg Boertlein, who both understood the future of a catheter-based minimal invasive aortic valve treatment. In 2001, they found Rob Michiels (managing director of CONSILIUM associates active in identification, funding and green-housing of start-up technologies) immediately interested, which led to the entire high risk "seed round" of CoreValve (mid-2002) and paved the way to the first-in-man in 2004 despite the fact that *"… well-regarded medical professionals told them that we were crazy and it would be over their dead body if one of these ever got implanted in a patient".*

The CoreValve technology featured a novel leaflet and construction design using porcine pericardium to allow for more compression capability, thereby reducing catheter size and developing a true "interventional" device. CoreValve chose a strategy of restricted use by a small number of centers in Europe that was continued after CE Marking in 2007 for the 3th generation to assure successful maturing of their technology, appropriate training of physicians and to gather additional clinical data for post-approval surveillance later submission to the FDA.

TAVI in the Netherlands

The first TAVI in the Netherlands was performed in the Erasmus Medical Center, Rotterdam on 15 November, 2005 using the self-expanding CoreValve (Fig. 3) [15]. The team first conducted a short animal experiment to get a feel for the catheter system and technique of delivery (September 2005). The product was not CE-marked and, therefore, permission for compassionate use was granted by the Ministry of Health. Given the experimental nature and limited experience, a script was written in which all steps in chronological order were summarised including the materials and responsibility of every team member throughout the procedure (Fig. 4). This was continued during the early years of TAVI (2005-2007), which established a disciplined surgical-type approach in the intervention room that became an undisputable and natural modus operandi. Shortly after this, and in close cooperation with the Erasmus Medical Center, in February 2006, the second TAVI and first inclusion in the CoreValve first-in-man study was performed in the Amphia Hospital, Breda in February 2006 (Tab. 1).

At that time, some sort of circulatory support was recommended. In the first and the second patient (4 April,2006) an extracorporeal membrane oxygenation system was used but replaced by the TandemHeart in the next three as it allowed a percutaneous insertion. It was also the period that an interventional radiologist experienced with percutaneous endovascular aortic repair (Lukas van Dijk) trained the team in echo-guided

Figure 3 First TAVI in the Netherlands in 2005 and milestones in 2006. Professor Serruys, Dr Kappetein and Dr de Jaegere during the first TAVI in the Netherlands on 15 November 2005. General anaesthesia, surgical cut-down, ECMO, CoreValve 26mm valve. The patient died 12 years later (2017). *Inset upper left*: Dutch newspaper reporting 'First heart operation via groin'. *Inset lower right*: first TAVI via the subclavian artery (30 June 2006), *inset lower left:* CoreValve press release on 20 October 2006 reporting first full percutaneous TAVI in the world on 12 October 2006

arterial access. This in combination with the use of a percutaneous closure device (Prostar) and the fact it turned out that TAVI could be performed without circulatory support (stable haemodynamics when reducing flow) led to the first fully percutaneous TAVI in the world (October 12, 2006, Fig. 3) [16]. A milestone that has been adopted world-wide and has become the standard for transfemoral TAVI (TF-TAVI). Of note, this was preceded by another first-in-the-world, namely TAVI via the subclavian artery on 30 June, 2006 (Fig. 4), which has become the dominant approach in Radboud University Medical Center.

The next major step was the use of local anaesthesia. This was pioneered in the Netherlands by the team at the Academic Medical Center Amsterdam and first performed in 2010. It was the stepping stone for further simplification of TAVI to a minimalist approach mimicking PCI [17]. Moreover, TF-TAVI is now possible via a two-arterial access only *(femoral artery for valve delivery and pacing over the wire, contralateral femoral or radial for pig-tale guidance)* [18]. In case of TAVI for failed bioprosthesis, single access (femoral) suffices as the radiopaque structures of the bioprosthesis can be used as reference for valve deployment. During all those innovations, a fully percutaneous TAVI via

Figure 4 Briefing before TAVI. Briefing before the first TAVI via the subclavian artery (CoreVale 26mm). Seating in front from *right to left*: M de Ronde (head nurse), Dr de Jaegere, Dr Kappetein (white coat, back), Professor Serruys. Standing behind Professor Serruys: Dr Klein (anaesthesiologist). Please note the 'script' in the hands of attendees summarising all procedural steps and materials that were needed in chronological order during the planned procedure

the axillary artery under local anaesthesia has become a reality and first performed on 13 September, 2011 (Fig. 5). In conjunction with experience gained , improved catheter- and valve-technology, a program of early discharge was instituted [18, 19, 20,21]. The Netherlands also played an important role in the adoption and evaluation of the use of cerebral protection devices for the prevention of perioperative stroke [22]. Last but not least and perhaps more importantly, the typical Dutch spirit of consultation and collaboration has led to a structured multidisciplinary treatment decision-making, planning, execution and evaluation involving medical specialists with various backgrounds and expertise ensuring a balanced treatment stratification via the heart-team [23]. Given the outstanding infrastructure in the Netherlands such as the nation-wide prospective registry that was created under the auspices of the Netherlands Society of Cardiology and Cardio-Thoracic Surgery to improve quality of care by monitoring patient demographics and clinical outcomes (BHN-registratie), clinical programs are incorporated into clinical-scientific ones. [24] The TAVI Care and Cure is an example of this [25].

Table 1 Summary start TAVI in the Netherlands

	Year	Month	Day	Hospital	City
1	2005	11	15	EMC	Rotterdam
2	2006	2	9	Amphia	Breda
3	2007	6	8	St Antonius	Nieuwegein
4	2007	10	1	AMC	Amsterdam
5	2007	11	8	LUMC	Leiden
6	2008	4	10	UMCU	Utrecht
7	2008	11	26	MCL	Leeuwarden
8	2008	-	-	Catharina	Eindhoven
9	2008	-	-	Radboud	Nijmegen
10	2008	-	-	UMCM	Maastricht
11	2009	5	27	UMCG	Groningen
12	2009	10	15	OLVG	Amsterdam
13	2009	12	2	Isala	Zwolle
14	2012	11	13	MST	Enschede
15	2013	8	27	Haga	Den Haag
16	2014	10	30	VUMC	Amsterdam

Population The Netherlands (2018): 17,2 million (population density of 488 people/km2)
Gross domestic product/capita (2018): 53,228$
Hospital beds/1000 people: 5.8 (1990) - 4.7 (2009). (USA 3.1 in 2009 - source WHO)

Table 2 Peer-reviewed papers (source PubMED, EndNote X9) by Dutch investigators (as of 1 March 2020)

year	*n*	≥15	≥10-15	0-10
2007	1	0		1
2008	3			3
2009	1			1
2010	15	1	1	13
2011	13			
2012	18	2	1	15
2013	22	2	3	17
2014	36	5		
2015	30	2	1	27
2016	33	2	1	30
2017	48	9	0	39
2018	48	6	0	42
2019	54	2	0	52
2020	24	2	0	22

Total number of publications (*n*) per year are subdivided by the journal Impact Factor (2019) using the following categories: ≥15, ≥ 10 – 15 *and* 0 – 10

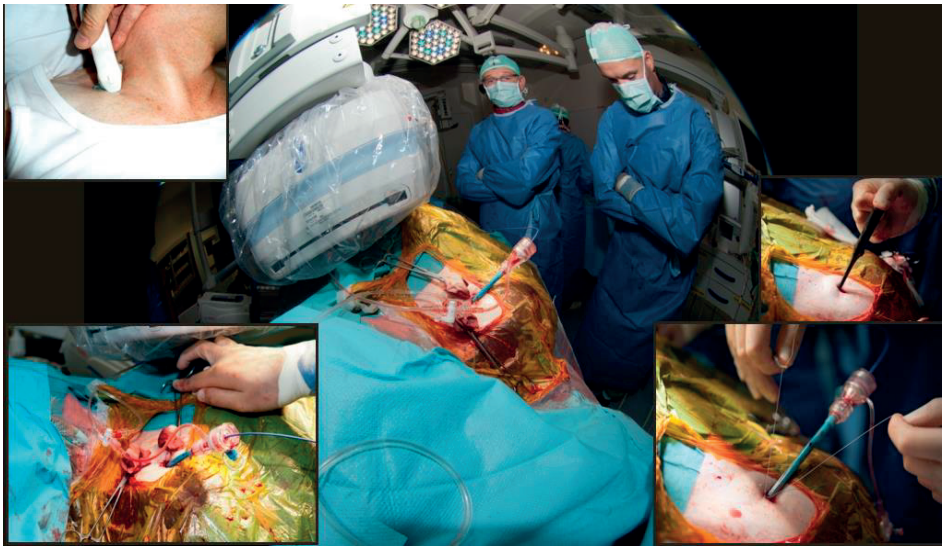

Figure 5 TAVI via the axillary artery under local anaesthesia. Procedure (Medtronic CoreValve 31mm) performed by Dr van Mieghem and Dr de Jaegere on 13 September 2011. Echoguided access followed by application of suture-based closure system, valve implantation and percutaneous closure

The clinical scientific output of the Netherlands are summarised in Tab. 2 and 3. Beyond the analysis of outcomes and the underlying mechanisms in single, multicentre national and international initiatives and collaborations, research has been initiated to elucidate and predict the interaction between the device and host as well as the role of Artificial Intelligence in TAVI [26-35]. The clinical drive of innovation providing the best possible care to the individual patient and the scientific work (volume and content) of all Dutch medical professionals is an expression of the stimulating environment in which they have the pleasure to live and work.

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Table 3. PhD Theses by Dutch Academic Institutions

	Year	Institute	1th Promotor	1th Copromotor	Candidate	Title
1	2011	EMC	Serruys	De Jaegere	Tzikas	The role of advanced imaging in TAVI
2	2011	EMC	Serruys	De Jaegere	Piazza	TAVI: from experiment to clinical practice and beyond
3	2012	AMC	Piek	Baan	Yong	Clinical and hemodynamic effects of TAVI
4	2013	EMC	De Jaegere	Van Domburg	Nuis	TAVI: Current results, insights & future chalenges
5	2014	AMC	Piek	Baan	Van Dijk	Percutaneous treatment of heart valve disease
6	2014	EMC	De Jaegere	n.a.	Van Mieghem	Transcatheter aortic valve therapies: from cutting edgde to main-stream
7	2014	EMC	De Jaegere	Van Domburg	Van der Boon	Insights into complications of TAVI
8	2014	LUMC	Bax	Delgado	Katsanos	Outcomes of TAVI
9	2014	UMCM	Prinzen	Van Gelder	Houthuizen	Left bundle branch block: controversies in aortic interventions and cardiac resynchronisation therapy
10	2014	UMCU	Doevendans	Stella	Samim	TAVI; optimisation of the technique, assessment of complications an future directions
11	2015	UMCU	Doevendans	Stella	Nijhoff	Evolving concepts in TAVI
12	2016	AMC	Piek	Baan	Wiegerinck	Replacing the valve, restoring flow. Effects of TAVI
13	2016	AMC	Van Bavel	Marquering	Elattar	Quantitative image analysis for planning of aortic valve replacement
14	2016	LUMC	Bax	Delgado	Ewe	Aortic valve disease: novel imaging insights from diagnosis to therapy
15	2018	AMC	Piek	Baan	Kesteren van	Screening complications and outcome of aortic valve implantation
16	2018	EMC	De Jaegere	Van Mieghem	Gils van	TAVI: insights and solutions for clinical complications and future perspectives
17	2018	UMCM	Prinzen	Houthuizen	Poels	Left bundle branch block in TAVI
18	2019	AMC	Piek	Delewi	Vlastra	Cerebral outcomes in patients undergoing TAVI
19	2019	AMC	De Winter	Tijssen	Abdelghani	Transcatheter interventions for structural heart disease: present and future
20	2019	AMC	Henriques	Vis	Van Mourik	Percutaneous treatment of Aortic Valve Disease- Towards optimal patient outcomes
21	2019	EMC	Kappetein	Piazza	Mylotte	Evolution of transcatheter heart valve technology
22	2020	UMCU	Doevendans	Stella	Kooistra	Individualised optimization of TAVI
23	2020	UMCU	Doevendans	Stella	Abawi	Role of novel predictive factors on clinical outcome after tran-scatheter aortic valve replacement
24	2020	EMC	Mattace Raso	Lenzen	Goudzwaard	The impact of frailty on outcome after TAVI in older patients
25	2020	EMC	De Jaegere	Lenzen	Faquir	Clinical application of patient-specific computer simulation and advanced imaging in TAVI
https://www.narcis.nl/search/coll/publication/Language/NL/uquery/TAVI						

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3

TAVI Care and Cure, The Rotterdam Multidisciplinary Program for Patients undergoing Transcatheter Aortic Valve Implantation: Design and Rationale

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ABSTRACT

Background: The capacity of TAVI-programs and numbers of sites performing TAVI has rapidly increased. This necessitated the initiation of the Rotterdam TAVI Care & Cure Program, aiming to improve patient-centered care during the TAVI pathway.

Methods: Consenting patients with severe aortic stenosis and an indication for TAVI will be included. The TAVI Care & Cure program will facilitate prognostic contributions to improve outcomes, patient satisfaction and quality of life in patients with valvular heart disease who are treated with a transcatheter aortic valve implantation in collaboration with the departments of cardiology, cardio-thoracic surgery, anesthesiology and geriatrics.

Conclusion: With a single center observational registry, we aim to assess the TAVI patient clinical pathway, focusing on pre, peri and post interventional variables including functional status and HRQoL. We will evaluate the patient's complexity by applying an extended multidisciplinary approach, which includes a systematic application of geriatric assessments of frailty and cognitive function.

Keywords: Aortic Stenosis (AS), Health related Quality of life (HrQoL), Transcatheter aortic valve implantation (TAVI), patient-centered care

1. INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is increasingly being utilized to treat patients with severe aortic stenosis (AS) who are considered at intermediate or high risk for surgical aortic valve replacement (SAVR). TAVI, a less-invasive therapeutic option, is expected to become the standard treatment in all patients with aortic stenosis but will predominantly be applied in an increasingly elderly population given the increase of this population group [1-3]. Elderly patients differ from younger patients in terms of frailty (a state of reduced physical, cognitive and social functioning, resulting in a reduction of reserve capacity for dealing with stressors) [4] due to a higher prevalence of medical co-morbidities leading to a more pronounced reduction in functional status and health related quality of life (HRQoL).

Despite improvements in immediate outcomes (i.e. safety) as a result of enhanced operator experience, progress in device technology and post-operative care, a proportion of patients do not survive beyond one year or at best show limited or no improvement in HRQoL after TAVI [1, 2, 5]. This is particularly evident for the elderly patient (>80 years) necessitating a more delicate and balanced decision-making (risk/benefit assessment) including the understanding of other factors that determine immediate and above all long-term outcomes [6-9]. In this context frailty is of significance, as it is associated with chronic diseases and increased age, negatively influencing morbidity and mortality after TAVI. Importantly, through advocacy of the European Society of Cardiology, frailty has now been incorporated into the decision-making process [10].

Also other components such as mental status, nutrition and socio-economic status, which are not only relevant for the elderly patient population, will be taken into account. This in combination with a higher prevalence of medical antecedents and co-morbidities renders formulating treatment strategies in the elderly complex and requires further analysis into whether specific geriatric interventions before and/or after TAVI may improve immediate and long-term outcome after TAVI [10]. For this reason, a dedicated TAVI program entitled TAVI Care & Cure was initiated in our institution of which the details are herein further described.

2. STUDY DESIGN

The TAVI Care & Cure study is a prospective single-center multidisciplinary observational cohort study in which a comprehensive set of predefined cardiovascular and non-cardiovascular variables are collected (Table 1a). "Care" entails the management of

the pre and post interventional patient pathway whilst "Cure" entails the interventional treatment phase. Inclusion criteria are all consecutive patients with severe symptomatic AS, not considered for conventional open heart valve surgery techniques, who are deemed eligible for TAVI by a multi-disciplinary heart valve team. Furthermore aspects as technical suitability, frailty and co-morbidities are considered in the decision making process. Patients will be excluded if co-morbidities and /or their general condition is not expected to improve their quality of life and/or a survival expectation of <1 year. Candidates who are not eligible for TAVI will be excluded from this study. Inherent in this observation cohort study, no control group will be used.

Patients older than 70 years with an indication for aortic valve replacement therapy (outpatient cardiology assessment) are referred for comprehensive geriatric assessment (CGA) which consists of hetero, social and functional anamnesis, medication review and frailty assessment to determine deficits in geriatric domains by using validated frailty assessment tools [11].

The primary objective of the TAVI Care & Cure program is to improve the treatment and care of patients with aortic stenosis undergoing a TAVI following a novel, dedicated clinical TAVI-pathway. This pathway encompasses pre-admission assessments, diagnostic work-ups, heart team consultations, interventional treatment and lastly outpatient follow-up. Collected data will provide additional information concerning the understanding of the safety and device performance and also how to treat patients in a real world setting including HRQoL.

Secondary objectives are to access the role of frailty in this population and to quantify patient characteristics and criteria for possible early discharge eligibility.

For these purposes immediate outcomes and clinical endpoints (i.e. safety, life-threatening or major bleeding, major vascular complications, in-hospital major stroke, in-hospital acute kidney injury, and 30-day mortality) are assessed using the Valve Academic Research Consortium criteria (VARC-2 criteria) [12] in addition to the occurrence of non-cardiovascular events with emphasis on delirium at time points summarized in Table1a.

Efficacy of treatment is assessed by monitoring survival freedom from major adverse cerebro-cardiovascular events, functional class and HrQoL at 30 days, one, three, and five year. Assessment of utility or futility of treatment will be based upon analysis of long-term outcomes such as survival, survival free from stroke, reduction or loss in/

of ADL. These analyses will help to formulate improvements in treatment allocation, patient preparation and postoperative care.

The Medical Ethics Committee of the Erasmus Medical Center reviewed the study (MEC-2014-277) and since this study was not subjected to the Dutch Medical Research Involving Human Subjects Act no approval was required. The study will be performed according to the Helsinki Declaration and all patients must consent for participation.

3. THE TAVI PATHWAY

3.1 Diagnostic assessments

Cardiac and geriatric examinations and assessments will be performed and include medical history and physical assessments, 12-lead ECG, laboratory results, thorax x-rays, diagnostic coronary angiogram, multi–slice computed tomography (MSCT), trans-thoracic and/or trans esophageal echocardiography and quality of life measurements. The following geriatric domains will be assessed: cognition and nutritional status, (instrumental) activity of daily living, mobility and muscle loss. (See Table 1b for used instruments)[13-18].

Table 1
A: Cardiology assessments

TIME-POINTS	Out patient Clinic	Day of admission	Day of admission	Peri-procedural	2-4 hrs (local anesthesia) ICCU ward	Post-procedural: Day 1 - 5	Discharge	4 weeks FU	12 months FU	3 years FU	5 years FU
Bloodtest: *e-GFR Cardiac enzymes, Ureum, Creatinine, CRP, NT-pro BNP, Hb*	X	X				X	X	X	X	X	X
12-lead EKG	X	X			X	X	X	X	X	X	X
NYHA & CCS class	X							X	X	X	X
VARC-2 definitions *	X							X	X	X	X
Trans Thoracic Echo	X			X	X		X				
Multi Slice Computer Tomography	X										
Coronairy Angiography	X										
Informed Consent		X									
Screening on allergic for contrast medium		X									
Pre-hydration prophylaxe		X									
Endocarditis prophylaxe (If indicated lifelong)		X		X			X				
Anti-thrombotic prophylaxe		X		X	X	X	X				
Telemonitoring						X					
Thorax X-ray Chest					X						
HR-QoL: EQ-5D VAS	X							X	X	X	X
Temporary Pacemaker Lead				If indicated	Removed 2-4 hrs						
Urinary catheter				If indicated							
Observation: *AC, Heamodynamics, Arrhytmias, Conduction-disturbances, Bleeding, Vascular complications, Neurological disorders (stroke, delirium)*					X	X					
Medication: *ASA 80 mg Clopidogrel 75 mg , If OAC-> OAC & Clopidogrel 75 mg (3 Months)*					X	X	X	X	X	X	X
Mobilization, revalidation (If indicated physiotheraphy)						X	X				
If PPM/ICD implantation pocketcontrol							X	X	X	X	X

B: Geriatric assessments

TIME-POINTS	*Out patient Clinic*	*Day of admission*	*Day of admission*	*Peri-procedural*	*2-4 hrs (local anesthesia) ICCU ward*	*Post-procedural: Day 1 - 5*	*Discharge*	*4 weeks FU*	*12 months FU*	*3 years FU*	*5 years FU*
Functional anamnesis: *ADL (KATZ), iADL (Lawton & Brody), Independence, Mobility, Fallrisk, Nutritional status and Incontinence*	X								X		
Social anamnesis: *Married, Divorced, Widowe, (no) Children, Life events, Care, Living environment*	X								X		
Cognitive function	X								X		
HR-QoL: RAND SF-36	X								X		
Mobility: *Time up-and go test*	X										
5 Meter walking test	X										
MMSE	X										
Medication (nr)	X										
Frailty assessment	X										
Handgrip strenght test	X										
Consult geriatrician	X	X			X	If indicated					
No geriatric involvement				X				X			
Delirium-observation		X			X	If indicated					

NYHA Class: New York Heart Association Functional Classification; CCS Class:Angina Grading Scale; EKG: electrocardiogram; MSCT:Multi Slice Computer Tomography;

Katz ADL: The Katz Index of Independence in Activities of Daily Living; Lawton & Brody IADL:The Lawton Instrumental Activities of Daily Living Scale;

MUST: Malnutrition Universal Screening Tool; TUGT: Timed Up and Go Test; MSSE: Mini-Mental State Examination; DOS: Delirium Observation Screening; HR-QoL: Health-Related Quality of Life;

RAND-36: 36-Item Short Form Health Survey; KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D-5L: EuroQoL Quality of Life Scale; VAS: Visual Analogue Scale;

ACT: Activated Clotting Time; TTE: Trans Thoracic Echo; CAG: Coronary Angiography; AR: Aortic regurgitation; PPM: Permanent Pacemaker; TPM; Temporary Pacemaker; ASA: Acetylsalicylic Acid; OAC: Oral Anticoagulant; ICD: Implantable Cardioverter Defibrillator; CRP: C-reactive Protein; NT-pro BNP: pro b-type Natriuretic Peptide; LDL: low density lipoprotein;

aPTT: Activated partial Thromboplastin time; DAPT: Dual Antiplatelet Therapy; e-GFR: estimated Glomerular Filtration Rate

3.2 Patient selection – Multidisciplinary Heart Valve Team Meeting

The TAVI Care & Cure program has been developed and initiated with the collaboration of the departments of cardiology, cardio-thoracic surgery, anesthesiology and geriatrics.

Using a well-designed multidisciplinary approach with collaborative input of diverse specialists of the heart valve team, the treatment decision process is not only thoroughly discussed leading to an improved treatment performance but also essential consideration is given to the potential risks and expected benefits of the selected treatment strategy. For instance, prevention of post procedural complications are deliberated in terms of either physical function such as stroke, vascular complications, renal failure, paravalvular leak and conduction disorders and in terms of cognitive function such as delirium. The treatment decision, incorporating diagnosis, complexity and multiple co-morbidities, be it for optimum medical therapy, TAVI or SAVR, are taken at the weekly multidisciplinary heart valve team meeting (Fig. 1). Importantly, the use of a multidisciplinary heart valve team for the management of patients with valvular heart diseases is strongly recommended (Class I, level C) in the current ESC guidelines [10].

All patients accepted, for either a TAVI or SAVR procedure, are scheduled for a preoperative visit at the outpatient clinic anesthesiology in order to complete the pre-procedural diagnostic workup.

3.3 Intervention procedure

The TAVI-procedure is performed under local anesthesia and antibiotic prophylaxis [10] in a cathlab suite with full facilities for general anesthesia, echocardiography and cardiopulmonary support if needed. Any commercially available trans catheter heart valve (THV) can be used. In our institution the balloon expandable Edwards Sapien 3 valve (Edwards Lifesciences Corp., Irvine, California), the self-expandable Acurate neo valve (Boston Scientific, Marlborough, Massachusetts) and the self-expandable Evolute R-and Pro valve (Medtronic Inc. Minneapolis, Minnesota) are currently used. Vascular access and pre-closure is performed under echo-guidance. After vascular access, all patients receive cerebral protection using a cerebral protection filter unless the anatomy of the brachiocephalic and/or left common carotid artery precludes its use or is contra-indicated [19, 20]. The valve size selection is based upon the screening MSCT of the aortic root and the valve implantation is performed without pre-balloon valvuloplasty (direct valve implantation). Contrast angiography and Trans Thoracic Echocardiography are used for implantation guidance and post implantation evaluation. In the case of a high degree atrioventricular (AV) block during the procedure a temporary pacemaker (TPM) is left in situ up to 24 hours and removed when clinically justified. Hemostasis is achieved by

using either a plug-or suture based vessel closure device followed by selective arterial angiography to assess for hemostasis [21, 22].

3.4 Post procedural management /discharge

After the TAVI procedure, patients are monitored for at least 2-4 hours at the Cardiac Care Unit. When the patient is considered to be hemodynamic stable and in the absence of complications, the patient is then transferred to the Medium Care Unit for further observation and mobilization until hospital discharge. Furthermore access site assessment for potential late bleeding and also telemetric monitoring supplemented with regular ECG's for potential conduction abnormalities up to 72 hours post intervention is mandatory. Moreover in terms of early recognition of delirium the geriatrician will evaluate daily the patient (Table 1b).

The expected discharge is between 3-7 days post procedure. Post-TAVI anti-thrombotic therapy consists of Aspirin (lifelong) and Thienopyridine (for three months). In patients indicated for oral anticoagulant therapy, Clopidogrel for three months will be administered.

In addition to a one-month follow-up visit, further follow-up is scheduled at one, three and five year's post-TAVI (Table 1a). In the context of evaluating changes for the degree of AS related symptoms and functional status, patients are asked to complete a generic health status questionnaire (i.e. EuroQOL five dimensions (EQ-5D)) including the Visual analogue scale (EQ-VAS) at baseline, twelve months, three and five years [23].

3.5 Patient safety and quality of care

The weekly TAVI meeting is attended by the TAVI interventionalist, accompanied by a team of dedicated interventional cardiology fellows involved in the TAVI program and the TAVI nurse coordinator. During this meeting in-hospital post-TAVI patients are discussed and reviewed for post-procedure in-hospital care, eventual complications, length of stay and discharge preparation. Furthermore patients undergoing a planned TAVI procedure in the following week are again assessed according to an adjusted format (i.e. medical history, comorbidities, established risk scores, status of the conduction-system, echo-outcomes, status of the coronary anatomy, use of embolic protection, access, closure and possible inclusion in a study).

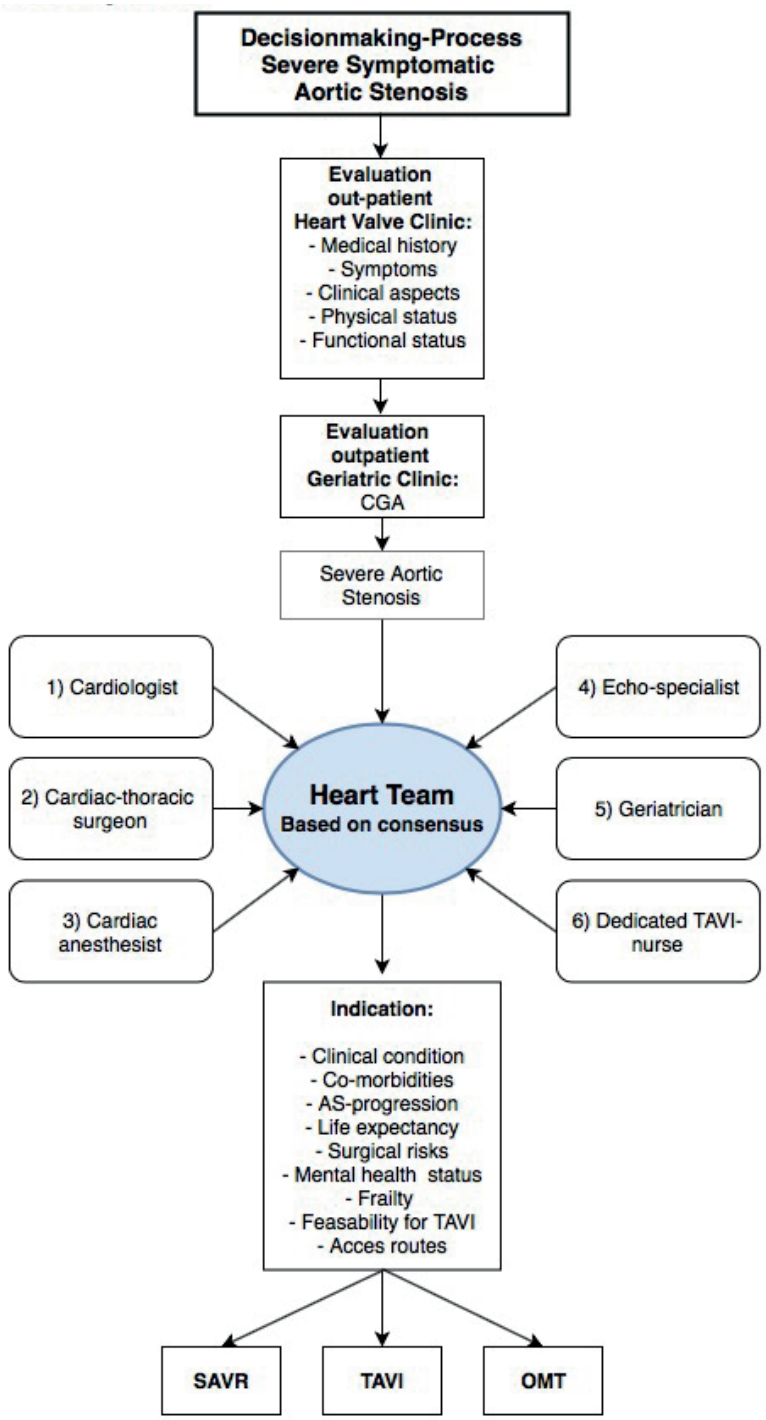

Figure 1. The Heart Team Multidisciplinary decision-making process

4. DATA MANAGEMENT

All demographic, clinical complications and related data such as laboratory assays, ECG and echocardiographic data will be collected during the outpatient visits at both the cardiac and geriatric departments. In addition a concise set of variables collected during TAVI are entered into a dedicated database.

Captured data is entered on a structural basis and a collaborative manner in the dedicated TAVI database by three groups of participants; a medical student team accompanying the TAVI-cardiologists during the outpatient clinic, the fellows involved in the TAVI program and by the geriatrician team members.

The dedicated database is hosted on an internal server. It is not accessible from an external point of contact and it features real time user tracking / logging and facilitates simultaneous /multiple user interaction.

4.1 TAVI nurse coordinator

The success of a multi-disciplinary team approach with special attention to patient care is dependent on the organizational skills of a central individual (Fig. 2).The TAVI-nurse coordinator informs at the pre-admission phase the patient and his/her relatives regarding the details of the procedure. Also the TAVI nurse oversees the patient's in-hospital, discharge and follow-up phases. Knowledge of the patient's pathway, therapy treatment, discharge management and social support is a key factor in the TAVI Care & Cure program. In addition offering a point of contact to the patient, both in–hospital and post discharge, enhances the patients well-being, benefiting a thorough preparation for, and information about the patient's treatment.

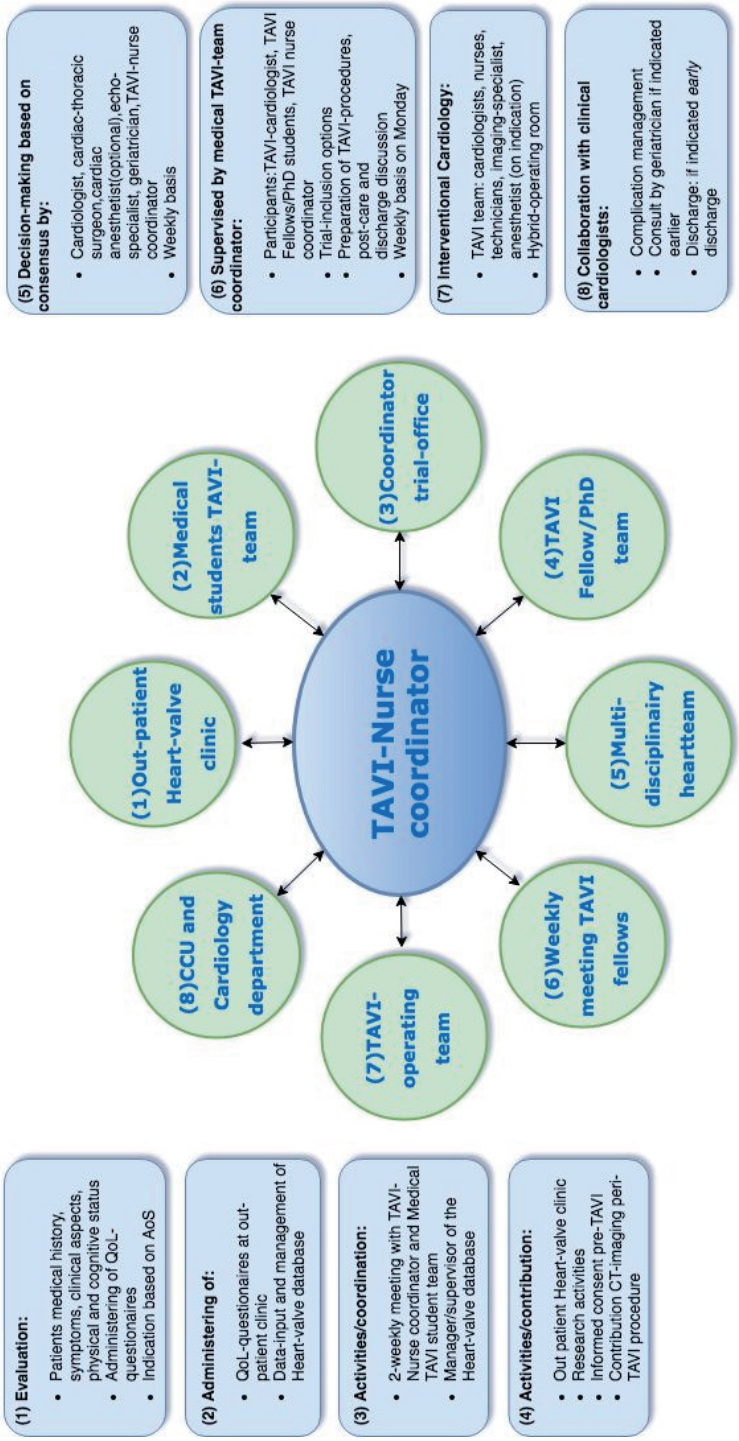

Figure 2. Contributors in the TAVI-pathway.

5. DISCUSSION

Aortic stenosis is the most common valve disease in elderly adults with a growing prevalence due to the aging population [3]. TAVI, currently performed in over 70 countries [24], has evolved as a less invasive, safe and effective alternative treatment of patients with severe symptomatic AS who are at high or prohibitive risk for surgical aortic valve replacement [2].

Evidence from randomized clinical trials comparing outcomes of SAVR versus TAVI has led to a broadening of indications for TAVI with an expansion from the initial high-risk surgical group onto currently an intermediate and low risk population [1, 25, 26] resulting in a exponentially volume growth of TAVI worldwide. A shared and balanced decision making strategy by the Heart Valve Team includes an individualized approach of patient specific risk assessment and the use of additional outcome measures reflecting patient related safety and clinical endpoints (i.e. 30-day mortality, VARC-2 variables) [10, 12].

Since the first TAVI was performed in 2002 [27], there has been a major evolution of developments and transformation of CE-marked TAVI systems. Furthermore technical advancements in the current device technology have led to amongst others i.e. lower profiles of the delivery systems, retrievable and repositionable features as also improvements in designs leading to a reduction in paravalvular leakage. The most preferred access route is the trans femoral (TF) route. Alternatives are the trans-apical, trans-subclavian and direct aortic route. In addition, the operator experience has intuitively increased, reflecting in a more specified case selection and procedural strategy leading to improved reduction of peri-procedural events and clinical outcomes post TAVI. The Dutch Guidelines for Competencies for Transcatheter Heart Valve Intervention stated that an institution must achieve at least 75 TAVI-procedures per year to be considered "established" within three years of inception of the program [28].

The afore mentioned developments have led to the establishment of this TAVI Care & Cure program in our center, initiated to collect data from all TAVI patients. Further formalizing and structuring this TAVI program by utilizing the captured data, enables real-time monitoring and improvement of the quality of care, to present transparent reports of site performance on a regular basis providing additional information on i.e. in-hospital and 30-day mortality, vascular complications, bleeding, conductions disturbances and disabling stroke, as well as frailty as predictor for mortality (30-day and 1 year) and HRQoL post TAVI. The advantages of the implementation of TAVI Care & Cure is the uniformity of data collection, data integrity and analysis, all stored in one dedicated database.

A comprehensive tailored TAVI dataset is now mandatorily, annually reported to the national health inspector via a national registry platform, the Dutch Heart Registry (NHR, Nederlandse Hartregistratie). The NHR is a major cardiovascular quality-of-care registry and aims to monitor and improve quality of care of heart disease for the individual patient by collecting and analyzing patient data, reporting relevant outcome indicators in annually public accessible reports. Additionally an independent academic Clinical Events Committee (CEC) will evaluate regularly adverse events according to international guidelines and definitions (VARC-2, Bleeding Academic Research Consortium (BARC), the ESC Myocardial Infarction Definitions) [29-31].

In terms of specific research questions, two distinct areas will be explored in detail.

Firstly as there is a growing interest in the assessment of frailty, which is associated with increased morbidity and mortality after SAVR and TAVI [8]. Frailty has been added in complement to the conventional risk scores (Society of Thoracic Surgeons (STS) score and European System for Cardiac Operative Risk Evaluation (EuroSCORE-II)) in the TAVI Care & Cure program. To incorporate frailty in terms of functionality, HRQoL and other existing disabilities in the patient selection process, we aim to predict more distinctly the differentiation between those patients who will benefit from TAVI and those who will not. Currently there is debate ongoing concerning the need to develop a dedicated TAVI orientated quality of life questionnaire. The TAVI Care & Cure data may also contribute to this debate.

Secondly improvements in risk-stratification and patient selection in conjunction with a shift to lower-risk patients coupled with the standardization of TAVI-procedures have led to an early discharge program in our institution. This program simplifies the TAVI-procedure, decreases its duration and reduces procedural related complications by including a fully percutaneous trans femoral access site entry and closure, performed under local anesthesia and early mobilization [32, 33].

There is currently no consensus over the definition 'early discharge'. A recent meta-analysis of 8 observational studies including 1775 patients, evaluating early discharge to 30-day mortality, suggests that early discharge by day 3 after TAVI in selected patients who underwent an uncomplicated TAVI is safe in terms of mortality, discharge to 30-day or need for a permanent pacemaker after discharge [34]. Incorporating a simplistic/minimalistic approach into clinical practice starts with performing a pre-procedure screening of patient's functional and cognitive status and suitability for an early discharge pathway. That includes a more refined selection of suitable valve type based upon integrating the pre-procedural ECG interpretations including P-R interval, QRS duration and the

electrical axis. It's important to inform the patient and his/her social network that an early discharge can be anticipated if the post-procedural period is uneventful to ensure that one patient's social support and network is prepared for a potential early discharge.

In essence, the ambition of this dedicated TAVI Care & Cure program is to gain more insights into existing and novel variables.

6. Conclusion

With a single center observational registry, we aim to assess the TAVI patient clinical pathway, focusing on pre, peri and post interventional variables including functional status and HRQoL. We will evaluate the patient's complexity by applying an extended multidisciplinary approach, which includes a systematic application of geriatric assessments of frailty and cognitive function.

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4

10 jaar transkatheter-aortaklepvervanging Een overzicht van de klinische toepasbaarheid en bevindingen

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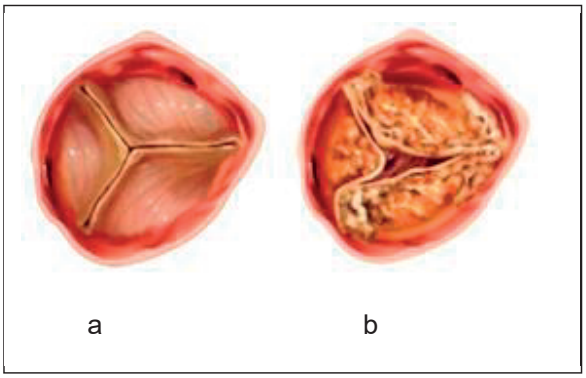
ABSTRACT

- Aortaklepstenose is een veel voorkomende hartklepaandoening bij volwassenen. De prevalentie ervan stijgt met de leeftijd en aortaklepstenose wordt dus vooral gezien bij oudere patiënten.
- Van de patiënten met symptomatische aortaklepstenose wordt 30-40% niet verwezen voor chirurgische klepvervanging, vanwege hoge leeftijd, voorgeschiedenis of comorbiditeit.
- In 2002 werd de eerste transkatheter-aortaklepvervanging (TAVI) uitgevoerd bij een inoperabele patiënt. Sinds 2012 is TAVI opgenomen in internationale richtlijnen voor hartkleplijden als behandelingsstrategie bij symptomatische patiënten met een groot risico op complicaties en een levensverwachting van meer dan 1 jaar.
- Besluitvoering over welke behandeling de voorkeur heeft vindt plaats tijdens een multidisciplinaire hartkleppenbespreking.
- Belangrijke complicaties van een TAVI zijn bloedingen, nierfunctiestoornis, beroerte, geleidingstoornissen, klepinsufficiëntie en overlijden.
- TAVI-procedures worden in Nederland alleen uitgevoerd in hartcentra waar specifieke expertise aanwezig is op het gebied van structurele hart- en vaatziekten.
- Wetenschappelijk onderzoek is van belang om verdere ontwikkelingen en verbeteringen mogelijk te maken.

INTRODUCTIE

Aortaklepstenose is een veelvoorkomende hartklepaandoening bij volwassenen.[1] De prevalentie ervan stijgt met de leeftijd en bedraagt 3-5% bij personen boven de 75 jaar; de aandoening wordt dus vooral gezien bij oudere patiënten.[2] Aortaklepstenose is een progressief en degeneratief ziekteproces dat lijkt op atherosclerose (figuur 1). De prognose is slecht als de patiënt klachten heeft als vermoeidheid, dyspneu, verminderd inspanningsvermogen, syncope, angina pectoris of verminderde ventrikelfunctie. Bij aanwezigheid van een van deze klachten is de kans op sterfte ieder jaar 30%. Een openhartoperatie waarbij de aangedane klep wordt verwijderd en vervangen door een nieuwe klep, kortweg 'aortaklepvervanging' (AVR),[3] wordt steeds meer uitgevoerd. Patiënten die een AVR ondergaan hebben een betere kwaliteit van leven en langere levensduur vergeleken met patiënten die een medicamenteuze behandeling krijgen. Rond de eeuwwisseling bleek dat 30-40% van de patiënten met symptomatische aortaklepstenose niet in aanmerking kwam voor AVR vanwege hoge leeftijd, voorgeschiedenis of comorbiditeit.

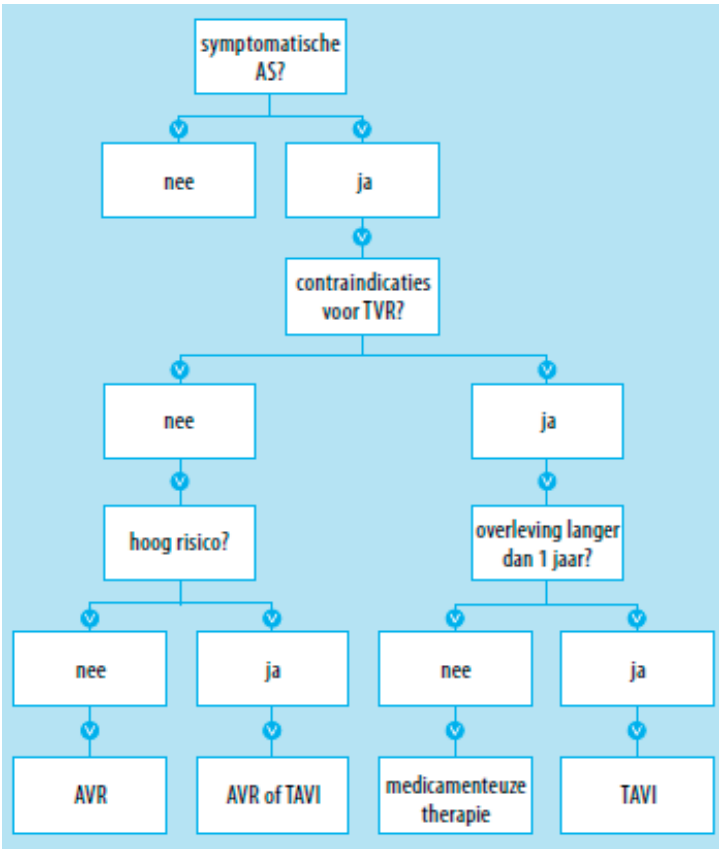


Figuur 1. Illustratie van (a) een normale aortaklep en (b) een verkalkte aortaklep (bron: www.brussels-heartcenter.be/fr/chirurgie-cardiaque/ interventions/implantation-d-endovalve.html).

Om deze redenen is de transkatheter-aortaklepvervanging (TAVI) ontwikkeld.[4] Het betreft een ingreep waarbij een biologische klep via de A. femoralis, A. subclavia, aorta ascendens of de apex cordis onder röntgendoorlichting geïmplanteerd wordt.[5] De procedure is minder ingrijpend dan een conventionele aortaklepvervanging, omdat het borstbeen niet wordt geopend, het hart niet wordt stilgelegd, er geen hart-longmachine nodig is en de ingreep ook uitgevoerd kan worden onder lokale verdoving met minimale sedatie. De eerste succesvolle TAVI vond plaats in 2002.[4] Sindsdien zijn er meer dan 100.000 patiënten met aortaklepstenose behandeld met deze kathetergeleide techniek.[6] Resultaten van gerandomiseerd onderzoek laten zien dat TAVI zorgt voor een betere overleving dan medicamenteuze therapie bij patiënten die niet meer

voor chirurgie in aanmerking komen. TAVI blijkt bovendien een gelijkwaardige klinische uitkomst te geven als chirurgische klepvervanging bij patiënten met een groot risico op complicaties.[7-10] Ten slotte is TAVI veilig uitvoerbaar, met een sterfte van 3,4% binnen 30 dagen na de ingreep.

Sinds 2012 is TAVI een behandelingsstrategie[12] bij symptomatische patiënten met een groot risico op complicaties, een berekende levensverwachting van langer dan 1 jaar en anatomische geschiktheid voor de ingreep (klasse 1B) (figuur 2).



Figuur 2. Stroomdiagram met een beslisboom voor de behandeling van aortastenose (bewerking van eerder gepubliceerd stroomdiagram[3]). AS=aortastenose; AVR=aortaklepvervanging; TAVI=transkatheter aortaklepvervanging.

In onderstaand artikel presenteren wij een overzicht van de klinische toepasbaarheid van TAVI vanaf 2002, met de focus op patiëntenselectie, indicatiestelling en perioperatieve complicaties.[11] In tabel 1 vindt u een overzicht van de studies die zullen worden besproken.

Tabel 1 Overzicht van de belangrijkste studies naar de complicaties bij transkatheter-aortaklepvervanging.

eerste auteur, jaartal	studie	opzet	type klep	aantal patiënten; n	leeftijd in jaren	vrouw %	EuroSCORE; %	STS Score %
Smith, 2011[9]	PARTNER A	RCT						
	TAVI		ESV	348	84	42	29.3	11.8
	SAVR			351	85	43	29.2	11.7
Leon, 2010[10]	PARTNER B	RCT						
	TAVI		ESV	179	83	54	26.4	11.2
	OMT			179	83	54	30.4	12.1
Adams, 2014[26]	CoreValve US	RCT						
	TAVI		MCS	394	83	46	17.6	7.3
	SAVR			401	84	47	18.4	7.5
Abdel-Wahab, 2014[23]	CHOICE	RCT						
	ESV		ESV	121	82	57	21.5	5.6
	MCS		MCS	120	80	72	21.1	6.2
Popma, 2014[32]	US Pivotal Extreme Risk	observationeel	MCS	489	83	52	22.6	10.3
Gilard, 2012[6]	FRENCH	observationeel	ESV	2107	83	53	22.2	15.6
	Registry		MCS	1043	82	40	21.3	14.2
Chieffo, 2013[33]	PRAGMATIC	observationeel	ESV	204	82	51	21.7	8.9
			MCS	204	82	55	22.1	9.3
Hamm, 2014[34]	GARY	observationeel						
	SAVR			9985	70	35	AVR:8.8/	
	TAVI		ESV+MCS	3875	80	56	AVR+CABG:11.0	
							TV AVI:25.9/	
							TA AVI:24.5	

ESV = Edwards Sapien Valve; MCS = Medtronic CoreValve; AVR = 'aortic valve rerurgitation'; CABG = 'coronary bypass artery surgery'; TV AV I = 'trans vascular aortic valve implantation'; TA AV I = 'trans apical aortic valve implantation'; STS Score = 'Society of Thoracic Surgeons Score'; OMT = 'optimal medical treatment'; SAVR = 'surgical aortic valve replacement'

PATIËNTENSELECTIE

Om technisch gezien in aanmerking te komen voor TAVI moeten patiënten voldoen aan een aantal specifieke anatomische voorwaarden voor het hart en de bloedvaten. Zo moet het arteriële vaatstelsel van voldoende kwaliteit en grootte zijn om de katheters waarop de klep is gemonteerd, met een diameter van ongeveer 6 mm, toe te laten en dient de aortawortel eveneens bepaalde afmetingen te hebben. Om dit te controleren wordt gebruikgemaakt van niet-invasief beeldvormend onderzoek, zoals echocardiografie of een cardiale CT-scan.[12] Met een CT-scan kunnen naast de afmetingen van hart en bloedvaten ook het aantal bochten in het vaattraject en de graad van verkalking onderzocht worden. Bij elke patiënt wordt daarnaast een hartkatheterisatie uitgevoerd, waarbij de kransslagaderen in beeld worden gebracht. Om een gewogen besluit te nemen over de indicatie en behandeling is het aantonen dan wel uitsluiten van coronairlijden nodig. Daarnaast dient een analyse plaats te vinden van alle andere patiëntgebonden kenmerken zoals demografie, voorgeschiedenis, comorbiditeit en hartfunctie.

In het Erasmus MC wordt voorafgaand aan de ingreep de somatische, geestelijke en sociale toestand van de patiënt beoordeeld door een geriater, omdat de doelgroep voor TAVI met name oudere patiënten betreft. Tijdens een multidisciplinaire hartkleppenbespreking met cardiologen, cardiochirurgen en cardio-anesthesisten[15] wordt op basis van alle gegevens de behandeling van voorkeur geselecteerd voor de patiënten, met een schriftelijke verslaglegging van het besluit inclusief motivatie.[13] Er wordt tijdens deze bespreking een keuze gemaakt tussen TAVI, AVR en een medicamenteuze behandeling.

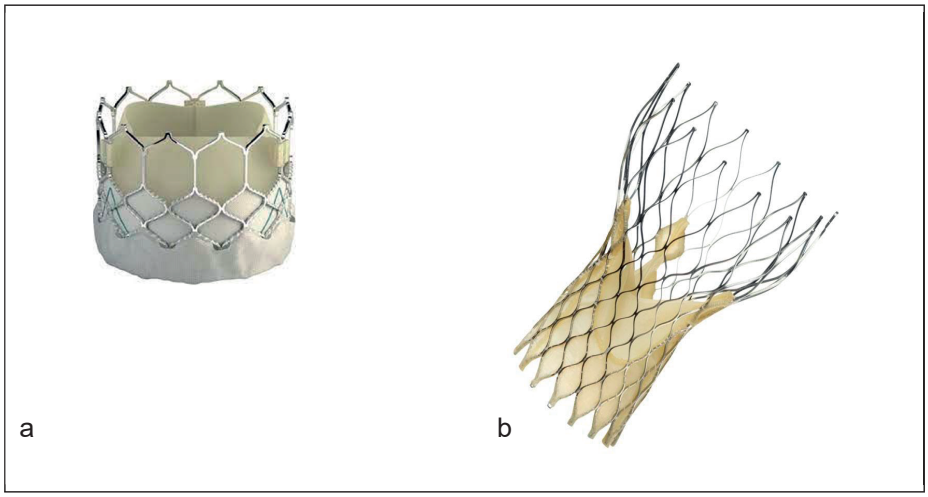
DE PROCEDURE

De meest gebruikte toegang voor TAVI is de A. femoralis communis, die bij voorkeur onder echogeleiding wordt aangeprikt om het risico op vasculaire complicaties te verkleinen. Deze arterie dient een diameter van ten minste 6 mm te hebben.[14]

Als het technisch niet mogelijk is om de TAVI via de A. femoralis te verrichten, zijn de A. subclavia, aorta ascendens of apex cordis de alternatieve toegangswegen. Alleen bij een transfemorale benadering kan de TAVI volledig percutaan uitgevoerd worden. Na de procedure kan met een speciale techniek de wand van de A. femoralis worden gesloten.[11]

De meest gebruikte TAVI-systemen in Nederland zijn momenteel de 'Edwards SAPIEN 3'-transkatheter-hartklep (Edwards Lifescienses Inc.) en het 'CoreValve ReValving'-sys-

teem (Medtronic Inc.) (figuur 3). De Edwards SAPIEN is een kobalt-chroomframe dat door een ballon uitklapbaar is en waarin 3 klepbladen van een runderpericard zijn bevestigd. Het CoreValve ReValving-systeem bestaat uit een uitklapbaar frame van nitinol, met daarin 3 klepbladen van een varkenspericard. Beide klepprothesen worden gecomprimeerd op een speciale ballonkatheter die via een canule in de slagader wordt gebracht en naar het hart wordt opgevoerd. De diameter van de arteriële introductiecanule is afhankelijk van de maat van de klepprothese en de keuze van het systeem en varieert van 14-18 French, wat overeenkomt met 4,7-6,0 mm. Voorafgaand aan plaatsing wordt de vernauwde aortaklep opgerekt door een ballondilatatie om ruimte de maken voor de nieuwe klep. Wanneer deze is geplaatst in de originele aortaklep, ter hoogte van de annulus, wordt de katheter teruggetrokken en via de canule verwijderd.



Figuur 3. Afbeeldingen van de 2 meest gebruikte TAVI-systemen in Nederland: (a) de 'Edwards SAPIEN 3' transkatheter-hartklep en (b) het 'CoreValve ReValving' systeem (bronnen: www.edwards.com en www.corevalve.com).

PERIOPERATIEVE COMPLICATIES

Ondanks dat een TAVI minder invasief is dan een AVR, heeft een TAVI risico op complicaties (tabel 2). Belangrijke complicaties zijn onder andere overlijden en beroerte (5-6%).[15-17] Tegenwoordig worden filters in de hoofd-hals-arteriën geplaatst om verschillende soorten embolieën tegen te houden en een beroerte te voorkomen.[18] Bovendien worden anticoagulantia en 'dual antiplatelet'-therapieën gebruikt om in geval van postoperatief atriumfibrilleren een beroerte te voorkomen.

Dankzij toegenomen ervaring, verbetering van kathetertechnologie en inzicht in de oorzaken, is het aantal complicaties in de afgelopen jaren verminderd.[19] Zo blijkt een perioperatieve bloeding vooral gerelateerd te zijn aan de diameter van de katheters en aan de ervaring van de interventiecardioloog, waarbij moet worden opgemerkt dat bloedingscomplicaties gepaard gaan met een hogere kans op sterven binnen 30 dagen. Daarnaast blijkt dat bloedtransfusies gepaard gaan met een hogere kans op postoperatief nierfalen.[20] Nierfalen geeft een hogere kans op sterven, wat het belang van zorgvuldige indicatiestelling van bloedtransfusies onderstreept. Bijna 85% van de patiënten die een TAVI ondergaan heeft pre-operatief een gestoorde nierfunctie, resulterend in een hoger risicoprofiel en een verminderde overlevingskans.[20] Een nierfunctiestoornis is een mogelijke complicatie bij TAVI en kan de morbiditeit en mortaliteit op korte en langere termijn negatief beïnvloeden. Het beperken van de contrastvloeistof tijdens TAVI kan deze complicatie mogelijk verminderen.

Geleidingsstoornissen bestaan vooral uit een linker-bundeltakblok (LBBB) en een volledig atrioventriculair blok of derdegraads-atrioventriculair blok (AV3B). [17,21] Deze worden veroorzaakt door beschadiging van het geleidingsweefsel in het hart tijdens de TAVI. Een LBBB kan gepaard gaan met interventriculaire dyssynchronie, wat effect kan hebben op de algehele hartfunctie en daarmee op de kwaliteit van leven op langere termijn. Ook is aangetoond dat LBBB gepaard gaat met een verhoogde kans op sterven.[22] Afhankelijk van de vorm en ernst van de geleidingsstoornis zal een tijdelijke of permanente pacemakerimplantatie (PPI) nodig zijn. Uit een recente studie blijkt dat de incidentie van PPI bij de CoreValve 37,6% is, terwijl PPI bij de Edwards SAPIEN een incidentie heeft van 17,3%.[23]

In tegenstelling tot bij AVR worden tijdens TAVI de zieke aortaklep en de calcificaties van de aortawortel niet weggesneden. Dit kan leiden tot onvolledige expansie van de prothese, wat kan zorgen voor para-valvulaire lekkage na de ingreep.[24] Para-valvulaire lekkage na TAVI is meestal gering.[25] Ten gevolge van volume-overbelasting van de linker kamer gaat een matige of ernstige para-valvulaire lekkage echter gepaard met een hogere kans op sterven na ontslag. De kans op para-valvulaire lekkage kan worden verminderd door dilatatie van de klepprothese na de ingreep en zo nodig het plaatsen van een tweede klep.[26]

Een levensbedreigende en zeldzame peri-procedurele complicatie is een obstructie van het ostium van de linker hoofdstam of rechter coronairarterie door een te hoog geplaatste klepprothese. Onmiddellijke percutane coronaire interventie is dan noodzakelijk.

De uitkomsten van recente studies ten zien dat de 1-jaarssterfte lager is bij TAVI-patiënten (14,2%) dan bij AVR-patiënten (19,1%) (tabel 2).[26] De incidentie van complicaties als ernstige vasculaire bloedingen en indicatie voor PPI bleek hoger bij TAVI-patiënten dan bij AVR-patiënten. Ook levensbedreigende bloedingen en blijvende nierschade kwamen meer voor bij de AVR-patiënten. Bij een vergelijking tussen het Edwards SAPIEN- en het CoreValve-systeem bleken het voorkomen van vasculaire complicaties en bloedingen en de 30-dagenmortaliteit niet significant te verschillen.[23]

POSTOPERATIEF BELEID

In de gemiddeld 5-10 dagen tussen de procedure en het ziekenhuisontslag wordt het beleid vastgesteld omtrent antistolling, revalidatie en het eventueel plaatsen van een permanente pacemaker. Patiënten krijgen meestal 3 maanden lang dagelijks clopidogrel 75 mg en acetylsalicylzuur 100 mg voorgeschreven en wanneer er een indicatie voor is ook orale anticoagulantia in plaats van acetylsalicylzuur.[27]

KWALITEIT VAN LEVEN

Een substudie van de PARTNER-studie heeft aangetoond dat TAVI-patiënten ondanks hun hoge leeftijd en eerdere comorbiditeiten, niet alleen een betere overleving maar ook een betere kwaliteit van leven hebben dan patiënten in de controlegroep.[28] Dit positieve effect werd bevestigd in een andere studie waarin de kwaliteit van leven tot 2 jaar na de TAVI werd geëvalueerd.[29] Een belangrijke observatie in deze studie was de constatering dat patiënten met comorbiditeiten als chronisch nierfalen en obesitas een suboptimale uitkomst op kwaliteit van leven lieten zien. Verder werd in een recente studie een relatie aangetoond tussen de aanwezigheid van risicofactoren en de combinatie van overlijden en kwaliteit van leven na 6 en 12 maanden.[30]

GESPECIALISEERDE HARTCENTRA

TAVI-procedures worden in Nederland, conform de vastgestelde richtlijnen door het ministerie van Volksgezondheid, Welzijn en Sport en de Inspectie voor de Gezondheidszorg, alleen uitgevoerd in hartcentra waar specifieke expertise aanwezig is op gebied van structurele hart- en vaatziekten. Deze expertise en onderlinge samenwerking in multidisciplinaire teams is zelfs een voorwaarde om deze hoog-complexe procedure te mogen uitvoeren (tabel 3). Een multidisciplinair team dat bestaat uit ten minste 1

Tabel 2. Overzicht van de belangrijkste studies (zie tabel 1) naar de complicaties bij transkatheter-aortaklepvervanging, 30 dagen na de ingreep.

studie	overlijden %	cardio-vasculair;%	CVA; %	myocard infarct;%	vasculaire complicatie;%	ernstige bloeding;%	AKI; %	Tamponade; %	PPI %
PARTNER A									
TAVI	3.4	3.2	3.8	0	11.0	9.3	1.2	-	3.8
SAVR	6.5	3.0	2.1	0.6	3.2	19.5	1.2	-	3.6
PARTNER B									
TAVI	5.0	4.5	6.7	0	16.2	16.8	0	-	3.4
OMT	2.8	1.7	1.7	0	1.1	3.9	0.6	-	5.0
CoreValve US									
TAVI	3.3	3.1	3.9	0.8	5.9	41.7	6.0	1.3	19.8
SAVR	4.5	4.5	3.1	0.8	1.7	69.5	15.1	0	7.1
CHOICE									
ESV	4.1	4.1	5.8	0.8	9.9	27.3	4.1	-	17.3
MCS	5.1	4.3	2.6	0	11.1	26.5	9.4	-	37.6
US Pivotal Extreme Risk									
	8.4	8.4	2.3	1.2	8.2	36.7	11.8	1.8	-
FRENCH Registry									
ESV	9.6	7.0	1.9	0.8	2.7	3.5	-	-	115
MCS	9.4	6.7	2.6	1.9	4.5	2.1	-	-	24.2
PRAGMATIC									
ESV	6.4	6.4		1.0	12.3	30.9	3.4		5.9
MCS	8.8	6.9		2.9	9.3	31.8	3.9		22.5
GARY									
SAVR	3.0		1.4		1.9		3.7	-0.03	3.5
TAVI	5.9		1.8		12.3		3.8	1.0	11.9

TAVI = 'transcatheter aortic valve implantation'; SAVR = 'surgical aortic valve replacement'; OMT = 'optimal medical treatment'; AKI = 'acute kidney injury'; PPI = 'permanent pacemaker implantation'; RCT = 'randomized controlled trial'; ESV = Edwards Sapien Valve; MCS = Medtronic CoreValve; AVR = 'aortic valve rerurgitation'; CABG = 'coronary bypass artery surgery'; TV AVI = 'trans vascular aortic valve implantation'; TA AVI = 'trans apical aortic valve implantation'; STS Score = 'Society of Thoracic Surgeons Score'.

thoraxchirurg en 1 interventiecardioloog, neemt op basis van risico('s) en baten van elke behandeloptie een gemotiveerd besluit.[3] Geadviseerd wordt om TAVI 's alleen uit te voeren in een volledig geoutilleerde cardio-interventiekamer of hybride operatiekamer met een luchtbehandelingsysteem conform OK-richtlijnen. Door het College voor Zorgverzekeraars is in 2011 vastgesteld dat een ziekenhuis op jaarbasis minstens 50 TAVI-procedures en minstens 200 aorta- of mitraalklepoperaties dient uit te voeren.

Tabel 3. Essentiële voorwaarden voor succesvolle introductie voor transkatheter-aortaklepvervanging[13]

1	Gespecialiseerde hartcentra met ervaren multidisciplinaire teams bestaande uit artsen en paramedische personeel.
2	Professioneel multidisciplinair hartkleppenteam bestaande uit:
	Thoraxchirurg(en), Interventie cardiolo(o)g(en), echocardiografie-beeldvorming Specialist(en), hartfalen specialist(en) en anesthesist(en).
3	Geprotocolleerde procedures
	Juiste setting van een hartkatheterisatie-afdeling en behandelkamer
	Indien aanwezig een hybride operatieruimte
4	Ontwikkeling van en participatie in klinische databanken voor evaluatie van uitkomsten, praktijkervaring en effectiviteit.
5	Patiënten selectie en complicatiemanagement .
6	Specifieke gestandaardiseerde procedures rondom de organisatie van de TAVI behandeling.
7	Adequate en herhaalde training van alle betrokken teamleden.

KLINISCHE PRAKTIJK IN NEDERLAND IN 2006-2013

In Nederland werd in november 2005 de eerste TAVI uitgevoerd in het Erasmus MC te Rotterdam.[11] Inmiddels zijn er 14 geaccrediteerde ziekenhuizen waar deze procedure wordt verricht. Er zijn een aantal centra in Nederland waar TAVI's onder minimale sedatie worden uitgevoerd, maar in de meeste centra vinden deze ingrepen plaats onder algehele anesthesie. De belangrijkste reden hiervoor is de complexiteit van de ingreep bij een zeer fragiele patiëntencategorie met comorbiditeiten. Toekomstig onderzoek kan op dit vlak meer duidelijkheid geven waarbij risicostratificatie en patiëntenselectie een rol kunnen spelen.

Naast samenwerking in een multidisciplinair team is ook samenwerking met huisartsen, geriaters en neurologen van belang.

Binnen de Nederlandse Vereniging voor Cardiologie is er een aparte werkgroep voor transkatheter-hartklepinterventies, waarin ook leden van de Nederlandse Vereniging voor Thoraxchirurgie zitting hebben. Beide specialismen hebben een gezamenlijk indicatieprotocol opgesteld om te zorgen voor een doelmatige en medisch verantwoorde

indicatiestelling voor TAVI. Hierin is onder andere vastgelegd dat TAVI niet is geïndiceerd bij patiënten met een verhoogd, maar aanvaardbaar operatierisico en dat met een multidisciplinair team moet worden vastgesteld wat een 'aanvaardbaar risico' is (tabel 4).

Tabel 4. Indicatiestelling voor transkatheter-aortaklepvervanging[31vw]

1	a. Patiënt leeftijd > 80 jaar met een geschatte levensverwachting van > dan 1 jaar en logistieke euroscore > 15%. b. Patiënt met 1 of meerdere complicerende factoren waardoor afgewezen of ongeschikt voor conventionele AVR. Indien sprake van geen van bovenstaande: hartteam neemt besluit tot AVR. Indien sprake van a of b: hartteam neemt geen besluit maar overlegt met hartkleppenteam van een chirurgisch centrum waar ook transkatheter-hartklepimplantaties worden uitgevoerd
2	Eerste beoordeling in een hartteambespreking in aanwezigheid van een interventiecardioloog en een cardiochirurg.
3	Voorlopige acceptatie, evt. terug verwijzing naar hartteam en aanvraag aanvullend onderzoek.
4	Verschillende behandelopties: medicamenteus, conventioneel en TAVI.
5	Akkoord patiënt.
6	Definitief besluit in hartteam en percutane-kleppenteam van keuze van behandeling: · Transkatheter-aortaklepvervanging; · Chirurgische aortaklepvervanging; · Medicamenteus beleid.

Op gebied van zorg en nazorg is inmiddels een professioneel netwerk ontwikkeld waarbij de specialisten en zorginstellingen nauw samenwerken met de overheid en zorgverzekeraars. In het belang van verdere ontwikkeling op gebied van de materialen is een interactie tussen de klinische praktijk en de fabrikanten van belang. Deze ontwikkelingen zijn erop gericht om het risico op complicaties tijdens en na de procedure verder te reduceren. Het gebruik van filtersystemen, kleinere maten canules en een tweede-generatiehartklep met mogelijk een verminderd risico op para-valvulaire lekkage en geleidingsstoornissen zijn actueel.

CONCLUSIE

Transkatheter-aortaklepvervanging heeft zich sinds 2002 ontwikkeld tot een volwaardige behandeling voor patiënten met symptomatische ernstige aortaklepstenose en een te hoog operatierisico. Uit de resultaten van de eerste studies blijkt dat TAVI na 1 jaar een afname van de mortaliteit en een afname van de ernst van het hartfalen tot gevolg heeft bij patiënten die niet in aanmerking komen voor chirurgie. Naast de dagelijkse klinische praktijk blijft wetenschappelijk onderzoek van belang om verdere ontwikkelingen en verbeteringen aan te tonen en te realiseren. Mogelijkheden om jongere generaties patiënten met aortaklepstenose en een licht verhoogd risico te behandelen

via TAVI worden momenteel nader onderzocht waarbij risicostratificatie een centrale rol speelt in de besluitvorming en behandelstrategie bij aortaklepstenose.[5] De verwachting is dat er in de toekomst steeds meer patiënten behandeld zullen worden met een TAVI.

LEERPUNTEN

- De prevalentie van aortaklepstenose stijgt met de leeftijd, bedraagt 3-5% bij personen > 75 jaar en de aandoening wordt vooral gezien bij oudere patiënten.
- Als bij aortaskleptenose klachten zoals vermoeidheid, dyspneu, verminderd inspanningsvermogen, syncope, angina pectoris of een verminderde kamerfunctie aanwezig zijn, is de prognose slecht, met een jaarlijkse kans op sterfte van 30%.
- Tot voor kort was een chirurgische klepvervanging de meest aangewezen behandeling bij patiënten met aortastenose.
- Bij een transkatheter-aortaklepvervanging (TAVI) wordt een biologische klep via de A. femoralis, A. subclavia, aorta ascendens of de apex cordis onder röntgendoorlichting geïmplanteerd.
- TAVI is minder ingrijpend dan een conventionele aortaklepvervanging, omdat het borstbeen niet wordt geopend, het hart niet wordt stilgelegd, er geen hart-longmachine nodig is en deze onder lokale verdoving met sedatie uitgevoerd kan worden.

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Incidence, determinants and consequences of delirium in older patients after Transcatheter Aortic Valve Implantation

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ABSTRACT

Background

Delirium is an event leading to negative health outcomes and increased mortality in patients. The aim of this study is to investigate the incidence, determinants and consequences of postoperative delirium (POD) in older patients undergoing transcatheter aortic valve implantation (TAVI).

Methods

The TAVI Care & Cure program is a prospective, observational registry in patients referred for TAVI at the Erasmus University Medical Centre. Presence of delirium was evaluated by daily clinical assessment by a geriatrician pre- and up to three days post TAVI. Mortality data were obtained from the Dutch Civil Registry.

Results

543 patients underwent TAVI between January 2014 and December 2017. Overall, the incidence of POD was 14% (75/543 patients) but declined from 18% in 2014 to 7% in 2017 (p=0.009). Patients who developed POD were older (81.9±5.8 vs 78.6±8.3 years, p<0.001), had higher prevalence of renal dysfunction and prior stroke (54% vs 40%,p=0.02; 31% vs 18%,p=0.01) and were more often frail (32% vs 25%, p=0.02). From a procedural perspective, general anesthesia (OR 2.31,95% CI 1.40-3.83,p = 0.001), non-transfemoral access (OR 2.37,95% CI 1.20-4.70,p = 0.01) and longer procedural time (OR 1.01,95% CI 1.01-1.02,p<0.001) were significantly associated with POD. One-year survival rate was 68% among patients who had suffered a POD and was 85% in patients without a POD (HR 1.8 (95% CI 1.01-3.10), p=0.045)

Conclusion

POD frequently occurs after TAVI and is associated with increased mortality. It might be speculated that patient selection and the minimalistic approach of TAVI may reduce the frequency of delirium.

Keywords: Aortic Stenosis (AS) - Postoperative Delirium (POD) - Transcatheter aortic valve implantation (TAVI) – Mortality, Older people.

Keypoints

- Delirium after Transcatheter aortic valve implantation (TAVI) occurs frequently.
- Delirium after Transcatheter aortic valve implantation (TAVI) is associated with increased mortality.
- Patient selection and minimalistic approach of Transcatheter aortic valve implantation (TAVI) may reduce postoperative delirium.

INTRODUCTION

The incidence of delirium after transcatheter aortic valve implantation (TAVI) is reported to vary between 12 and 53% and proved to exert a significant and negative impact on hospital stay and long-term mortality, especially in frail and older patients [1-6]. TAVI is increasingly used to treat patients with aortic stenosis and as a result of increased experience, new generation heart valves and minimizing the treatment itself, periprocedural complications have decreased [7-11]. The impact of better procedural outcomes on the incidence of postoperative delirium (POD) are thus far unknown.

Notwithstanding the expansion of the indication of TAVI to low risk patients[12], the majority of patients who undergo TAVI have an advanced age with a high risk of POD given the presence of substantial co-morbidity and frailty[13-15].

The aim of this study is to investigate the incidence, determinants and consequences of POD in older patients undergoing TAVI, as well as the consequences of the changes in TAVI practice on the incidence on delirium.

METHODS

Patient selection

The study population consists of 543 consecutive patients who received TAVI because of severe aortic stenosis between January 2014 and December 2018 and who were enrolled in the TAVI Care & Cure program [16]. In brief, the TAVI Care & Cure program is a prospective single-center multidisciplinary observational cohort study that was initiated in November 2013 and consists of a prospective collection of a comprehensive set of predefined cardiovascular and non-cardiovascular data including a comprehensive geriatric assessment (CGA), baseline characteristics in addition to procedural and postoperative data of all patients referred for- and treated with TAVI. There were no specific exclusion criteria. Treatment decision and strategy was decided during the multidisciplinary heart team meeting (interventional cardiologists, cardiac surgeons, anesthesiologist, geriatricians and a TAVI-nurse coordinator) [17, 18]. The TAVI Care & Cure program was approved by the Medical Ethics Committee of the Erasmus Medical Center (MEC-2014-277) and was conducted according to the Helsinki Declaration. All patients provided written informed consent.

Study measurements

Cardiology assessment

Cardiology assessment included patient's history, presence of symptoms using the New York Heart Association (NYHA) and the Canadian Cardiovascular Society (CCS) score, physical examination, electrocardiogram (ECG), transthoracic echocardiography, coronary angiography and multislice computed tomography (MSCT) as described before[19, 20].

Geriatric assessment

Frailty was defined by the Erasmus Frailty Score (EFS) that has been reported to be associated with post-operative delirium and one-year mortality [15]. The EFS uses 5 geriatric domains that are relevant for this specific population; cognition was measured by the mini mental state examination (MMSE) [21]), strength by the Hand Grip Strength Test [22]), (mal)nutrition by the Malnutrition Universal Screening Tool (MUST) [23]), inactivity in basic activities of daily living (measured by the Katz index (Katz ADL) [24] and inactivity in instrumental activities of daily living (measured by the Lawton and Brody index) [25]. Patients were considered frail if the score on 3 or more domains were below predefined standard cut off points[15].

TAVI procedure

TAVI was initially performed under general anesthesia and from September 2015 onwards under local anesthesia, using the transfemoral approach as default choice. After TAVI, patients were admitted to the intensive care unit for early monitoring for a minimum of 4 h and then transferred, if no conduction disturbances or hemodynamic events occurred, to the general cardiology ward with telemonitoring facility.

Delirium assessment and management of delirium

One day before TAVI, all patients were seen by the geriatrician to assess the risk of delirium based on known risk factors of post-operative delirium [1, 3]. All patients were given information on symptoms of delirium and non-pharmacological intervention for delirium prevention were taken. From the day of admission up to 4 days post TAVI, a geriatrician evaluated patients on a daily basis. Delirium was defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

Delirium features necessary for diagnoses were: acute onset and fluctuating coarse AND inattention AND/OR disorganized thinking AND/OR altered level of consciousness AND/OR hallucinations. The diagnosis of delirium was made by clinical diagnosis of a geriatrician and was based on the psychiatric examination of the patient. Patients were seen by a geriatrician at least once a day on a daily basis and besides the evaluation of

the patient, we continuously evaluated with the nursing staff on the cardiology ward to learn if there was any fluctuations in symptoms during the day or overnight. When caregivers of patients were present, we evaluated with the caregivers symptoms and fluctuations of symptoms.

Severity of delirium was defined by the Delirium Observation Score (DOS)[26]. In case of delirium, patients were treated according to current national guideline 'Delirium in adults', Dutch Geriatrics Society[27].

Outcome measures

The primary objective of this study is the incidence and predictors of delirium after TAVI. Secondary objective was the impact of delirium on all-cause mortality within one year after TAVI. The Dutch Civil Registry was used for the collection of all-cause mortality data.

Data management and statistical analysis

All data was entered into a dedicated online database hosted on an internal server. Categorical variables are presented as numbers and percentages. Differences between patients with and without delirium were compared with the chi-square or Fisher's exact test, as appropriate. Continuous variables are expressed as means with standard deviation (± SD) or median values with corresponding interquartile ranges (IQR). Differences within the two groups were compared using the independent t-test or its non-parametric equivalents, respectively. Univariate analysis was performed, variables with a p-value < 0.10 was entered in the multivariate regression models.

For the multivariate model, covariates were operationalized as follows: 1) Prior stroke: Transient Ischemic Attack or Cerebrovascular Accident prior to TAVI; 2) Renal dysfunction: estimated Glomerular Filtration Rate (eGFR) < 50 ml/min; 3) Limitation of mobility (gait speed): Walking speed < 1.0 m/s; 4) Frailty Measured with the Erasmus Frailty Score: 5 component score, frail when 3 components are scored below predefined cut off points.

For the outcome incidence of delirium, Odds ratios (OR) and corresponding 95% confidence interval (95% CI) were computed with multivariate logistic regression analysis. We tested multicollinearity for the multivariate regression model. Obtained VIF values ranged between 1 and 2. Cox regression analysis was performed to investigate the association between delirium and mortality. The multivariate model was based on the results form a univariate analysis for the outcome 'one year mortality'. Variables with a p-value <0.10 were entered in the multivariate regression models. Hazard ratio's (HR) and corresponding 95% confidence interval were computed. To investigate the changes over time, patients were divided into four cohorts, depending on the year in which the

TAVI took place: cohort 1: 2014; cohort 2: 2015; cohort 3: 2016; cohort 4: 2017. Categorical variables were compared using the chi-square test, while continuous variables were compared with the ANOVA test. Statistical significance across the years was calculated using the chi-square method adjusting the p values after te Bonferroni correction for the proportions. For the continues variables the Games-Howell method was used as a post hoc test. Analyses were performed using SPSS version 21 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Patient Characteristics

Between January 2014 and December 2017 a total of 543 patients underwent a TAVI for symptomatic aortic valve stenosis. Clinical baseline characteristics and procedural features are shown in table 1. Mean age of the population was 79.1 ± 8.0 years and 55% were men. Hypertension (80%), hypercholesterolemia (65%), atrial fibrillation (32%) and diabetes mellitus (32%) were prevalent comorbidities. In this cohort there were no patients with existing diagnosis of dementia (diagnosis noted in primary care records or records from referring hospitals). There were 7 patients (=1.3%) with mild cognitive impairment, but with no interference in daily activities.

The incidence of delirium was 14% (75/543 patients). Patients who developed POD were older (82.1 ±5.8 vs 78.6 ±8.3 years, p<0.001), had higher prevalence of renal dysfunction and prior stroke (54% vs 40%, p=0.02; 31% vs 18%, p=0.01) and were more often frail (32% vs 25%, p=0.02). Cognitive impairment (OR 2.28, 95% CI 1.25-4.13, p=0.007), reduced gait speed (OR 3.69, 95% CI 1.68-10.72, p=0.02), limitation in IADL activity (OR 2.15, 95% CI 1.16-3.98), p=0.02) and the presence of frailty (OR 2.50, 95% CI 1.30-4.82, p=0.006) were significantly associated with POD (table 1).

From a procedural perspective, general anesthesia (OR 2.31, 95% CI 1.40-3.83, p = 0.001), non-transfemoral access (OR 2.37, 95% CI 1.20-4.70, p = 0.01) and longer procedural time (OR 1.01, 95% CI 1.01-1.02, p<0.001) were significantly associated with POD (table 1).

Information on the onset of POD was available for all patients. POD occurred on day 0 and 1 in 68% of the patients. The median onset of POD was day 1 (IQR 0.0-2.0 days) (Appendices 1). The incidence of post procedural stroke (11% vs 3%; p=0.001), new pacemaker implantation (24% vs 14%; p=0.02), vascular complication (24% vs13%; p=0.009), post-operative urinary tract infection (13% vs 2%; p<0.001) and post-operative pneumonia (9% vs 4%; p=0.03) was higher in patients with POD than those without

POD. Yet, independent variables predicting POD were found to be prior stroke (OR 4.29, 95% CI 1.85-9.96, p=0.001), the presence of frailty (OR 2.37, 95% CI 1.12-5.07, p=0.025) and the length of the procedure (OR 1.02, 95% CI 1.01-1.03, p<0.001)(table 2).

Table 1 Baseline characteristics and procedural features of the total study population

Variable (n,%)	All Patients	Delirium		Association with delirium		
	N= 543	Present (n = 75)	Absent (n = 468)	OR	95% CI	P value
Male sex (n, %)	297 (55%)	44 (59%)	253 (54%)	0.83	0.51-1.36	0.48
Age (mean ± SD)	79.1 ± 8.0	81.9 ± 5.8	78.6 ± 8.3	1.06	1.02-1.10	0.001
BMI (mean, SD)	27.3 ± 4.9	27.1 ± 4.2	27.3 ± 5.1	0.99	0.93-1.05	0.76
Aortic valve area, cm^2	0.77 ± 0.25	0.74 ± 0.24	0.78 ±0.25	0.54	0.18-1.60	0.27
Cardiovascular risk factors						
Diabetes mellitus	176 (32%)	20 (27%)	156 (33%)	0.73	0.42-1.26	0.25
Hypertension	432 (80%)	62 (83%)	370 (79%)	1.26	0.67-2.39	0.47
Hypercholesterolemia	352 (65%)	45 (60%)	307 (66%)	0.79	0.48-1.30	0.35
Comorbidities						
Prior MI	118 (22%)	18 (24%)	100 (21%)	1.16	0.65-1.06	0.61
Prior Stroke	108 (20%)	23 (31%)	85 (18%)	1.92	0.98-3.76	0.01
Renal dysfunction	227 (42%)	40 (54%)	187 (40%)	1.76	1.07-2.88	0.02
COPD	117 (22%)	13 (18%)	104 (22%)	0.74	0.39-1.40	0.35
Symptoms						
NYHA class III/IV	358 (66%)	53 (72%)	305 (65%)	1.34	0.78-2.30	0.25
Angina CCS class III/IV	64 (13%)	8 (11%)	56 (13%)	0.88	0.40-1.93	0.74
Frailty indices (n=330)						
Cognitive impairment	107 (31%)	26 (48%)	81 (28%)	2.40	1.34-4.39	0.003
Malnutrition probable	38 (11%)	8 (15%)	30 (10%)	1.60	0.69-3.70	0.29
Reduced gait speed	219 (67%)	41 (79%)	178 (38%)	2.09	1.03-4.26	0.04
Reduced muscle strength	160 (48%)	302(62%)	128 (45%)	1.94	1.06-3.55	0.03
Limitation in ADL activity	107 (30.4%)	19 (35%)	88 (30%)	1.30	0.70-2.39	0.41
Limitation in IADL activity	189 (54%)	37 (69%)	152 (51%)	2.09	1.13-3.88	0.02
Frailty identified (EFS)	97 (28.5%)	24 (32%)	71 (25%)	2.60	1.41-4.80	0.002
Procedural features						
General anesthesia	232 (43%)	45 (59%)	187 (40%)	2.31	1.40-3.83	0.001
Non-transfemoral access	51 (9%)	13 (17%)	38 (8%)	2.37	1.20-4.70	0.01
Cerebral protection	274 (51%)	36 (49%)	238 (51%)	0.93	0.57-1.53	0.78
Procedure time, minutes (mean ± SD)	140 ± 61.5	184 ± 93.4	133 ± 51.6	1.01	1.01-1.02	<0.001

Values are n(%), mean ± SD. Abbreviations used: BMI = Body Mass Index, MI= Myocardial infarction, COPD= Chronic obstructive pulmonary disease, NYHA= New York Heart Association, CCS = Canadian Cardiovascular Society, ADL= Activities of Daily Living, IADL= Instrumental Activities of Daily Living, EFS = Erasmus Frailty Score.

The presence of POD was associated with prolonged in-hospital stay, independent of other periprocedural complications (uncomplicated TAVI 8.2 vs 7.5 days, p=0.003 and complicated TAVI 17.8 vs 11.1 days, p<0.001).

Impact of POD on Mortality during follow up.

Median follow up was 1.4 years (IQR: 0.6 to 2.5 years), overall mortality was 29,5% (n=190). One-year survival rate was 68% among patients who had suffered POD and 85% in patients without POD (HR 1.8 (1.01-3.10), p=0.045)(figure 1).

Table 2 predictors for POD within a multivariate model

Variable	OR	95% CI	p-value
Age	1.06	0.99-1.13	0.097
Prior stroke	3.10	1.49-6.47	0.003
Renal dysfunction	1.18	0.57-2.48	0.655
Limitation of mobility (Gait speed)	1.04	0.44-2.46	0.926
Frailty identified (EFS)	2.37	1.12-5.07	0.025
General anesthesia	1.71	0.70-4.20	0.24
Non transfemoral access	1.07	0.35-3.31	0.905
Procedural time (min)	1.02	1.01-1.03	<0.001
Abbreviations used: EFS= Erasmus Frailty Score			

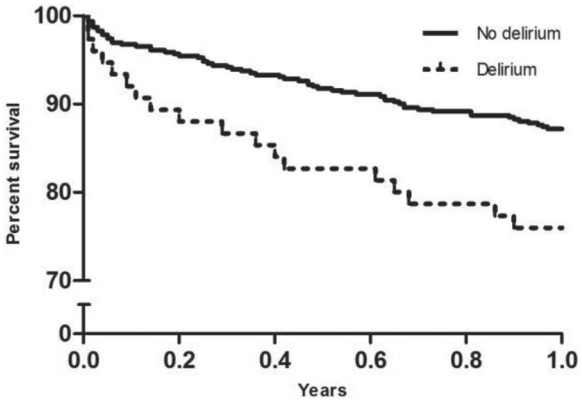

Figure 1 One year mortality of patients with and without a delirium
One year mortality of patients with and without delirium.
HR 1.8 (1.01-3.10), p=0.045. Adjusted for age, sex, dyslipidemia, atrial fibrillation, New York Heart Association class 3 or 4, renal dysfunction

Changes over time

In the period from January 2014 to December 2017, the mean age, prevalence of frailty and prior stroke of patients who underwent TAVI remained the same (p=0.332,p>0.999 and p=0.467 respectively). Yet, the proportion of patients with renal dysfunction was higher in those treated in 2014 and 2015 versus those treated in 2016 and 2017 (53% and 52% vs 37% and 32% respectively, p<0.001). The main change was found to be of procedural nature; the use of general anesthesia fell from 100% in 2014 to 19% in 2017 (p<0.001), non-transfemoral access dropped from 18% in 2014 to 8% in 2017(p=0.08) and procedure time was reduced from 191.6 ±65.7 min. in 2014 to 91.0 ± 37.8 min. in cohort 2017 (p<0.001) (Appendices 2). During this observation period, the incidence of delirium decreased from 18% in 2014 to 7% in 2017 (p=0.009).

DISCUSSION

In this study we found that delirium frequently occurs after TAVI in older patients and is associated with increased mortality. Frailty and prior stroke as well as procedural time were independent predictors of POD.

Frailty is known to be a risk factor of POD in patients undergoing TAVI and can be explained by the fact that frailty is the result of reduced physical, cognitive and social functioning and, thus, associated with a reduction of an adaptive or reserve capacity in case of stressors. [14, 15, 28, 29]. Despite the minimal invasive nature of TAVI, this procedure remains a stressful event in particular when considering the profile of patients undergoing TAVI who are in general old and have multiple comorbidities and frailty. Age remains and will remain advanced in patients undergoing TAVI as shown in this study in addition to the ageing society, notwithstanding the expansion of indication of TAVI to lower risk patients [13]

According with previous studies, we found prior stroke to be a predictor of POD [1, 2, 5, 30]. In the present analysis, prior stroke was associated with a 4-fold increased risk of POD. The risk factors for stroke overlap with those of cognitive impairment and dementia [31], which are also associated with increased risk for delirium [15, 32].

Not unexpectedly, procedural factors predicted POD. Previous studies have shown that the use of general anesthesia and the non-transfemoral access may lead to a 4-fold increase on POD [2, 28]. In the present study, we found by multivariable analysis that procedure time was the only independent procedural factor predicting POD.

There is still controversy on the effect of the anesthetic technique (general vs. local anesthesia) on POD [2, 33]. General anesthesia has been linked to post-operative cognitive dysfunction, but it has not been shown to have the same effect on POD, when considering POD a form of temporary cognitive dysfunction [34]. In the present study, the use of general anesthesia dropped from 100% in 2014 to 20% in 2017, in conjunction with a similar decrease in procedure time and a slight increase of transfemoral TAVI to 92% following a global trend in minimizing the invasive nature of TAVI[35-37]. Yet, the effect of these procedural changes have not systematically been assessed in relation to POD, although one intuitively would expect a beneficial effect on the occurrence of POD as shown in this study (i.e. a reduction of > 10% over 4 years).

One of the possible confounders in the assessment of the incidence of POD in the present study is the fact that the geriatrician assessed the risk of POD before TAVI in the framework of the TAVI Care & Cure program and implemented preventive measures if deemed necessary. It has been shown that preventive strategies, can lead to a 30% reduction in POD [38-40]. We have no control group with patients who did not receive delirium preventive measures, and therefore we could not add the presence or absence of delirium prevention into the multivariate model. Yet, we believe that both this delirium preventive strategy in conjunction with minimizing the TAVI procedure to a PCI-like intervention explains the reduction in POD in this study[41]. In addition to the limitation already addressed above, one must also acknowledge that the present analysis stems from a single center observational study conducted in a tertiary referral center. The population and findings may, therefore, not be representative for a general population of patients.

In addition to observation bias inherent to an observational study without independent adjudication of outcomes, some variables associated with POD such as cognitive impairment and dependence in IADL activity were not available for all patients. There were no patients in the cohort with existing diagnosis of dementia found in primary care records or records from referring hospitals. We performed a cognitive analysis in 330 out of 543, therefor there is a chance we underestimated the presence of mild cognitive impairment in our study cohort.

Concerning the data extracted from our CGA: a complete data set was available in 330 patients. The current study numbers are based on complete case analysis. There were no baseline differences on cardiovascular and non-cardiovascular data between those with and without CGA.

In conclusion, delirium occurs frequently after TAVI in older patients and is associated with impaired prognosis. Given the ageing of the general population, the burden of delirium post TAVI will remain a matter of concern notwithstanding the expansion of TAVI to lower risk patients. It can be speculated whether patient selection and the minimalistic approach on TAVI might lower the incidence of delirium.

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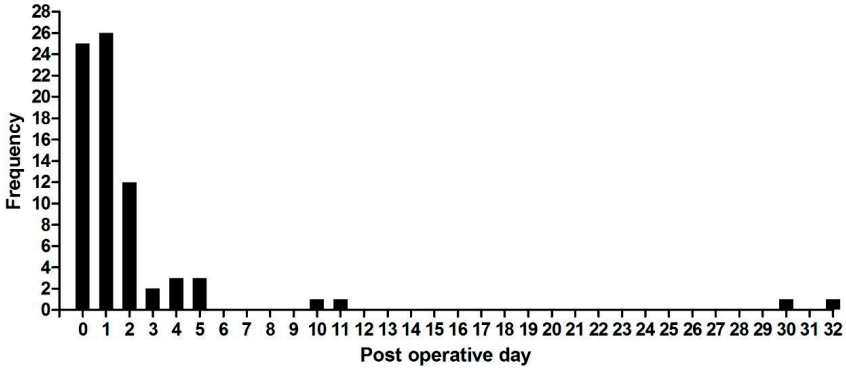
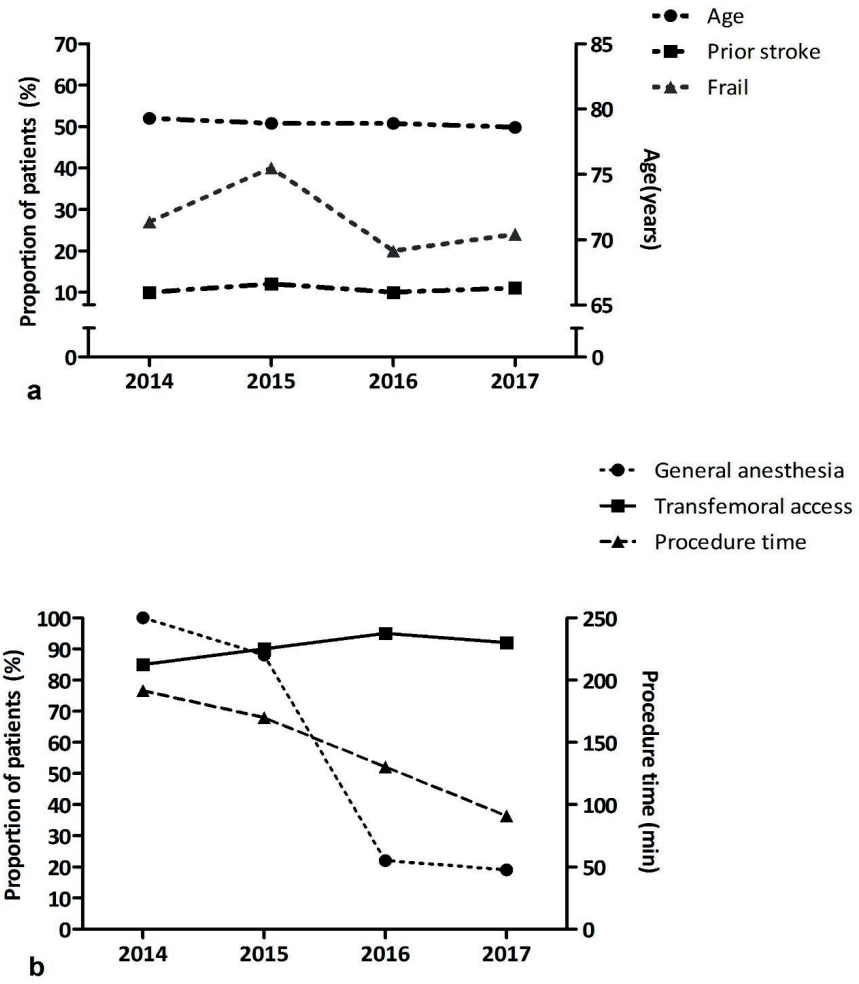
SUPPLEMENTARY MATERIAL

Supplementary Data

Appendices 1: Time of delirium onset after TAVI



Appendices 2: Changes in patient characteristics (a) and TAVI features over time (b).



6

Impact of frailty on health-related quality of life 1 year after transcatheter aortic valve Implantation

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ABSTRACT

Background

Transcatheter aortic valve implantation (TAVI) brings symptom relieve and improvement in Health Related Quality of life (HRQoL) in the majority of patients treated for symptomatic, severe aortic stenosis. However, there is a substantial group of patients that do not benefit from TAVI. The aim of this study is to investigate the impact of frailty on HRQoL one year after TAVI.

Methods

The TAVI Care & Cure program is an ongoing, prospective, observational study including patients referred for TAVI to our institution. A comprehensive geriatric assessment was performed to evaluate existence of frailty using the Erasmus Frailty Score (EFS). HRQoL was assessed using the EQ-5D-5L at baseline and one year after TAVI.

Results

239 patients underwent TAVI and completed HRQoL assessment one year after TAVI. Seventy (29.3%) patients were classified as frail (EFS ≥ 3). In non-frail patients the EQ-5D-5L index did not change (0.71(± 0.22) to 0.68(± 0.33) points, p=0.22), in frail patients the EQ-5D-5L index decreased from 0.55(±0.26) to 0.44 points(±0.33) (p=0.022). Frailty was an independent predictor of deteriorated HRQoL one year after TAVI (OR 2.24, 95% CI 1.07-4.70, p=0.003). In frail patients, absence of peripheral artery disease (OR 0.17, 95% 0.05-0.50, p=0.001) and renal dysfunction (OR 0.13, 95% CI 0.04-0.41, p=<0.001) at baseline was associated with improved HRQoL one year after TAVI.

Conclusion

Frailty is associated with deterioration of HRQoL one year after TAVI. Notably, HRQoL did improve in frail patients with no peripheral arterial disease or renal impairment at baseline.

Keywords: Aortic stenosis (AS),Transcatheter aortic valve implantation (TAVI), Mortality, Quality of life, EQ-5D, Frailty, Older people

Key points

- Frailty is an independent predictor of deteriorating quality of life 1 year after TAVI.
- In frail patients, quality of life deteriorated 1 year after TAVI with no change in self-rated health status.
- In frail patients, the absence of peripheral artery disease and renal dysfunction is associated with improvement of quality of life.
- In non-frail patients, quality of life did not deteriorate, and self-rated health status improved.

INTRODUCTION

Aortic stenosis (AS) is a common valve disease in older patients affecting about 3% of the population above 65 years. If not treated, the risk of mortality and deterioration of Health Related Quality of Life (HRQoL) is high [1-3]. HRQoL of patients with severe AS is impaired due to symptoms of impaired exercise tolerance, dyspnea and eventually angina pectoris and/or syncope [4]. TAVI is increasingly used to treat patients with AS and is proven to be safe and effective in a wide variety of patient groups, including older patients [5-7]. Although the indication for TAVI has expanded to low risk patients, the majority of patients who undergo TAVI are old and frail and have substantial comorbidities. For this specific population, the absolute gain in years may be of less importance than improving their HRQoL.

Previous studies showed an improvement of HRQoL in the majority of patients who underwent TAVI [8-10]. However, some patients do not report improvement in HRQoL [10, 11]. Little is known on the factors determining lack of improvement of even deterioration of HRQoL after TAVI. Frailty has proven to be associated with an increased mortality and a higher rate of poor outcome up to one year after TAVI [12, 13], but studies on the impact of frailty on HRQoL after TAVI are limited[11]. The aim of this study, therefore, is to investigate the potential impact of frailty on HRQoL after TAVI.

METHODS

Study population

The study population consists of 239 patients who underwent TAVI (November 2013 – June 2018) within the frame work of the TAVI Care & Cure program[14]. In brief, the TAVI Care & Cure program is a prospective single-center multidisciplinary observational cohort study that was initiated in November 2013 and consists of a prospective collection of a comprehensive set of predefined cardiovascular and non-cardiovascular data including a comprehensive geriatric assessment (CGA) and baseline characteristics in addition to procedural and postoperative data of all patients referred for and treated with TAVI. There were no specific exclusion criteria. Treatment decision and strategy were decided during the multidisciplinary heart team meeting (interventional cardiologists, cardiac surgeons, anesthesiologists, geriatricians and a TAVI-nurse coordinator) [15, 16]. The TAVI Care & Cure program was approved by the Medical Ethics Committee of the Erasmus Medical Center (MEC-2014-277) and was conducted according to the Helsinki Declaration. All patients provided written informed consent.

Cardiology assessment

Cardiology assessment included determining symptoms using the New York Heart Association (NYHA) classification and the Canadian Cardiovascular Society (CCS) grading of angina pectoris, medical history including cardiovascular and non-cardiovascular comorbidities (Appendices 1 for the complete list of co-morbidities), physical examination, laboratory assessment and electrocardiogram. Echocardiography, coronary angiography and multislice computed tomography (MSCT) were examined to evaluate the condition of the aortic valve and to determine access site [17].

Comprehensive Geriatric Assessment

In the CGA the following frailty domains and instruments were examined: cognition; measured by the Mini Mental State Examination (MMSE) [18], strength; measured by the Hand Grip Strength Test [19], (mal)nutrition; measured by the Malnutrition Universal Screening Tool (MUST) [20], inactivity in basic activities of daily living; measured by the Katz index (Katz ADL) [21]; inactivity in instrumental activities of daily living; measured by the Lawton and Brody index [22]; limitation of mobility using the Timed Up and Go Test (TUGT)[23] and 5 Meter Gait Speed Test (5MGST) [24]. A comprehensive explanation of the frailty domains and cut-off points can be found in Appendices 2. Frailty was defined by the Erasmus Frailty Score (EFS) that has been reported to be associated with post-operative delirium and one-year mortality[12]. The EFS uses 5 geriatric domains; cognition, strength, (mal)nutrition, inactivity in basic activities of daily living and inactivity in instrumental activities of daily living. Patients were considered frail if the score on 3 or more domains was below predefined standard cut off points[12]. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) was used to rate existing co-morbidities, measuring chronic medical illness burden while taking into account the severity of the chronic disease in 14 items representing individual body systems. The cumulative final score can vary theoretically from 0 to 56. The severity index is calculated dividing the total score through the total number of categories endorsed [25].

Quality of Life measurement

HRQoL was assessed using the EuroQol 5 dimensions questionnaire (EQ-5D-5L) pre operatively and one-year after TAVI. The EQ-5D-5L is a generic health utility HRQoL instrument and is qualified for measuring health status within an older population [26]. The EQ-5D-5L consists of 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which is divided in five levels of functioning: no problems (level 1), some or moderate problems (level 2 and 3), and severe or extreme problems (level 4 and 5). Based on the responses to these dimensions, a single index value is estimated using a general population-based algorithm, ranging from -0.446 to 1 (a value of 1 indicating full health, while a value lower than 0 represents a status

considered to be worse than death). The EQ-5D index value scores are country specific. Value sets and coefficients for the Dutch population were used for the estimations of the individual EQ-5D index [27]. The second component of the EQ-5D-5L is the VAS-score (Visual Analogue Scale). This is a standardized instrument to assess self-rated health on a scale with a scoring range from 0 (worst imaginable health state) to 100 (best imaginable health state) [28]. To incorporate data on mortality into the EQ-5D-5L outcome, we divided our patient group into patients with either improvement or deterioration in HRQoL one year after TAVI. Improvement was defined as survival without any worsening in the EQ-5D index one year after TAVI compared to baseline. Deterioration was defined as death within one year or a decrease in the EQ-5D-5L index one year after TAVI. This approach is comparable to a method previously used for the Kansas City Cardiomyopathy Questionnaire [29].

TAVI procedure

TAVI was initially performed under general anesthesia and from September 2015 onwards under local anesthesia, using the transfemoral approach as default choice. After TAVI, patients were admitted to the intensive care unit for early monitoring for a minimum of 4 h before transferring to the general cardiology ward. From the day of admittance up to at least three days after procedure, the geriatric consulting team is involved in delirium vigilance and preventing functional decline during admission.

Statistical Analysis

Continuous data are expressed as mean values with standard deviations ± SD. Differences between patients who were frail and non-frail were compared with non-parametric equivalents (Mann-Whitney-U and Wilcoxon test). Categorical values were noted as percentages and differences between patients who were frail and non-frail were compared with the chi-square test or Fisher's exact test as appropriate. Paired sample t tests were used to analyze the difference between HRQoL measurements on baseline and one-year follow up. The Reliable Change Index (RCI) was calculated measuring the difference between the EQ-5D-5L index value on baseline and the EQ-5D-5L index value at follow up divided by the standard error of the difference between both EQ-5D-5L index values. For the outcome deterioration of HRQoL one year after TAVI, univariate analysis was performed, entering variables with a p-value < 0.10 in the multivariate regression models. For the multivariable model Odds ratios (OR) and corresponding 95% confidence interval (95% CI) were computed, adjusted for age, sex, EQ-5D-5L index on baseline, current smoking, peripheral artery disease, renal dysfunction, limitation of mobility (5 Meter Gait Speed Test) and frailty (EFS). p value < 0.05 (two-tailed) was considered statistically significant. Statistical analysis were performed using IBM Statistical Package for Social Science (SPSS) for Windows version 25.

Table 1 Baseline characteristics (n=239)

Age (years, ±SD)	80.8 (±6.5)
Male gender (%)	119 (49.8%)
BMI (kg/m^2, ±SD)	27.2 (± 4.9)
Cardiovascular risk factors	
Hypertension (%)	197 (82.8%)
Current smoker (%)	23 (10.2%)
Diabetes mellitus (%)	79 (33.1%)
Hypercholesterolemia (%)	151 (63.2%)
Peripheral artery disease (%)	108 (45.2%)
Comorbidities	
CIRS G score (points, ±SD)	15.4 (±4.4)
CIRS G index (points, ±SD)	1.90 (±0.3)
Symptoms	
NYHA class 3 or 4 (%)	149 (62.3%)
Angina CCS classification 3 or 4 (%)	29 (12.1%)
Vertigo (%)	93 (38.9%)
Echocardiography:	
Aortic valve area (cm^2, ±SD)	0.8 (±0.2)
Peak AoV PG (mmHg, ± SD)	66.4 (±21.6)
Peak AoV velocity (m/s, ±SD)	4.0 (±0.7)
Frailty indices:	
Cognitive impairment probable (%)	74 (31%)
Malnutrition probable (%)	27 (11.3%)
Limitation of mobility, TUGT (%)	35 (14.6%)
Limitation of mobility, 5MGS (%)	153 (64%)
Reduced muscle strength, (%)	113 (47.3%)
Limitation in ADL activity (%)	70 (29.3%)
Limitation in iADL activity (%)	128 (53.6%)
Erasmus Frailty Score ≥ 3 (%)	70 (29.3%)

Abbreviations used: BMI: body mass index; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; NYHA: New York Heart Association functional class; CCS: Canadian Cardiovascular Society; AoV: Aortic Valve; PG: Pressure Gradient; TUGT: Timed Up and Go test; 5MGS: 5 Meter Gait Speed Test; ADL: activities of daily living; iADL: instrumental activities of daily living.

RESULTS

Patients characteristics

A total of 239 patients with severe symptomatic AS who underwent TAVI between November 2013 and May 2019 were assessed with CGA at baseline. 197 patients completed HRQoL follow-up after 12 months and forty-two patients died within 12 months after TAVI. The mean age of patients was 80.8 ± 6.5 years and 49.8 % were men. Seventy (29.3%) patients were frail (Erasmus Frailty Score ≥ 3). Detailed baseline characteristics are shown in Table 1.

New York Heart Association Functional Class

Pre-operatively, 62.3% (n=149) were in NYHA class III or IV (Frail patients 81.4%; non-frail patients 54.5%, p<0.001). One year after the procedure, 51.5% of the frail patients reported an improvement in NYHA functional class compared to 60.6% of non-frail patients (p=0.224). One year after TAVI, 20.4% of the frail patients were still in NYHA class III or IV vs. 14.3% of the non-frail patients (p=0.67) (Appendices 3).

Table 2 Quality of life at baseline and 12 months follow-up in frail and non-frail patients

Frail patients	Baseline	12 months	P value *
EQ-5D index	0.55 (± 0.26)	0.44 (±0.33)	0.022
EQ-VAS	58.4 (±16.8)	63.4 (±14.6)	0.095
Non-Frail patients			
EQ-5D index	0.71 (±0.22)	0.68 (±0.33)	0.22
EQ-VAS	66.2 (±16.8)	72.0 (±14.8)	<0.001
Values are expressed as means (±). VAS: Visual Analogue Scale			

Table 3 Predictors of deterioration of Quality of life one-year after TAVI

Variable	**OR**	**95%CI**	**p-value**
Age	1.01	0.96-1.07	0.647
Gender	1.13	0.56-2.27	0.737
Eq5D-5L index on baseline	10.62	2.32-48.52	0.002
Current smoker	3.21	1.06-9.77	0.040
PAD	1.40	0.73-2.66	0.312
Renal dysfunction	2.12	1.11-4.04	0.023
Limitation of mobility (5mGST)	2.29	1.35-6.17	0.006
Frailty (EFS)	2.25	1.07-4.70	0.003
Abbreviations used: PAD; Peripheral Arterial Disease, 5mGST; 5 meter Gait Speed Test, EFS; Erasmus Frailty Score.			

Quality of life one year after TAVI (Eq-5D-5L)

Improvement of HRQoL was seen in 125 patients (52.3%). Deterioration and/or death within one year was found in 110 patients (46.0%). Improvement of HRQOL at one-year after TAVI was seen more often in non-frail patients as compared to frail patients (58.3% versus 39.7% respectively, p=0.014). In frail patients, the EQ-5D-5L index decreased from 0.55 points (±0.26) at baseline to 0.44 points (±0.33) at one year (p=0.022). The VAS score did not change (58.4 points (±16.8) and 63.4 points (± 14.6) (p= 0.095). In non-frail patients, the EQ-5D-5L index did not change from baseline to one year after TAVI (0.71 points (±0.22) vs 0.68 points (±0.33) (p=0.22), but the VAS score did increase (66.2 points (±16.8) to 72.0 points ±14.8) <0.001) (Table 2). The RCI was 2.2, concluding changes in EQ-5D-5L index values are assumed to be reliable.

The baseline Eq5D dimensions and the change in Eq5D dimensions is shown in Appendices 4.

Frailty was an independent predictor of deteriotation of HRQoL one year after TAVI (OR 2.24, 95% CI 1.07-4.70). Current smoking (OR 3.21, 95% CI 1.06-9.77), renal dysfunction (OR 2.12, 95% CI 1.11-4.04) and limitated mobility (5MGST) (OR 2.29, 95% CI 1.35-6.11) were other predictors. (table 3). Post operative delirium was associated with deterioration of HRQoL one year after TAVI in models adjusted for baseline predictors (univariate p-value< 0.10) and baseline QoL status (OR 3.45, 95% CI 1.27-9.4). In frail patients, the absence of peripheral artery disease (OR 0.17, 95% 0.05-0.50) and renal dysfunction (OR 0.13, 95% CI 0.04-0.41) at baseline were associated with improved HRQoL one year after TAVI.

Nineteen (27.1%) frail patients died within one year after TAVI versus 22(13.3%) non frail patients (p=0.014).

DISCUSSION

In this study we found that frailty at baseline is an independent predictor of deterioration of HRQoL one year after TAVI. In frail patients HRQoL deteriorated where the self-rated health status did not change. In non-frail patients HRQoL did not deteriorate and the self-rated health status improved. Importantly, in the absence of peripheral arterial disease and renal impairment frail patients did experience improvement in HRQoL. In both frail and non-frail patients we found an improvement in New York Heart Association functional class after TAVI.

Previous studies found an improvement in HRQoL after TAVI in the majority of patients [8, 10, 30], however, even in large registry studies [10, 30] there was a sizable group of patients who did not derive benefits in terms of improving HRQoL. Several factors including comorbidities, high mortality risk and frailty have been associated with poor outcome after TAVI [11-13, 31, 32]. A previous study found that if frailty was the indication for TAVI, the risk of not improving HRQoL after one year was twice as high compared to patients that had more technical indications for TAVI [8]. A substudy of the PARTNER Trial showed that frailty was associated with impaired HRQoL 6 months after TAVI, but this association was not found after 12 months of follow up, in contrast to our results. In this PARTNER Trial substudy, frailty was estimated by the composite of four items, eg: gait speed, grip strength, ADL scores and albumin and almost 50% of the patients was classified as frail. [11]. In our study we use a different frailty score (EFS) where a more comprehensive set of frailty assessment tools are combined and where 30% of our patients were classified as frail, possibly indicating a more strict definition of frailty. Differences in HRQoL outcomes between the PARTNER Trial substudy and our study could be explained by the difference in frailty definition. There is still a lack of consensus of defining frailty in an optimal frailty assessment[33]. Frail patients are impaired in physical activity, endurance, mobility, strength etc., because of diminished physiological reserve[34, 35], therefore treating AS alone might not be sufficient to improve overall HRQoL because there still remain factors impairing HRQOL [34, 36]. Although we found an improvement in NYHA class in 50% of frail patients, this did not translate into an improvement in general HRQoL. However, in frail patients, the absence of peripheral artery disease and renal dysfunction at baseline was associated with improvement of HRQoL. Renal dysfunction is one of the most frequent comorbidities in TAVI patients and has been found to significantly worsen the prognosis of patients at short and long-term follow up [37]. This study shows that the combination of frailty and certain comorbidities could be associated with a higher chance of not improving HRQoL after TAVI. Although frailty has been associated with higher mortality rates compared to non-frail patients [11-13], survival rates are still higher compared to conservative therapy [38]. The determination of frailty is one of many variables needed in the process of shared decision making: concurrent comorbidities, treatment goals, expectations for the future, possible geriatric interventions, technical possibilities; all these aspects are unbearable for optimizing treatment for this mostly older, frail and comorbid patient population. The treatment of this group of patients calls for intense collaboration between the geriatrician and cardiologist.

This study has several limitations. First, results should be interpreted within the framework of a local population, because of the single-center aspect of this study. Second, the Erasmus Frailty Score has not been formally validated in a different cohort, therefore, it

should not be used in the clinical practice as a risk score to aid decisions. Nonetheless, we do believe that this frailty score is a reflection of the patient's general condition, since it quantifies deficits in geriatric domains essential for optimal functioning in patients. It can be helpful in identifying those patients with frailty and therefore a higher chance of negative outcomes after TAVI.

In addition, the study population is relatively small, however, previously described studies included a similar number of patients. In this study we used the Eq-5D to measure general health-related quality of life. Because of its generality, the Eq-5D might fail to capture and incorporate factors in valueing QoL, such as socio-economic status, home support or incorporating events like falls or rehospitalization.

Further research in a larger cohort focused on post-operative HRQoL and QoL in the broader sense is necessary to evaluate our current findings.

In conclusion, we found that frailty at baseline was associated with deterioration of HRQoL one year after TAVI and with no change of self-estimated health status. However, HRQoL did improve in frail patients with no peripheral arterial disease or renal impairment. Finally, patients who suffered from post-operative delirium had a poorer outcome, necessitating more diligence in delirium prevention strategy.

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SUPPLEMENTARY DATA

Appendix 1: Co-morbidities considered in medical history

- Diabetes Mellitus
- Hypertension
- Dyslipidemia
- Peripheral Artery Disease
- Previous Percutaneous Coronary Intervention
- Previous Coronary Artery Bypass Surgery
- Atrial fibrillation
- Previous Cerebrovascular Accident or Transient Ischaemic Attack
- Pacemaker implantation
- Previous valve intervention
- Pulmonary hypertension
- Chronic Obstructive Pulmonary Disease
- Renal dysfunction
- Previous kidney transplantation
- Any previous or current malignancy
- Gastro-intestinal diseases

Other risk factors for cardiovascular disease:

- Smoking (current/ stopped)
- Family history of cardiovascular disease

Appendix 2: Definition and explanation of the frailty domains tested

Cognition

We screened for cognitive impairment using the Mini Mental State Examination (MMSE). This is a validated screening tool for cognitive performance, scoring van 0 to 30 points maximum. A score of less than 27 points means cognitive impairment is probable [1].

Strength

Hand grip strength was measured using a hand-held dynamometer (Hand dynamometer 90kg/0,1kg EH101, Vetek, Sweden). Hand grip strength is a validated and useful instrument for determining functionality[2]. The best of three measures for the dominant and the non-dominant arm was used for the analysis. Grip strength was stratified by gender. A grip strength of > 20 kg and > 30 kg was considered normal for females and males respectively.

Malnutrition

The Malnutrition Universal Screening Tool (MUST) was used to determine the nutritional status. Scores range from 0 to 6, in which a lower score means a better nutritional status. A MUST score of ≥ 2 points makes malnutrition probable[3].

Inactivity

Activities of Daily Living (ADL)

The Activities of Daily Living are a series of basic activities performed by individuals on a daily basis necessary for independent living at home or in the community. ADL are self-care tasks as bathing, personal hygiene, functional mobility and self-feeding. For scoring the individual's level of assistance we used the Katz ADL index checklist. ADL dependency was defined as having ≥ 1 limited activity [4]

Instrumental Activities of Daily Living (IADL)

The Instrumental Activities of Daily Living are tasks that are not necessary for fundamental functioning, but are tasks necessary to let an individual live independently in a community. IADL tasks include more complex elements like managing housekeeping and money, independently move within the community, preparing meals, taking prescribed medications and using the telephone or other form of communication. The ADL Lawton and Brody index was used for scoring IADL dependency. IADL dependency was defined as ≥ 2 limited activities [5].

Mobility

For examining mobility we used two validated tests: the 5M Gait Speed Test and the Timed Up and Go test. A gait speed of ≤ 1m/s is suspect of moderate or severe limitation of mobility [6]. Slowness was evaluated with the Timed Up and go Test. A timed up and go test of ≥20 seconds is confirming moderate or severe limitation of mobility[7].

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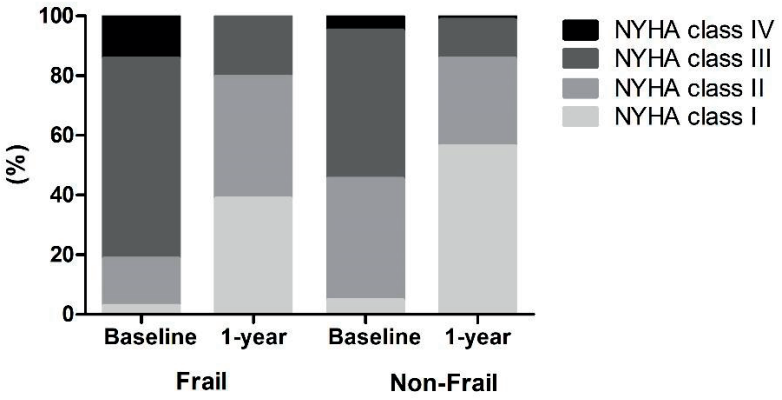
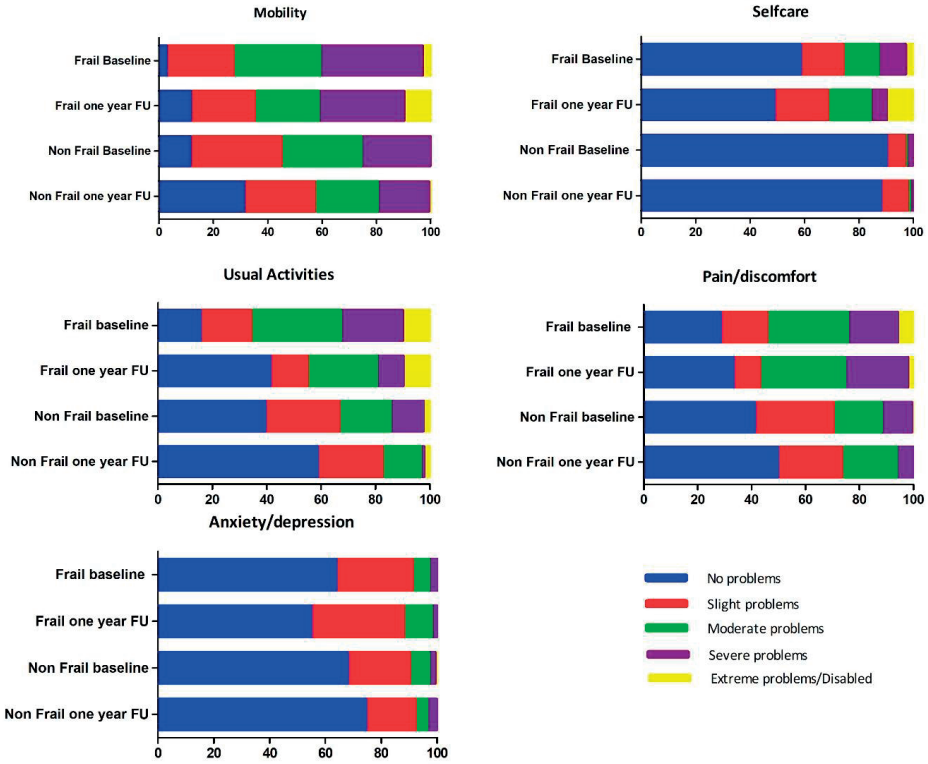
Appendix 3: NYHA functional class



New York Heart Association (NYHA) functional class at baseline and one-year follow up in frail and non-frail patients.

Appendix 4: Eq-5D-5L dimensions at baseline and one year follow up in frail and non-frail patients



Abbreviations used: FU; Follow up

7

Long-term Follow-up of Quality of Life in High-Risk Patients Undergoing Transcatheter Aortic Valve Implantation for Symptomatic Aortic Valve Stenosis

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ABSTRACT

Background

Transcatheter aortic valve implantation (TAVI) has become the standard treatment for patients with severe symptomatic aortic stenosis (AS) considered at very high risk for surgical aortic valve replacement.

Aims:

The purpose of this sub-study was to evaluate long-term (> 4 years) health-related quality of life (QoL) in octogenarians who underwent TAVI.

Methods:

A single center observational registry in twenty patients who underwent frame analysis assessment ≥4 years after TAVI. Health-related QoL was evaluated, using the Short Form-36 (SF-36), the EuroQoL-5D (EQ-5D) and the visual analogue score (EQ-VAS) questionnaires.

Results:

The mean SF-36 subscale scores at follow-up were physical functioning 40.8 ± 26.3, role physical functioning 67.7 ± 34.9, vitality 54.6 ± 21.6, general health 52.1 ± 20.4, social functioning 63.8 ± 37.7, role emotional functioning 70.2 ± 36.0, mental health 73.2 ± 23.3 and bodily pain 80.9 ± 22.9. The mean EQ-VAS score >4 years after TAVI was 64.7 ± 15.1. With respect to functional class, 80% of the patients were in NYHA class I/II at follow-up compared to 15% prior to TAVI.

Conclusions:

This sub-study reports a significant improvement in functional class (NYHA) in a selected group of very elderly patients >4 years after TAVI. Furthermore, all patients showed a satisfactory quality of life despite their age and multiple comorbidities. In addition, our study reveals a lower quality of life when compared with the general age matched Dutch population.

Keywords: Octogenarians, Quality of Life, Transcatheter Aortic Valve Implantation

1. INTRODUCTION

Degenerative aortic valve stenosis is a very common valvular heart disorder in adults aged >65 years in industrialized countries, with a prevalence rate of 3-9%. [1, 2] Surgical aortic valve replacement (SAVR) has been the standard of care for these patients. However, at least one third of the patients are considered too high at risk or inoperable for SAVR due to multiple comorbidities. In the last decade transcatheter aortic valve implantation (TAVI) has emerged as a less-invasive treatment for these patients with >300.000 procedures performed to date. Importantly, its use is still growing [3-6], as the field of TAVI is rapidly evolving due to improvements in catheter and valve technology, procedural techniques and refined patient selection. Consequently, knowledge of long-term structural device integrity and patient-reported outcomes are important to guide this development. [7, 8]

Most patients undergoing TAVI are octogenarians with multiple co-morbidities and reduced health related quality of life (QoL). [9] In these patients the importance of QoL may be as or even more important than survival. [10, 11] Moreover, meaningful long-term benefit of QoL post-TAVI is of importance to guide patient-centered decision-making as well as identifying predictors for improvement of QoL post-TAVI. Yet, information on true long-term results is lacking.

Accordingly, we initiated study on the long-term integrity of the self-expanding Medtronic CoreValve System (Medtronic Inc. Minneapolis MN) to analyse QoL and functional health status at a minimum of 4 years after TAVI. [12]

The main objective of this sub-study is to investigate long-term health related quality of life and functional health status. A sub-analysis was performed to compare QoL of TACT participants with the general age matched Dutch population.

2. METHODS

Between November 2005 and March 2012, a total of 259 patients with severe symptomatic aortic valve stenosis received a TAVI in the Erasmus Medical Centre, Rotterdam. After checking survival status in January 2016 at the Municipal Civil Registry, survivors were evaluated for assessment of long-term valve function (transthoracic echocardiography) and frame integrity of the self-expanding CoreValve (Multi Slice Computed Tomography - TACT study). [12]

Only patients who underwent TAVI >4 years earlier were eligible. Given the nature of the study that included MSCT, patients with renal failure, known hypersensitivity or contraindication to intravenous contrast in addition to patients with previous stroke, a language barrier and treatment with a valve other than the self-expanding CoreValve were not included in the present study. Patients who fulfilled these study-criteria were contacted for both long-term valve & frame analysis as well as health-related status. The Medical Ethics Committee approved the study (MEC-2013-331) and all participants signed the informed consent. After written informed consent patients were scheduled for a one-day out-patient visit during which data on valve function, health status and QoL were collected. A sub-analysis was performed to compare the measured health related QoL at follow-up in TACT patients with the general Dutch population as stratified by age >70 years. No data on baseline QoL was available.

2.1 Baseline characteristics

Socio-demographic characteristics included gender and age. Cardiovascular risk factors included: diabetes mellitus, hypertension, pulmonary vascular disease, previous stroke, atrial fibrillation, previous pacemaker, chronic obstructive pulmonary disease, pulmonary hypertension and chronic kidney disease. Clinical characteristics included: history of coronary artery disease, peak aortic valve velocity, left ventricular ejection fraction, NYHA classification and Log EuroSCORE (European System for Cardiac Operative Risk Evaluation).

All data on baseline and the medical history of patients were collected from the medical records.

2.2 Health status

Health-related QoL was measured with the generic Short Form 36 Health Survey (SF-36) and the EuroQoL-5-dimensions-5 levels (EQ-5D-5L) questionnaires. The SF-36 questionnaire is a validated and widely accepted instrument to measure overall physical and mental health status. It consists of 36 items, which measures eight health-related dimensions covering physical functioning, role physical, bodily pain, general health, role emotional, social functioning, vitality and mental health. Each item is scored in a 0-100 range, with higher scores reflecting a better QoL. [13]

The EQ-5D-5L is a generic health utility QoL instrument and is qualified for measuring health status within an elderly population (EuroQoL Group, Rotterdam, The Netherlands). [14] This descriptive system consists of five domains (i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which is divided in 5 levels of functioning (i.e. no problems (level 1), some or moderate problems (level 2 and 3),

and severe or extreme problems (level 4 and 5)). Theoretically, 3125 different health status can be generated by this classification, which can be converted to a utility score, ranging from -0.446 to 1 (a value of 1 indicating full health, while a value lower than 0 represents a status considered to be worse than death). The second part of the EQ-5D includes a visual analog scale (EQ-VAS), ranging from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state"). [15] Both, SF-36 and EQ-5D, questionnaires were administered and collected during in-person visits >4 years after TAVI.

2.3 Statistical analysis

Continuous variables are expressed as mean with standard deviation (± SD). Dichotomous variables are presented as numbers and percentages. To evaluate differences between TACT participants and surviving non-participants chi-square tests, students *t*-test or Mann-Whitney tests were applied as appropriate. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 21 for Windows (SPSS Inc, Chicago, IL).

3 RESULTS

3.1 Patient characteristics

Of the 259 patients who underwent TAVI between 2005 and 2012, 158 (61%) patients died before the time of inclusion (January 2016) with a mean survival time for the total cohort of 4.7 years (CI: 4.16-5.14). Out of the 101 remaining patients, 81 patients did not participate in the TACT study due to exclusion criteria or non-response. Other reasons were the lack of social support or due to physical or mental disabilities. The remaining 20 patients with a mean follow-up period of 5.5 years (range 4-10 years) provided written informed consent and were included in the current analysis (Fig. 1**).**

Baseline data of all 101 patients are shown in Tab. 1, including a comparison between participants (n = 20) in the TACT (sub)-study and surviving non-participants (n = 81). Most patients suffered from multiple comorbidities and high surgical risk (mean logistic EuroSCORE 15.4% ± 9.8). The mean age at the time of TAVI was 80 ± 8.0 years, and almost half were men. The majority of participants (77%) had a poor functional status (NYHA III/IV) before TAVI. Overall, there were no significant differences on baseline characteristics between participants and surviving non-participants, except for left ventricular ejection fraction (LVEF).

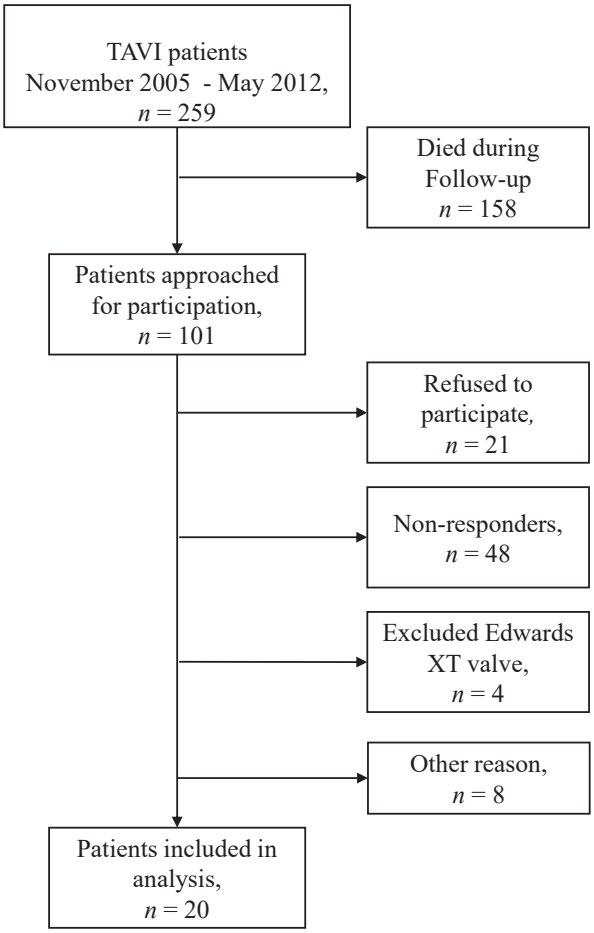

Figure 1. Study flowchart of number of total TAVI patients between 2005 and 2012, non-responders (n = 81) and the final study population with more than 4 years follow-up data post- TAVI (n = 20). TAVI: transcatheter aortic valve implantation.

3.2 (Post-) Procedural outcomes

On (post-) procedural outcomes no differences between participants and non-participants were found. As shown in Tab. 2, all participants underwent successful TAVI with femoral access, general anesthesia as standard of care at that time, a mean procedure time of 203 minutes ± 64.7 and a mean hospitalization time of 10.4 ± 7.6 days. Post-procedural complications included 1 participant with a major vascular complication and 4 participants who required a permanent pacemaker. Major bleeding after more than 1 day occurred in 6 participants of which 2 were life threatening.

Table 1.
Baseline patient characteristics

	Total population (n= 101)	Non-participants (n= 81)	TACT- participants (n= 20)	*P*-value
Mean age, years ± SD	79.7 ± 8.0	80.2 ± 8.0	77.9 ± 7.7	0.26
Male sex	49 (49%)	38 (47%)	11 (55%)	0.52
Body mass index, kg/m^2 ± SD	26.8 ± 3.9	26.5 ± 3.4	27.9 ± 5.3	0.16
Cardiovascular risk factors				
Diabetes mellitus	21 (21%)	18 (22%)	3 (15%)	0.48
Hypertension	60 (59%)	47 (58%)	13 (65%)	0.57
PVD	8 (8%)	7 (9%)	1 (5%)	0.59
Previous stroke	20 (20%)	15 (19%)	5 (25%)	0.52
Atrial fibrillation	22 (22%)	17 (21%)	5 (25%)	0.70
Previous pacemaker	12 (12%)	9 (11%)	3 (15%)	0.63
COPD	21 (21%)	15 (19%)	6 (30%)	0.26
PHT	7 (7%)	5 (6%)	2 (10%)	0.55
Chronic kidney disease	16 (16%)	12 (15%)	4 (20%)	0.57
History of CAD	50 (50%)	38 (47%)	12 (60%)	0.30
Peak AoV, (m/s) ± SD	4.3 ± 0.8	4.3 ± 0.8	4.3 ± 0.9	0.75
LVEF, % ± SD	51.7 ± 14.1	53.7 ± 12.7	44.4 ± 17.0	**0.01**
NYHA classification				.30
- I / II	23 (23%)	20 (25%)	3 (15%)	
- III / IV	78 (77%)	61 (75%)	17 (85%)	
Log EuroSCORE, % ± SD	15.4 ± 9.8	14.5 ± 9.5	18.9 ± 10.8	0.07

Data are presented as mean ± SD or *n* (%) unless other indicated.
AoV: Aortic valve velocity; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; Log EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PHT: pulmonary hypertension; PVD: pulmonary vascular disease

3.3 Health status

The SF-36, EQ-5D-5L and EQ-VAS scores are shown in Tab. 3. The mean SF-36 subscale scores at follow-up were physical functioning 40.8 ± 26.3, role physical functioning 67.7 ± 34.9, vitality 54.6 ± 21.6, general health 52.1 ± 20.4, social functioning 63.8 ± 37.7, role emotional functioning 70.2 ± 36.0, mental health 73.2 ± 23.3 and bodily pain 80.9 ± 22.9. With attention to EQ-5D, mobility was found to be the most frequent reported limitation (75%) while self-care was the least frequent reported limitation (35%). The majority of the participants had moderate limitations in all sub-domains. The mean utility index and EQ-VAS score were 0.69 ± 0.29 and 64.7 ± 15.1. Tab. 3 also shows a comparison of the QoL in TACT participants with the mean QoL values of the age adjusted Dutch population.

Table 2.
Procedural and post-procedural outcomes

	Total population (n = 101)	Non-participants (n = 81)	TACT- participants (n = 20)	*P*-value
Procedural outcomes				
Access trans femoral	100 (99%)	80 (99%)	20 (100%)	0.62
Pre-dilatation	97 (98%)	78 (98%)	19 (95%)	0.49
MCV	97 (96%)	77 (95%)	20 (100%)	0.31
Device success	98 (97%)	78 (98%)	20 (100%)	0.38
Post-dilatation	14 (14%)	9 (11%)	5 (25%)	0.11
Total contrast, cc ± SD	135 ± 68.5	132.9 ± 69.1	146.3 ± 66.7	0.47
Post-procedural outcomes				
Aortic valve regurgitation				0.58
Mild	27 (27%)	22 (28%)	5 (25%)	
Moderate / severe	6 (6%)	4 (5%)	2 (10%)	
Permanent pacemaker	15 (15%)	11 (14%)	4 (20%)	0.47
Bleeding more than 1 day				0.85
Minor	9 (9%)	7 (9%)	2 (10%)	
Major	11 (11%)	9 (11%)	2 (10%)	
Life threatening	6 (6%)	4 (5%)	2 (10%)	
Major vascular complication	6 (6%)	5 (6%)	1 (5%)	0.58
Place of discharge				0.61
Home	91 (90%)	71 (88%)	20 (100%)	
Other location	10 (10%)	10 (12%)	0 (0%)	
Length of stay, days ± SD	9.2 ± 5.1	9.0 ± 4.3	10.4 ± 7.6	0.28

Data are presented as mean ± SD or n (%) unless other indicated. MCV: Medtronic CoreValve.

With respect to functional class expressed by NYHA, 80% had mild symptoms (class I or II) at follow-up versus 15% before TAVI, indicating a significant functional improvement (Tab. 1 and 3).

4 DISCUSSION

The main findings of the present study in a selected group of octogenarians who underwent TAVI >4 years ago because of severe AS are a significant improvement in functional class (NYHA) and a satisfactory quality of life.

Although we recognize that the herein included patients represent a selected group of TAVI patients, this study confirms the improvements reported in other studies but over

Table 3.
Quality of Life Scores at follow-up (6 years) in TACT-participants.

	TACT-subgroup (*n* = 20) Mean ± SD	Dutch population* Mean ± SD
SF-36		
% Physical functioning	40.8 ± 26.3	58.9 ± 30.8
Role physical functioning	67.7 ± 34.9	56.9 ± 44.0
Vitality	54.6 ± 21.6	61.8 ± 23.6
General health	52.1 ± 20.4	58.9 ± 21.1
Social functioning	63.8 ± 37.7	75.6 ± 27.0
Role emotional functioning	70.2 ± 36.0	74.5 ± 38.2
Mental health	73.2 ± 23.3	73.0 ± 19.9
Bodily pain	80.9 ± 22.9	68.1 ± 27.4
EQ-5D (% of patients indicating a problem)		
Mobility	75.0	36.5
Self-care	35.0	11.7
Usual activities	65.0	26.0
Pain/discomfort	60.0	48.5
Anxiety/depression	40.0	3.6
Utility score	0.69 ± 0.29	0.85 ± 0.15
VAS	64.7 ± 15.1	72.9 ± 24.3
NYHA classification (%)		
I/II	16 (80%)	
III/IV	4 (20%)	

Data are presented as mean ± SD or n (%) unless other indicated. *Dutch population norms for the SF-36 are stratified by age > 70 years;[29] Dutch population norms for the EQ-5D are stratified by age > 75 years. [15] EQ-5D: EuroQoL 5 Dimensions; SF-36: Short Form (36) Health Survey; VAS: Visual Analogue Score.*Dutch population norms for the SF-36 are stratified by age >70 [29]. *Dutch population norms for the EQ-5D are stratified by age >75 years [15].

a longer period of time. [16-18] Indeed previous studies mainly focus on the first post-procedural period (up to one year) while in this study the mean follow-up time was 5.5 years. The improvement in functional class and the findings in health related outcome is noteworthy given the age and comorbid conditions in these patients. In line with others, sustainable improvement of NYHA class has been observed in long-term survivors, as NYHA class I/II has been observed in most patients, who were in NYHA III/IV prior to TAVI. [19, 20] This indicates that these patients, despite multiple comorbid conditions and advanced age, clearly benefit from this invasive procedure.

With respect to health-related QoL, the majority of the participants showed satisfactory QoL scores >4 years after TAVI. In addition, our study reveals a lower QoL when com-

pared with the general age adjusted Dutch population. [15] Ware et all. described that a 5-point difference between groups or a 5-point change over time is considered clinically and socially relevant. [21] Our participants scored lower on most SF-36 subscales and all EQ-5D subdomains when compared to the Dutch population as stratified by age >70 years. [15, 22] The differences in health scores on the physical scales of the SF-36 are more than 5 points and therefore should be considered clinically and socially relevant. With attention to bodily pain, the participants scored higher on the SF-36 subscale. A possible explanation is that patients are getting used to their physical limitations and multiple comorbidities [23, 24], which could result in a lower sensitivity for pain. These findings indicate that within elderly people, large QoL differences exist and may under scribe the need for more long-term follow-up research, with standardized QoL instruments specific developed for patients with AS.

In comparison, the Partner study was the first to show a substantial improvement of QoL at 1-year follow-up after either TAVI or SAVR in high-risk elderly patients. [25] Baseline EQ-5D utility score increased by 14% to 0.66 at 1-year post-TAVI. Fairbairn. *et al.* had shown that QoL, as measured with the EQ-5D and EQ-VAS, improved early after TAVI and was maintained at 1-year post-TAVI. [18] The German TAVI registry revealed that patients with a low baseline EQ-5D had a significantly better improvement in QoL one year after TAVI. [17]

Other studies also showed a significant improvement at one-year follow-up in all SF-36 domains with higher summary scale scores than the general population-norms. [26, 27] Unfortunately, we could not perform an age- and co-morbidity matched comparison precluding firm conclusions or interpretation. Of note, the mean age of the reference data in the general Dutch population is standardized to 70+ whereas the mean age in our population was 79.7 years. It is important to note that an increase in age is associated with a decrease in QoL, indicating a decline in the slope of people 's self-rated health over the decades of their life. [15] Mangen, *et al.* reported that impairment increases rapidly with age, but health status is also associated with socio-demographic variables and comorbidities. [28] These findings are consistent with our findings that increasing age and multiple co-morbidities can be associated with lower QoL.

4.1 Limitations

Our study is a single-center study and based on a small group of selected patients (20 participants of long-term survivors) most likely representing a group of most vital patients who agreed to participate in a clinical research project. Therefore, selection bias may have occurred. Second, our analyses are based on a population including the first TAVI patients in the Netherlands. All procedures were performed under general anes-

thesia in patients with an extremely high-risk status and therefore might not represent a contemporary TAVI population.

4.2 Conclusions

This sub-study in a selected group of very elderly patients who underwent frame analysis assessment ≥4 years after TAVI reports significant improvement in functional class (NYHA). Furthermore, all patients showed a satisfactory quality of life despite their age and multiple comorbidities. In addition, our study reveals a lower QoL when compared with the general age matched Dutch population. The observed improvement in functional status reflects a positive long-term outcome of TAVI in this selected group of octogenarians. These benefits should be taken into account when discussing the indication for elderly patients undergoing TAVI. Further research is warranted on long-term health-related QoL in a high-risk population with aortic stenosis.

4.3 Implications for practice

- Finding of this study indicate that included patients who survived TAVI > 4 years (49%) showed an improvement at long-term follow up on functional class and satisfied QoL outcomes.
- Detailed knowledge on changes in QoL after TAVI could provide more insight in the effects and benefits for the patient themselves and provide a better patient selection for the right treatment of choice regarding not only life expectancy but also QoL.

4.4 Conflict of interest

The authors declare that there is no conflict of interest.

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8

Referring hospital involvement in early discharge post transcatheter aortic valve implantation: The TAVI (R-) EXPRES program

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ABSTRACT

Aim: Over the past decade transcatheter aortic valve implantation (TAVI) has matured into a valid treatment strategy for elderly patients with severe aortic stenosis. TAVI programs will grow with its adoption in low risk patients. The aim of this study was to evaluate safety and feasibility of early discharge protocols, either home or back to a referring hospital.

Methods: Consecutive patients undergoing TAVI between July 2017 and July 2019 were stratified into 3 discharge pathways from TAVI center: 1) early home (EXPRES); 2) early transfer to referring hospital (R-EXPRES); 3) routine discharge (standard). Baseline, procedural and 30-day outcome were prospectively collected and compared per discharge pathway.

Results: 22 (5%) patients were enrolled in the EXPRES cohort (median age 78 [73 – 81]; mean Society of Thoracic Surgeons (STS) risk score2.4% ± 1.5); 121 (29%) in the R-EXPRES cohort (median age 81 [77 – 84]; mean STS 4.3% ± 2.8) and 269 (65%) were enrolled in the routine discharge cohort (median age 80 [75-85]; mean STS 4.4% ± 3.1). EXPRES patients trended to be younger (p=0.13) and had lower STS (p=0.02). Early clinical outcome was similar through the different pathways including rehospitalization rate. Median length of stay was one day longer for R-EXPRES vs. routine discharge patients (5 [4 – 7] vs. 4 [3 – 6], p<0.01). Median length of stay (LOS) was 2 [1-2] days for EXPRES patients.

Conclusion: Early discharge pathways home and to referral hospitals are safe and help streamline TAVI programs. LOS in referring hospitals may be further reduced.

Keywords: Aortic valve stenosis, transcatheter aortic valve implantation, early discharge, length of stay

INTRODUCTION

Severe aortic stenosis is the most common valve disease requiring treatment in the Western world and its prevalence is growing due to an ageing population[1]. The only curative option for aortic stenosis is surgical or transcatheter valve implantation. Transcatheter aortic valve implantation (TAVI) is indicated for patients with a high- or intermediate surgical risk[2,3]. Recent trials have also shown TAVI feasibility in low surgical risk patients[4,5]. Every patient requiring a bioprosthesis for aortic stenosis should now be informed about the transcatheter option.

As a result, European and Northern-American annual TAVI volume is expected to increase from 180 000 to 270 000 cases per year[6]. Contemporary society guidelines recommend to centralize TAVI care in high-volume (>85 procedures/year) sites because of an inverse volume-mortality correlation[7]. To reconcile TAVI demand/supply and maintain high-quality healthcare at an affordable price, high-volume centers need to modify the TAVI cascade and streamline discharge policy. Early home discharge protocols aim to limit in-hospital stay to less than 3 days after TAVI with favorable early and mid-term outcome and no penalty for readmissions or delayed need for definite pacemakers[8].

For this purpose we installed the TAVI EXpedited discharge Program Rotterdam EraSmus MC (TAVI EXPRES) and TAVI referral-EXPRES (TAVI R-EXPRES) programs in our institution. Various characteristics specific to the individual patient, the procedure and the post-procedural recovery determine early discharge eligibility either home or to a referring hospital. Early discharge protocols have been described, but so far involvement of referring hospitals in the TAVI cascade has not been specifically studied[9,10].

Early discharge to referring hospitals could optimize patient flow and bring post procedural quality care closer to (elderly) patients' home environment. R-EXPRES program is a collaboration between the Erasmus MC and referring hospitals to organize patient work up before and care after TAVI in the referring hospital.

Herein we report on the Rotterdam approach to promote early discharge home or to a referring hospital in the perspective of contemporary clinical practice and compare 30-day outcome in different discharge pathways.

METHODS

Study population

All patients who underwent TAVI at the Erasmus MC between July 2017 and July 2019 and had complete 30-days follow-up were included. Patients were further identified in the TAVI EXpedited discharge Program Rotterdam Erasmus MC (EXPRES) and the referral EXPRES (R-EXPRES) program.

Patients who were deemed eligible for the EXPRES program were earmarked in the outpatient clinic by TAVI operators based on clinical criteria [Table 1]. These patients were then approached by a TAVI coordinating nurse who explained the "early discharge" concept, confirmed adequate social/familial support and consented eligible candidates. For EXPRES patients without a pacemaker at baseline preferably an Edwards Sapien S3 (Edwards Lifesciences Corp., Irvine, California) or Acurate NEO (Boston Scientific, Marlborough, Massachusetts) valve was implanted because these transcatheter heart valve (THV) platforms seem associated with the lowest risk for high-degree conduction disorders[11,12].

Table 1. Criteria for EXPRES eligibility

TAVI Strategy
Transfemoral approach Suitable for Edwards Sapien3 or Acurate NEO Any TAVI device when permanent pacemaker is in place
Cardiac criteria should exclude
Poor systolic LV function defined by LVEF < 35% More than moderate tricuspid or mitral regurgitation Severe pulmonary hypertension (sPAP > 60 mmHg) Untreated high degree AV-block or RBBB
Pulmonary criteria should exclude
COPD Gold class > 2
Kidney Criteria should exclude
eGFR < 35 ml/min
Frailty
Independent in Katz activities of daily living Presence of adequate social or family support
TAVI – Transcatheter aortic valve implantation; LVEF – Left ventricular ejection fraction; sPAP – systolic pulmonary artery pressure; AV – Atrioventricular; RBBB – Right bundle branch block; COPD – Chronic Obstructive Pulmonary disease; eGFR – estimated glomerular filtration rate

Patients who were scheduled for early transfer to a referring hospital after the procedure were included in the R-EXPRES cohort. All patients were eligible for R-EXPRES except those who were enrolled in the EXPRES cohort. Patients were only transferred to the referring hospital if (1) hemodynamically stable, (2) device success was confirmed, (3) there were no unresolved major procedure related complications, (4) there was no need for a temporary pacemaker and (5) the referral hospital had logistics in place to accommodate patients post TAVI.

Study procedures

All patients were discussed in a multidisciplinary heart team including a cardiac surgeon, an interventional cardiologist, an imaging specialist and a geriatrician. For R-EXPRES patients all imaging including transthoracic echocardiogram (TTE)-, multislice computed tomography (MSCT)- and coronary angiogram was provided by the referring hospital. THV size and access strategy was determined by the valve center. All TAVI procedures took place at the heart valve center.

Discharge policy

Standard post-procedural clinical pathway consisted of daily electrocardiograms, laboratory assessment and TTE pre discharge.

Patients earmarked for the EXPRES pathway were scheduled to be discharged home within 24 hours unless longer observation was required (*e.g.* because of lingering conduction disorders or unresolved procedure related complications). They were followed up through phone calls 1 and 7 days post discharge. Discharge policy was always left at the treating physicians discretion.

Patients in the R-EXPRES program were discharged to the referring hospital within 24 hours in the absence of a temporary pace wire or unresolved major procedure related complications.

Clinical outcomes and event screening

Baseline demographics, procedure characteristics and in-hospital and 30-day clinical outcome were collected in a dedicated prospective database. Discharge letters from referring hospitals were collected in order to determine length of stay and screen for in-hospital events (for R-EXPRES patients). All patients were seen at the outpatients clinic 4-6 weeks after the procedure, clinical events that occurred between hospital discharge and 30 days follow-up were collected. All events were classified according to Valve Academic Research Consortium (VARC-2) definitions[13].

Statistical analysis

Baseline characteristics are presented as numbers and percentages for categorical values. Continuous variables are presented as mean and standard deviation or median and interquartile range. Differences in baseline characteristics between cohorts were compared with ANalysis Of VAriance (ANOVA) for continuous variables and with Pearson chi-Square for categorical variables.

The percentage of new permanent pacemaker implantation was determined excluding patients with a pacemaker at baseline. Rehospitalization rates for EXPRES and R-EXPRES cohorts were compared with the standard cohort using Fishers Exact Test. Total length of stay for R-EXPRES patients was compared with length of stay for standard patients using Mann-Whitney U test.

RESULTS

From July 2017 until July 2019, 412 patients underwent successful implantation of at least one THV and had complete 30 days follow-up. A routine discharge pathway was followed in 269 patients (65%) while 121 patients were included in the R-EXPRES cohort (29%) and 22 in the EXPRES cohort (5%).

Baseline and procedural characteristics

Baseline characteristics stratified for discharge pathway are depicted in Table 2. In brief: EXPRES patients trended younger, were less symptomatic according to New York Heart Association ($p<0.01$) and at lower estimated surgical risk according to Euroscore II ($p < 0.01$) and STS-score ($p<0.02$) [Table 2].

Procedural characteristics are shown in Table 3. The vast majority of patients were treated through the femoral artery (93%, 95% and 100% for the standard, R-EXPRES and EXPRES cohort respectively). Almost all patients were treated under local anesthesia. There was an equal share of embolic protection use in all cohorts (44%, 45% and 50% for the standard, R-EXPRES and EXPRES cohort respectively, $p = 0.86$).

The share of balloon-expandable valves was higher in the EXPRES cohort as compared to the standard and R-EXPRES cohort (73% *vs.* 41% and 36%; $p < 0.01$). Although EXPRES patients were treated with either an Edwards Sapien3 or Acurate NEO valve per protocol, three patients underwent TAVI with the self-expanding Evolut Pro/R platform (Medtronic, Fridley, Minnesota); one because of inclusion in a registry on bicuspid valves, two due to small caliber femorals [Table 3].

Clinical outcomes

Clinical outcomes are shown in Table 4. In total 7 (2%) patients died, one in the R-EXPRES cohort, and 6 in the standard cohort. There were no deaths, stroke/transient ischemic attack (TIA) or access site complications in the EXPRES cohort [Table 4].

New permanent pacemaker implantation (PPI) was 17% in the total cohort. In the R-EXPRES cohort 20 patients (18%) required a new permanent pacemaker; 45% of the pacemakers were implanted in the referring hospital, 55% of pacemakers were implanted at the heart valve center. One EXPRES patient needed a permanent pacemaker.

Table 2. Patient characteristics

Baseline characteristics	Standard	R-EXPRES	EXPRES	p-value	Total
	n = 269	n = 121	n = 22		n = 412
Age (years)	80 [75 – 85]	81 [77 – 84]	78 [73 – 81]	0.13	80 [75 – 85]
Male gender	146 (54)	61 (51)	14 (64)	0.49	221 (54)
Body mass index (kg/m^2)	27.3 ± 5.5	27.6 ± 5.4	26.2 ± 3.0	0.57	27.3 ± 5.4
Diabetes mellitus	86 (32)	38 (32)	5 (23)	0.67	132 (32)
Hypertension	190 (71)	83 (69)	14 (64)	0.76	287 (70)
Hypercholesterolemia	150 (56)	68 (57)	10 (46)	0.63	228 (55)
Creatinine (mmol/L)	113 ± 84	113 ± 69	86 ± 20	0.28	111 ± 78
Peripheral vascular disease	98 (36)	48 (40)	4 (18)	-	150 (36)
COPD	35 (13)	24 (20)	1 (5)	-	60 (15)
Permanent pacemaker	35 (13)	10 (8)	0 (0)	-	45 (11)
Prior coronary artery bypass graft	41 (15)	13 (11)	2 (9)	-	56 (14)
Prior percutaneous coronary intervention	75 (28)	34 (28)	3 (14)	0.34	112 (27)
Prior aortic valve surgery	8 (3)	3 (3)	0 (0)	-	11 (3)
Prior cerebrovascular event	25 (9)	13 (11)	0 (0)	-	38 (9)
New York Heart Association class ≥ III	146 (54)	74 (61)	2 (9)	<0.01	222 (54)
Canadian Cardiovascular Society class ≥ II	52 (19)	24 (20)	6 (27)	-	82 (20)
European System for Cardiac Operative Risk Evaluation II (%)	5.3 ± 6.0	4.7 ± 4.1	2.0 ± 1.5	<0.01	5.0 ± 5.4
Society of Thoracic Surgeons' score (%)	4.4 ± 3.1	4.3 ± 2.8	2.4 ± 1.5	0.02	4.2 ± 2.9

Categorical variables are presented as numbers (percentage), continuous variables are presented as median [IQR] or mean ± SD. COPD – Chronic Obstructive Pulmonary Disease.

Although overall numbers were low, rates of re-hospitalization at 30 days for the R-EXPRES and EXPRES cohort were not different from the standard cohort (10% *vs*. 7%, $p = 0.45$ and 14% *vs.* 7%, $p = 0.23$ respectively). Twelve R-EXPRES patients (10%) were rehospitalized, 4 because of conduction disorders, 2 because of heart failure, 2 because of infections and 4 for various reasons (among them 2 patients that collapsed without

Table 3. Procedural characteristics

Procedural characteristics	Standard	R-EXPRES	EXPRES	p-value	Total
	n = 269	n = 121	n = 22		n = 412
Transfemoral access	250 (93)	115 (95)	22 (100)	-	387 (94)
Transaxillary access	18 (7)	5 (4)	0 (0)	-	23 (5.5)
Transapical access	1 (0)	1 (1)	0 (0)	-	2 (0.5)
General anesthesia	12 (4)	1 (1)	0 (0)	-	13 (3)
Conscious sedation	4 (1)	0 (0)	0 (0)	-	4 (1)
Local anesthesia	253 (94)	120 (99)	22 (100)	-	395 (96)
Cerebral embolic protection	119 (44)	54 (45)	11 (50)	0.86	184 (45)
Single prosthetic valve implanted	263 (98)	118 (98)	22 (100)	-	403 (98)
- Balloon expandable	106 (41)	42 (36)	16 (73)	<0.01	164 (41)
- Self- or mechanically expandable	156 (59)	76 (64)	6 (27)	<0.01	238 (59)
Multiple valves implanted	6 (2)	3 (2)	0 (0)	-	9 (2)
Median procedural time (minutes)	67 [55 – 84]	60 [47 – 82]	69 [50 – 86]	0.15	66 [51 – 84]

Categorical variables are presented as numbers (percentage), continuous variables are presented as median [Interquartile range or mean ± standard deviation

documented conduction disorders during telemetric observation). All 4 patients that were rehospitalized because of conduction disorders required a permanent pacemaker. Three EXPRES patients were rehospitalized: 2 patients required IV antibiotics (one because of pneumosepsis, the other because of a pacemaker lead infection) and 1 patient was readmitted due to heart failure. All three recovered [Figure 1].

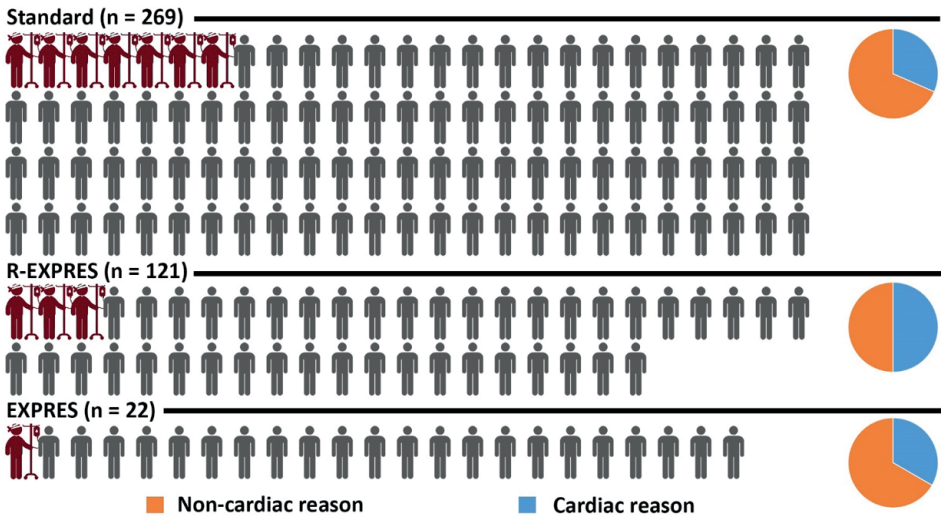

Figure 1. Rehospitalization rate stratified by cohort.

Table 4. Clinical Outcomes at 30 days follow-up

	Standard	R-EXPRES	EXPRES	Total
Clinical Outcomes	**n = 269**	**n = 121**	**n = 22**	**n = 412**
All-cause mortality	6 (2)	1 (1)	0 (0)	7 (2)
Stroke	6 (2)	2 (2)	0 (0)	8 (2)
Transient Ischemic Attack (TIA)	4 (2)	1 (1)	0 (0)	5 (1)
Access site complication	27 (10)	10 (8)	0 (0)	37 (9)
Life-threatening bleeding	7 (3)	8 (7)	0 (0)	15 (4)
Major bleeding	11 (4)	4 (3)	0 (0)	15 (4)
Minor bleeding	16 (6)	3 (3)	1 (5)	20 (5)
New permanent pacemaker[i]	42 (18)	20 (18)	1 (5)	63 (17)
- Implanted at valve center		11 (55)		
- Implanted at referring hospital		9 (45)		
(I)CCU stay				
- No (I)CCU-stay	73 (27)	35 (29)	7 (32)	115 (28)
- < 24 hours	163 (61)	72 (60)	14 (64)	249 (60)
- 24 – 48 hours	23 (9)	9 (7)	1 (4)	32 (8)
- ≥ 48 hours	9 (3)	4 (3)	0 (0)	14 (3)
Median length of stay (total)	4 [3 – 6][ii]	5 [4 – 7][ii]	2 [1 – 3]	5 [3 – 6]
- Length of stay at valve center		1 [1 – 2]		
- Length of stay at referring hospital		4 [3 – 5]		
Rehospitalization	19 (7)[iii,iv]	12 (10)[iii]	3 (14)[iv]	34 (8)
- For heart failure	3 (1.1)	2 (1.7)	1 (4.5)	6 (1.5)
- For conduction abnormalities	2 (0.7)	4 (3.3)	0 (0)	6 (1.5)
- Infection	9 (3.3)	2 (1.7)	2 (9.1)	13 (3.2)
- Other reasons	5 (1.8)	4 (3.3)	0 (0)	9 (2.2)

Categorical variables are presented as numbers (percentage), continuous variables are presented as median [IQR]. [i]Pacemakers at baseline were excluded; [ii]p<0.01; [iii]p=0.45; [iv]p=0.23.

R-EXPRES cohort

Of the 121 patients included in the R-EXPRES cohort, 14 patients (12%) did not go to the referring hospital. There was 1 intra-procedural death (hemodynamic collapse due to tamponade, unsuccessful resuscitation), 3 were discharged home because of quick recovery, 9 faced unresolved complications and 1 patient refused transfer. Of the unresolved complications, 5 had vascular or access-site related complications, 2 had unexplained neurological symptoms and 2 patients had temporary pacemaker wires and went directly home after implantation of a permanent pacemaker in the valve center. One patient was discharged to the referring hospital, but transferred back to the valve center after a complicated pacemaker implantation.

The remaining 105 patients (88%) went to the referring hospital. Median length of stay for R-EXPRES patients was longer than length of stay in the reference cohort (5 (IQR 4 – 7) *vs.* 4 (IQR 3 – 6); $p < 0.01$). Median length of stay in EXPRES was 2 (IQR 1 – 3) days.

DISCUSSION

TAVI thrives on meticulous patient selection, even more so when considering patients for early discharge. This single-center experience illustrates 3 discharge pathways including next day discharge from the TAVI site either home or to the referring hospital. The main findings of this single center experience with 3 different post TAVI pathways can be summarized as follows: 1) a significant number of patients can be safely discharged home (EXPRES) or to the referral hospital (R-EXPRES) if proper logistics and/or social support are in place. 2) Heart failure, conduction disorders and infections were main reasons for hospital re-admission. 3) Further data and experience exchange may streamline and reduce LOS in the referral hospitals.

Early discharge

Changing patient phenotype to younger age with a more active and independent lifestyle demands an appropriate discharge policy. Over time there has been a gradual reduction in LOS after TAVI, irrespective of surgical risk[14]. The implementation of early discharge protocols as described in the Vancouver 3M and FAST-TAVI registries will further reduce LOS after TAVI.

Patients in the Vancouver 3M and FAST-TAVI registries on early discharge protocols were still old (84 (IQR 78-87) and 81.4 (SD ±6.0) respectively)[9,10]. Due to cultural differences and geographical differences in addition to different reimbursement policies between countries, it is uncertain if such a progressive discharge policy in elderly will be accepted worldwide or is applicable for the majority of elderly more dependent patients. Involving referring hospitals could alleviate TAVI expert centers by reducing prolonged in-hospital stay and bringing care closer to the patient's home environment. Barbanti *et al.*[10] touched upon this option in FAST-TAVI. They showed feasibility of early discharge when adhering to a set of clinical discharge criteria; median length of stay was 2 days (IQR 1-4 days) and patients were either discharged home (79%) or to a referring hospital (16.2%). Our single-center cohort corroborates this concept of early transfer to a referring hospital as a specific discharge pathway.

Procedure simplification

Over the last couple of years efforts to streamline the TAVI cascade focused on various facets within the expert TAVI center including the likes of local anesthesia protocols, simplified TAVI execution and reducing invasive instrumentation to a minimum. As such, in our cohort, 96% of the patients were treated under local anesthesia. Globally, there is a clear shift to perform transfemoral TAVI under local anesthesia/conscious sedation rather than general anesthesia[15]. Local anesthesia is associated with shorter in-hospital- and ICCU-stay. Taking into account the heterogeneity of the patient population and selection bias, TAVI under local anesthesia shortens length of stay (LOS) by approximately one day and a half when compared to general anesthesia[16]. Moreover, procedural time and procedural turnover time can be substantially decreased. Shorter procedure time also precludes urinary catheter insertion, which minimizes the risk for urinary tract infections and bleeding[17]. In our experience median procedural time was approximately one hour (66 min [51-84]) and there were no differences between the cohorts ($p = 0.14$).

Another important adjustment in our simplified TAVI protocol, is to pace on the left ventricular (LV) guidewire with alligator clamps and no longer insert a temporary pacemaker through a deep venous access. [Figure 2]. Only when a high-degree atrioventricular block occurs during the procedure, venous access for a temporary pacing wire in the right ventricular apex is obtained[16].

Cerebral debris embolization is omnipresent in TAVI and up to 90% of patients will develop brain injury as demonstrated by post TAVI brain magnetic resonance imaging (MRI). Use of filter based cerebral embolic protection may cut new brain lesions after TAVI in halve[18]. We use embolic protection in all our patients when feasible. In this cohort embolic protection was used in 45% of the cases. Reasons for not using an embolic protection device were: no calcium in the aortic annulus (*e.g.* in pure aortic regurgitation), transaxillary access or unsuitable anatomy of the filter-landing zone.

In this contemporary cohort, access site related complications remained relevant (37 patients, 9%). The routine implementation of ultrasound guided femoral access may reduce access site complications, it precludes radiation and allows for real time visual monitoring of the vessel puncture. Notably angiographic confirmation of successful closure device deployment after TAVI may further avoid covert retroperitoneal bleedings or flow limiting dissections and occlusions.

Rehospitalization

In total 34 patients (8%) were re-hospitalized. Heart failure (18%), conduction abnormalities (18%) and infections (38%) were the most common reasons. Our results are in

line with previous reports on readmissions after TAVI which showed that in more than half of the cases the reason for readmission was non-cardiac[19,20]. Infections remain an important issue after discharge, also in our study. Surgical cutdown of the femoral artery, overweight (BMI ≥25 kg/m^2), bleeding complications and intensive coronary care unit (ICCU)-stay have been identified as predictors for developing infections after TAVI[21,22]. Modifiable factors such as avoiding surgical cutdown, in-dwelling (urinary) catheters and shortening ICCU stay have been adjusted in our streamlined TAVI protocol. As such, the vast majority of patients did not go to the ICCU (*n* = 115, 28%) or were only observed for a period shorter than 24 hours (*n* = 249, 50%). Also the number of patients that underwent TAVI through surgical cutdown of the femoral or subclavian artery was low (3% in total, results not shown). In order to further reduce respiratory and wound infections; patients should be actively mobilized and ICCU-stay should become an exception instead of standard practice.

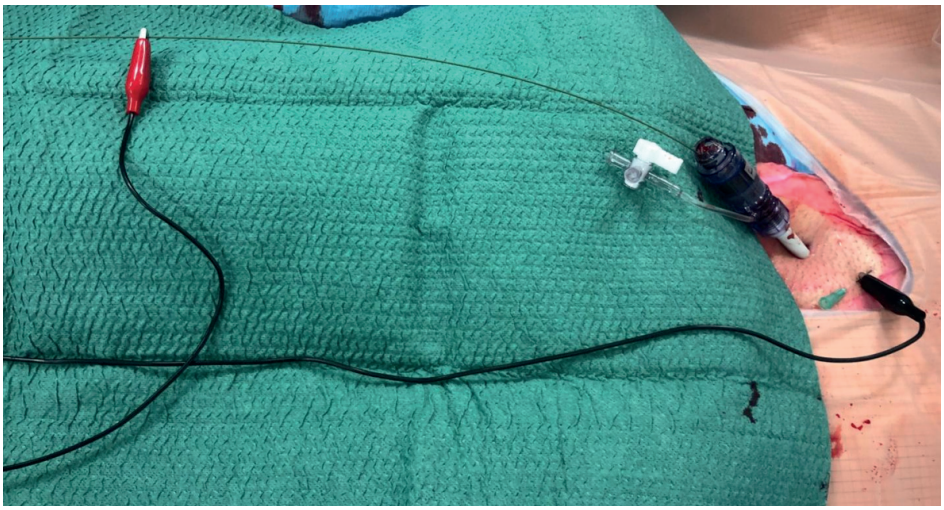

Figure 2. Pacing over a left ventricular guidewire

Of note, conduction disorders were the most frequent cause of readmission in the R-EXPRES cohort, that in our experience always required a permanent pacemaker. Ambulatory event monitoring after TAVI could further optimize discharge policy and detect conduction disorders before they cause harm. A recent pilot study showed an 8% incidence of delayed high-grade AV-block (≥2 days post-TAVI) with a median time to AV-block of 6 days (range 3 to 24 days)[23].

Referring hospital involvement

Latest European Society of Cardiology (ESC) guidelines on valvular heart disease recommend centralized TAVI care in heart valve expert centers[2]. This recommendation specifi-

cally aims to centralize heart valve interventions including TAVI in order to maximize local experience and offer optimal procedure outcome. TAVI guidelines require heart valve centers to have specific institutional resources such as on-site cardiac surgeons and the capability of running cardiopulmonary bypass, which precludes the TAVI-operator from performing the procedure at the referring hospital without these logistics in place. Therefore we believe referring hospitals need to be involved in the work up before and care after TAVI to reinforce the concept and viability of expert heart valve centers and bring overall TAVI care closer to the patient's home environment.

Inter-hospital collaborations face specific challenges. In our study LOS was one day longer for R-EXPRES patients compared to patients who were not transferred after TAVI (LOS: 5 [4 – 7] *vs.* 4 [3 – 6]; $p < 0.01$). This could suggest a knowledge and expertise gap between referring and TAVI expert centers and a lack of a harmonized protocol. Digital information transfer, shared electronic health records and continued training and information exchange could further optimize this inter-hospital collaboration.

Limitations

Selection bias is an intrinsic limitation of every single center retrospective analysis. The EXPRES cohort had a larger proportion of the Sapien and Acurate valve platforms: whether short LOS and equal rehospitalization rate is attributed to patient selection rather than device selection is unsettled. Also, this trial was performed before introduction of the cusp overlay technique which could have influenced the pacemaker rate with self-expandable valves[24]. Discharge policy was defined by protocol, but in reality per treating physician's discretion and referring hospitals did not collect reasons for prolonged stay, variation in discharge policy among different physicians (*e.g.* due to difference in experience) might have influenced these results. Yet, to the best of our knowledge this is the first study comparing three different discharge pathways. Our findings require confirmation in a prospective multicenter design.

In conclusion

Early discharge pathways home and to referral hospitals are safe and help streamline TAVI programs. LOS in referring hospitals may be further reduced.

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9

Insights in a restricted temporary Pacemaker strategy in a Lean Transcatheter Aortic Valve Implantation Program

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ABSTRACT

Objectives: To study the safety and feasibility of a restrictive temporary-RV-pacemaker use and to evaluate the need for temporary pacemaker insertion for failed left ventricular(LV) pacing ability(no ventricular capture) or occurrence of high-degree AV-blocks mandating continuous pacing.

Background: Ventricular pacing remains an essential part of contemporary Transcatheter Aortic Valve Implantation(TAVI). A temporary-right-ventricle(RV)-pacemaker lead is the standard approach for transient pacing during TAVI but requires central venous access.

Methods

An observational registry including 672 patients who underwent TAVI between June 2018 and December 2020. Patients received pacing on the wire when necessary, unless there was a high-anticipated risk for conduction disturbances post-TAVI, based on the baseline-ECG. The follow-up period was 30 days.

Results

A temporary-RV-pacemaker lead(RVP-cohort) was inserted in 45 patients, pacing on the wire(LVP-cohort) in 488 patients and no pacing(NoP-cohort) in 139 patients. A bail-out temporary pacemaker was implanted in 14 patients(10.1%) in the NoP-cohort and in 24 patients(4.9%) in the LVP-cohort. One patient in the LVP-cohort needed an RV-pacemaker for incomplete ventricular capture. Procedure time was significantly longer in the RVP-cohort(68 minutes[IQR 52-88.], vs 55 minutes[IQR 44-72] in NoP-cohort and 55 minutes[IQR 43-71] in the LVP-cohort($p<0.005$). Procedural high-degree AV-block occurred most often in the RVP-cohort(45% vs. 14% in the LVP and 16% in the NoP-cohort($p=<0.001$)). Need for new PPI occurred in 47% in the RVP-cohort, vs. 20% in the NoP-cohort and 11% in the LVP-cohort ($p=<0.001$).

Conclusion

A restricted RV-pacemaker strategy is safe and shortens procedure time. The majority of TAVI-procedures do not require a temporary-RV-pacemaker.

Keywords: TAVI, Pacing on the wire, Rapid pacing, temporary pacemaker, conduction disturbances

1. INTRODUCTION

Transcatheter Aortic Valve Implantation (TAVI) is a less invasive alternative to surgical Aortic Valve Replacement (SAVR) for elderly patients across the entire operative risk spectrum.(1-3) Over the last 2 decades TAVI patient selection, pre-procedure planning and refined device technologies have molted the procedure to a simplified intervention under local anesthesia with abbreviated hospital stay.(4) Ventricular pacing is often required for balloon dilatation or transcatheter heart valve deployment and high degree conduction blocks may mandate immediate (at least temporary) pacing. Conduction abnormalities are common surrounding a TAVI procedure. The incidence of new left bundle branch block (LBBB) is between 10 and 37%.(5) The need for a definite pacemaker varies between 5 and 35% and is associated with anatomical substrate (short membranous septum, left ventricular outflow tract calcification), conduction issues at baseline and transcatheter heart valve (THV) design.(6-7)

A stiff wire in the left ventricle (LV) is essential to introduce, position and deploy a THV. This LV wire can be connected to an external pacemaker for LV stimulation obviating the need for additional central venous access for a temporary transvenous pacemaker.(8) A French multi-center randomized controlled trial demonstrated safety and feasibility of LV pacing including shorter procedure and fluoroscopy time as compared to systematic use of a temporary right ventricular (RV) pacemaker.(6,9,10)

Pacing on the LV wire could complement simplified TAVI in order to reduce resources, time and complications. Still, concerns remain about safety of more systematic use of LV pacing in TAVI with different THV designs. The aim of this study was to evaluate the safety and efficacy of more systematic LV pacing on the wire in terms of need for bail out temporary RV pacemaker insertion for failed pacing ability or occurrence of high-degree blocks mandating continuous pacing.

2. MATERIALS AND METHODS

2.1 Study population and study procedures

We included all patients undergoing TAVI in our center since the more systematic introduction of the pacing on the LV wire technique on 7 June 2018 until 31 December 2020. Patient eligibility for TAVI, access strategy and THV selection was per multidisciplinary heart team consensus. A dedicated prospective database captured relevant patient demographics, medical history and comorbidities, ECG, Transthoracic Echocardiography (TTE), Multislice computed tomography (MSCT) and procedural and clinical outcome

data. All patients provided written consent for the TAVI procedure and use of anonymous individual data for research purposes. The study was conducted in accordance with the declaration of Helsinki and did not fall under the scope of the Medical Research Involving Human Subjects Act per Institutional Review Boards' review.

2.2 Ventricular Pacing strategy during TAVI

We identified three cohorts: cohort 1 represents the patients with planned LV wire Pacing (= LVP-cohort). Cohort 2 features the patients who received a transvenous RV pacemaker (= RVP-cohort) prior to TAVI because of pre-existing high likelihood for procedure related high degree atrioventricular block that could make the patient pacemaker dependent including 1) Right Bundle Branch Block(RBBB) with a QRS duration >140ms, 2) LBBB >150ms, 3) bifascicular or trifascicular block. A third cohort of patients was scheduled for TAVI with no rapid pacing (= NoP-cohort); the external pacemaker was connected to the LV wire to provide temporary pacing only when needed.

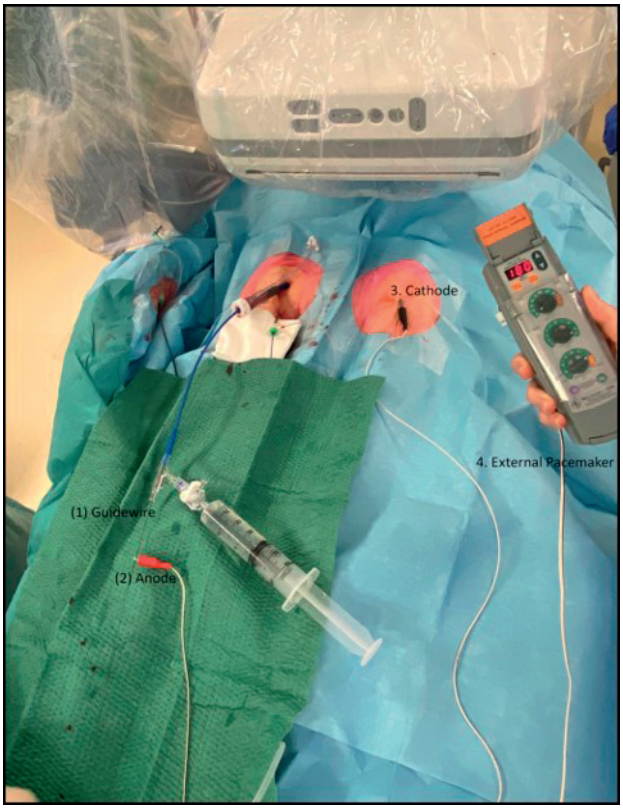

Figure 1: Pacing on the wire set-up

1. A guidewire was inserted in the right femoral artery. 2. the (red) anode of an external pacemaker was connected to the distal end of the wire. 3. the (black) cathode to a 15- or 18-gauge needle that partially pierced the skin. 4. Ventricular sensing and electrical capture with the external pacemaker was checked prior to the valve intervention.

A Safari wire (Boston Scientific, Marlborough, Massachusetts, USA) was the LV wire of first choice. The (red) anode of an external pacemaker was connected to the distal end of the wire and the (black) cathode to a 15- or 18-gauge needle that partially pierced the skin (see figure 1). Ventricular sensing and electrical capture were checked prior to any valve intervention (balloon aortic-valvuloplasty (BAV) or THV implantation). Anode and cathode could be exchanged in case of insufficient ventricular sensing or electrical capture. Central venous access was obtained prior to TAVI if the operator decided to proceed with a balloon tipped RV temporary pacemaker lead (St. Jude Medical, Saint Paul, Minnesota, USA) (RVP-cohort) or during TAVI if the patient developed high-degree AV-block with inadequate escape rhythm.

2.3 Outcomes and definitions

The primary endpoint for the LVP and NoP-cohorts was the need for bail-out temporary RV pacemaker insertion for failed pacing ability (no ventricular capture) or occurrence of high degree blocks mandating continuous pacing. Secondary endpoints included relevant clinical endpoints at 30 days follow-up and 'unnecessary' RV-pacemakers (i.e. a transvenous pacemaker that was inserted prior to TAVI but not used for BAV, THV implantation or high-degree AV-block). Relevant clinical endpoints at 30 days follow up were reported according to the VARC definitions and included the need for permanent pacemaker.(11)

Statistical analysis

Distribution of continuous variables were tested for normality with the Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation or median (interquartile range) and analyzed with a student's T-test, Mann Whitney U- or Kruskal-Wallis-test as appropriate. Categorical variables were reported as percentage and compared with Chi-Square or Fishers Exact test. A 2-sided P-value <0.05 was considered statistically significant. All statistics were performed with SPSS software version 25.0 (SPSS, Chicago IL, United States).

RESULTS

Study population

A total of 672 patients were included in the study and 365 (54.3%) were male. Median age was 80[IQR 74-84.] and the median BMI was 26.5[IQR 23.6-30.3]. LVP was initiated in 488 patients (73%) and a "no-pacing" strategy was applied in 139 patients.(figure 2) An RVP was inserted a priori in 45 patients (6.7%) because of LBBB in 13 (29%) and RBBB in 32 patients (71%). Baseline characteristics are summarized in table 1. There were no

differences in medical history, except for peripheral vascular disease (36.0% in the NoP-cohort vs. 42.2% in the RVP-cohort and 23.4% in the LVP-cohort, p=<0.001) and history of myocardial Infarction (18.0% in the NoP-cohort, 28.9% in the RVP-cohort and 12.9% in the LVP-cohort, p=0.009). A permanent pacemaker was present prior to TAVI in 18.0% and 17.2% of the NoP and LVP-cohorts respectively and in no patient in the RVP-cohort.

Table 1: baseline characteristics

	Total	NoP-cohort	RVP-cohort	LVP-cohort	P-value
N	672	139	45	488	
Age	80 (74-84)	79 (73-84)	81 (78-86)	79 (73-84)	0.07
Male	365 (54.3)	62 (44.6)	32 (71.1)	271 (55.5)	**0.005**
BMI	26.5 (23.6-30.3)	25.9 (22.5-29.7)	26.3 (23.4-29.6)	26.8 (24.0-30.5)	0.07
Medical History					
Hypertension	482 (71.7)	107 (77.0)	33 (73.3)	342 (70.1)	0.27
Hypercholesterolemia	372 (55.4)	90 (64.7)	26 (57.8)	256 (52.5)	**0.035**
Diabetes	201 (29.9)	41 (29.5)	16 (35.6)	144 (29.5)	0.92
Peripheral Vascular Disease	183 (27.2)	50 (36.0)	19 (42.2)	114 (23.4)	**0.001**
History of Myocardial Infarction	101 (15.0)	25 (18.0)	13 (28.9)	63 (12.9)	**0.009**
History of PCI	175 (26.0)	36 (25.9)	15 (33.3)	124 (25.4)	0.51
History of CABG	79 (11.8)	21 (15.1)	7 (15.6)	51 (10.5)	0.24
Stroke	146 (21.7)	38 (27.3)	9 (20.0)	99 (20.4)	0.20
COPD	101 (15.1)	27 (19.4)	5 (11.1)	69 (14.1)	0.23
Renal Failure	211 (31.4)	48 (34.5)	16 (35.6)	146 (30.1)	0.51
Pacemaker at baseline	109 (16.2)	25 (18.0)	0	84 (17.2)	**0.009**
Indication TAVI					0.61
Aortic Stenosis	647 (96.4)	132 (94.9)	44 (97.8)	471 (96.5)	
Aortic Regurgitation	5 (0.7)	3 (2.2)	0	2 (0.4)	
Mixed Aortic disease	9 (1.3)	2 (1.4)	0	7 (1.4)	
Failed bioprosthesis	11 (1.6)	2 (1.4)	1 (2.2)	8 (1.6)	

N = number, BMI = Body Mass Index, PCI = Percutaneous Coronary Intervention, CABG = Coronary Artery Bypass Graft, COPD = Chronic Obstructive Pulmonary Disease

3.2 Procedural characteristics and outcomes

Table 2 displays the procedural characteristics. The majority of patients received TAVI under local anesthesia for symptomatic severe aortic stenosis. Overall, a transfemoral access was applied in 94%. Transaxillary approach was used in 15% of the patients with NoP vs. 6.7% in the RVP and 3.3% in the LVP-cohort (P=<0.001). The Sapien3-valve (Edwards Lifesciences, Irvine, California, United States) was used in 12.3% of the patients, Evolut R and Pro (Medtronic, Minneapolis, Minnesota, United States) was respectively used in 18.3% and 20.4%, Lotus Edge and Acurate (Neo) (Boston Scientific, Marlborough,

Massachusetts, United States) in 10.4% and 8.3% and JenaValve (JenaValve Technology, Irvine, California, United States) in 0.3% of the patients.

Predilatation was performed in 33.3% of the RVP-cohort and 37.1% in the LVP-cohort and postdilatation in 26.7% in the RVP-cohort vs. 38.5% in the LVP-cohort and 0% in the NoP-cohort. There were no significant differences in complications during the TAVI-procedure, except for the need for a second valve (0% in the NoP-cohort, vs. 6.7% in the RVP-cohort and 2.5% in the LVP-cohort, p=0.025). A bail out temporary pacemaker during the TAVI procedure was implanted in 14 patients (10.1%) in the NoP-cohort and in 24 patients (4.9%) in the LVP-cohort. Reasons for bail out temporary pacemaker were (transient or permanent) high-degree AV-block in the majority of these patients (23 patients, 95.8%). One patient in the LVP-cohort required a temporary RV pacemaker lead for inadequate electrical ventricular capture during LV pacing. Rapid Pacing for pre- or postdilatation or valve deployment was performed in 84.4% in the RVP-cohort and a high-degree AV-block occurred in 45% of the patient in the RVP-cohort. In 4 patients (8.9%) a temporary pacemaker was not necessary for rapid pacing or as bail-out during the procedure. Procedure time was significantly longer in the RV pacing cohort (68 minutes[IQR 52-88.], vs 55 minutes [IQR 44-72] in NoP-cohort and 55 minutes [IQR 43-71] in the LVP-cohort.(p=0,005))

The 30-day outcomes are tabulated in table 3. There were no significant differences in vascular or bleeding complications between the three groups. Any neurological events occurred more in the RVP-cohort (8.9% in RVP vs 5.0% in NoP vs 1.6% in LVP, p=0.004). However, there was no significant difference in disabling stroke(4.4% in RVP vs. 1.4% in NoP vs. 1.0% in LVP, p=0.16). Twenty-one patients (46.7%) received a definite pacemaker in the RVP-cohort vs. 27 (19.7%) in the NoP and 53 (10.9%) in the LVP-cohorts (p=<0.001).

3.3 Conduction disturbances

Subgroup analysis excluding procedural deaths and patients with a pacemaker at baseline showed high degree AV-block during the procedure occurred most often in the RVP-cohort (45%. vs. 14% in the LVP-cohort and 16% in NoP-cohort (p=<0.001))(Figure 3). In the RVP-cohort, 50% of the RBBB-patients developed a high-degree AV-block, compared to 31% of the LBBB patients (p=0.33) In 23(4.7%) patients in the LVP-cohort, the temporary pacemaker was left in, compared to 13 (9.7%) in the NoP-cohort and 36 (80%) in the RVP-cohort. Of these 36 patients from the RVP-cohort, 20 patients (56%) had a temporary pacemaker due to procedural high-degree AV-block and in 16 (44%) patients the temporary pacemaker was left in due to their high pre-procedural risk factors for conduction disturbances.

Table 2: procedural characteristics

	Total	NoP-cohort	RVP-cohort	LVP-cohort	P-value
Procedure					
Anesthesia					0.11
Local	659 (98.1)	138 (99.3)	42 (93.3)	479 (98.2)	
General	13 (1.9)	1 (0.7)	3 (6.7)	9 (1.9)	
Access					**<0.001**
Femoral	633 (94.2)	119 (85.6)	42 (93.3)	472 (96.7)	
Subclavian/Axillary	39 (5.8)	20 (14.4)	3 (6.7)	16 (3.3)	
Cerebral protection	303 (45.1)	54 (38.8)	24 (53.3)	225 (46.1)	0.16
Rapid Pacing total	526 (78.3)	0	38 (84.4)	488 (100)	**<0.001**
Predilatation	196 (29.2)	0	15 (33.3)	181 (37.1)	**<0.001**
Postdilatation	200 (29.8)	0	12 (26.7)	188 (38.5)	**<0.001**
Valve deployment	298 (44.3)	0	23 (51.1)	275 (56.4)	**<0.001**
Implantation depth NCC	6.4 [4.6 – 8.6]	7.7 [4.7 – 10.2]	5.9 [4.8 – 8.1]	6.3 [4.6 – 8.0]	**0.04**
Implantation depth LCC	6.2 [4.5 – 8.6]	8.1 [5.3 – 10.8]	5.5 [4.8 – 6.6]	5.9 [4.4 – 7.7]	**<0.001**
Transcatheter heart Valve					**<0.001**
Sapien3	284 (42.3)	0	22 (48.9)	262 (53.7)	
Evolut (R and Pro)	260 (38.7)	96 (69.1)	14 (31.1)	150 (30.7)	
Lotus	70 (10.4)	41 (29.5)	4 (8.9)	25 (5.1)	
Acurate	56 (8.3)	0	5 (11.1)	51 (10.5)	
Jenavalve	2 (0.3)	2 (1.4)	0	0	
Procedural complications					
Procedural death	3 (0.4)	2 (1.4)	0	1 (0.2)	0.14
need second valve	15 (2.2)	0	3 (6.7)	12 (2.5)	**0.025**
Valve embolisation	10 (1.5)	1 (0.7)	1 (2.2)	8 (1.6)	0.67
Conversion AVR	2 (0.3)	0	0	2 (0.4)	0.69
Coronary Obstruction	3 (0.4)	2 (1.4)	0	1 (0.2)	0.14
Need temporary PM during procedure	83 (12.4)	14 (10.1)	45 (100)	24 (4.9)	**<0.001**
Need temporary PM due to no capture	1 (0.1)	0	0	1 (0.2)	
new high-degree AV-block	76 (13.6)	18 (16.1)	20 (44.5)	38 (9.4)	**<0.001**
new LBBB	255 (45.5)	56 (50.0)	6 (13.3)	193 (47.9)	**<0.001**
Temporary PM left in	72 (10.7)	13 (9.4)	36 (80.0)	23 (4.7)	**<0.001**
procedure time	56 (44-74)	55 (44-72)	68 (52-88)	55 (43-71)	**0.005**

NCC = Non-coronary cusp, LCC = Left-coronary cusp, AVR = Aortic valve Replacement, PM = pacemaker, AV = atrioventricular, LBBB = left bundle branch block

Table 3 : 30-day outcomes

30-day outcomes	Total	NoP-cohort	RVP-cohort	LVP-cohort	P-value
Death	15 (2.2)	2 (1.4)	2 (4.4)	11 (2.3)	0.49
Any neurological Event	19 (2.8)	7 (5.0)	4 (8.9)	8 (1.6)	**0.004**
Disabling Stroke	9 (1.3)	2 (1.4)	2 (4.4)	5 (1.0)	0.16
Vascular complication (overall)					0.43
Major	43 (6.4)	13 (9.4)	1 (2.2)	29 (5.9)	
Minor	56 (8.3)	12 (8.6)	3 (6.7)	41 (8.4)	
Bleeding (overall)					0.56
life-threatening	18 (2.7)	5 (3.6)	1 (2.2)	12 (2.5)	
major	22 (3.3)	7 (5.1)	0	15 (3.1)	
minor	41 (6.1)	6 (4.3)	2 (4.4)	33 (6.8)	
Vascular complication heart	11 (1.6)	3 (2.2)	1 (2.2)	7 (1.4)	0.80
Bleeding heart	10 (1.4)	3 (2.1)	1 (2.2)	6 (1.2)	0.38
Conduction					
new LBBB	156 (27.9)	41 (36.6)	1 (2.2)	114 (28.3)	**<0.001**
New Pacemaker	101 (15.1)	27 (19.7)	21 (46.7)	53 (10.9)	**<0.001**
New Pacemaker in pacemaker naïve patients	101 (18.0)	27 (24.1)	21 (46.7)	53 (13.2)	**<0.001**
Indication Pacemaker					0.068
high-degree AV-block	83 (82.2)	24 (88.9)	20 (95.2)	39 (73.6)	
Brady-Tachy syndrome	12 (11.9)	1 (3.7)	0	11 (20.8)	
1st degree AV-block + LBBB with prolonged conduction times	6 (5.9)	2 (7.4)	1 (4.8)	3 (5.7)	
Length of stay (days)	4 (3-7)	5 (4-7)	6 (4-7)	4 (3-7)	**0.004**
Rehospitalisations	75 (11.2)	19 (13.9)	9 (20.0)	47 (9.7)	0.060

LBBB = Left bundle branch block. AV = atrioventricular

In total, 101 patients (18%) received a new PPI. Indications for a definitive PPI were high-degree AV-block (82%), brady-tachy syndrome (12%) and first-degree AV-block with LBBB with excessive QRS duration (6%). Need for new PPI occurred in 47% in the RVP-cohort, compared to 20% in the NoP-cohort and 11% in the LVP-cohort, p=<0.001. In the RVP-cohort, 59% of the patients with a RBBB received a new PPI, compared to 15.4% of patients with LBBB. Patients who developed a per-procedural high-degree AV-block received a new PPI in 57% of cases, compared to 12% in the patients without a per-procedural high-degree AV-block (p<0.001). Of the patients with a procedural transient high-degree AV-block, 42% needed a definitive PPI, compared to 84.6% of the patients with a persistent high-degree AV-block(P<0.001).

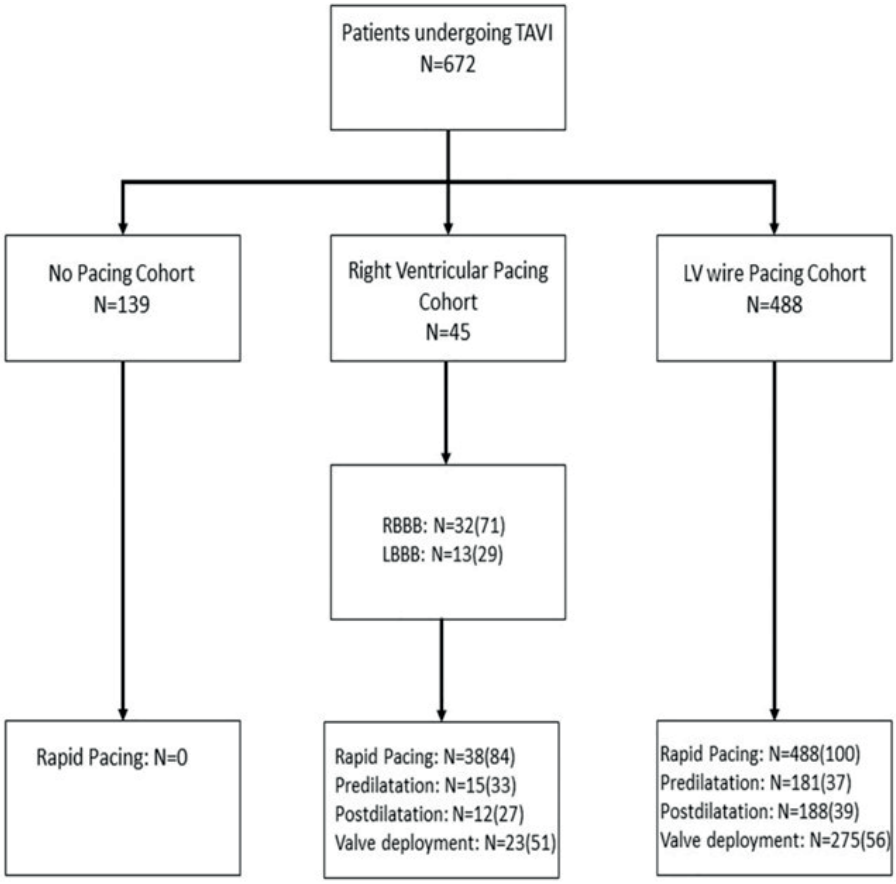

Figure 2 : flow chart of patient selection and distribution. LV= left ventricular. RBBB=right bundle branch block. LBBB=Left bundle branch block

4 DISCUSSION

Our experience with a restricted RV pacing strategy during TAVI highlighted the following: 1) majority of TAVI procedures can be safely performed without a temporary RV pacemaker and a no-RV pacemaker strategy contributes to a lean procedure by reducing overall procedure time. 2) Pacing on the LV wire is reliable and safe and a bail-out temporary RV pacemaker was required in only 5% of cases because of the occurrence of permanent high-degree AV-block. 3) TAVI induced conduction disorders require observation but most often no temporary RV pacemaker. 4) RV pacing remains reasonable in patients at high-risk for permanent high-degree AV-block (e.g. selected RBBB and LBBB phenotypes).

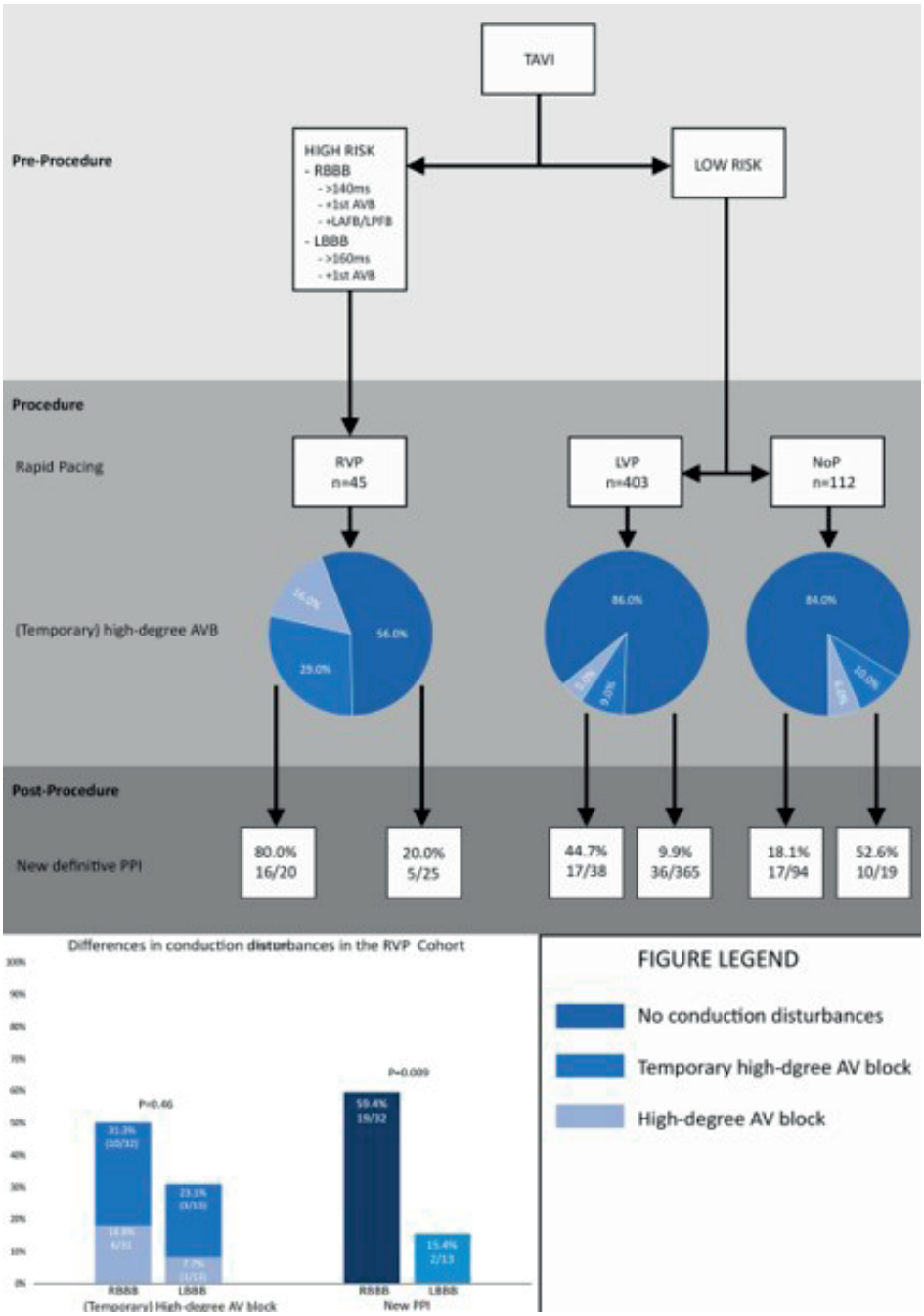

Figure 3: overview of conduction disturbances in a subgroup of patients without a pacemaker at baseline or procedural death. RBBB=Right Bundle Branch Block. LBBB=Left Bundle Branch Block, RVP=Right ventricular temporary pacemaker, LVP = Left ventricular rapid pacing, NoP=No rapid pacing, AVB=AtrioVentricular Block. PPI=permanent pacemaker implantation

TAVI transformed into a simplified procedure characterized by local anesthesia or conscious sedation and minimized instrumentation. A temporary RV pacemaker through central venous access was originally deemed a prerequisite to abate new conduction disorders and to deliver rapid RV pacing for balloon- pre- or postdilatation and transcatheter valve deployment. Our restricted RV pacing practice refuted this paradigm demonstrating that the vast majority of TAVI cases could be executed without temporary RV pacemaker lead: a temporary pacemaker was deemed necessary at the start of the TAVI procedure because of extensive conduction issues at baseline at high likelihood for a high-degree AV-block in only 6.7% of cases. Pacing on the LV wire was safely used in 72.6% of patients and no pacing was delivered in 20.7% of patients. Strategy was determined by THV design selection and patient characteristics. Any kind of pacing is essential for the deployment of balloon-expandable THV and in selected cases of self-expanding THVs or when balloon dilatation is required. Importantly, new conduction disorders were not rare but did not require pacing in the vast majority of events. Indeed, a bail-out temporary pacemaker was required for permanent high-degree AV-block in 5% of the LVP-cohort and in 10% of patients with an initial no-pacing strategy. Only 1 patient in the LVP-cohort needed a temporary pacemaker because of insufficient electrical ventricular capture during LV pacing.

The EASY TAVI randomized trial demonstrated similar pacing safety and efficacy and shorter procedure times with LV pacing as compared to RV pacing in 307 patients undergoing TAVI with a balloon expandable THV. Our experience extend these findings to a clinical practice that included various THV designs and also demonstrated no need for any pacing in a significant portion of patients (undergoing TAVI with a self-expanding THV and without any need for balloon dilatation).(9) We confirmed that this restricted RV pacing strategy may complement a lean TAVI program by further curtailing overall procedure time by > 10 minutes. As expected need for permanent pacemaker was higher in the RVP-cohort because of the risk profile of patients. In this cohort new permanent pacemakers were required particularly in patients with RBBB at baseline (59%). RBBB is an established risk factor with new pacemaker rates of up to 40%.(12) In the RVP-cohort, the risk for a permanent pacemaker was even higher as we only included RBBB-patients with a prolonged QRS-duration(>140ms) or bi- or trifascular block. A procedural temporary pacemaker remains reasonable in these patients. However, also the LVP and no-pacing cohorts demonstrated relevant permanent pacemaker needs despite no temporary pacemakers were used. This seems to illustrate that TAVI related high-degree AV-blocks are often transient or with sufficient escape rhythms that allow to bridge to a permanent pacemaker implantation without the need of a temporary pacemaker. We believe this is clinically relevant because central venous access and insertion of a temporary pacemaker in the RV apex may not be harmless and could result in clinically relevant

bleeding or access site complications (including pericardial effusion and tamponade). In fact, data from Milan suggested that more than half of the pericardial tamponade cases after TAVI were related to RV perforation by a temporary pacemaker.(13)

The 2020 American College of Cardiology expert consensus document recommended 1) a temporary RV pacemaker lead, preferably inserted through the right internal jugular vein over LVP in patients at high-risk for conduction disturbances, which included a RBBB or first-degree AV-block, a heavily calcified aortic valve or a short membranous septum and 2) to keep a central venous access and preferably transvenous pacemaker in situ for at least 24 hours also in patients who developed new LBBB or an increase in PR/QRS duration ≥ 20msec.(14) A Journal of the American College of Cardiology Scientific Expert Panel also recommended to keep a transveous temporary pacemaker lead in situ for 24 hours after TAVI (or at least overnight) in all patients except those with no new conduction disorders and no RBBB.(15) Our data tone down the formal requirement for an indwelling transvenous pacemaker for 24 hours because only 10% of the patients had a temporary pacemaker in situ after the procedure with no additional conduction issues requiring bail-out temporary pacemaker in the remaining patients.

4.1 Study limitations

Our study is a single center registry analysis with inherent limitations. Valve selection and choice of (pacing) wire was per operators discretion, with innate selection bias. Also 10% of patients received a mechanically expanded THV that was associated with the highest need for permanent pacemaker implantation, but is no longer commercially available.

Our study aimed to demonstrate the safety of a restricted temporary pacemaker use in every-day practice. Patient selection for RVP was predominantly based on ECG criteria. Other known risk factors for conduction disorders post-TAVI, such as membranous septum length and LVOT calcifications, were not used as a specific criteria. These factors could further refine conduction management after TAVI.

5 CONCLUSIONS

A restricted RV pacemaker strategy is safe and shortens procedure time. The majority of TAVI procedures do not require a temporary RV pacemaker lead.

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Changes in demographics, treatment and outcomes in a consecutive cohort who underwent transcatheter aortic valve implantation between 2005 and 2020

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ABSTRACT

Introduction Transcatheter aortic valve implantation (TAVI) has matured to the treatment of choice for most patients with aortic stenosis (AS). We sought to identify trends in patient and procedural characteristics, and clinical outcomes in all patients who underwent TAVI between 2005 and 2020.

Methods A single-centre analysis was performed on 1500 consecutive patients who underwent TAVI, divided into three tertiles (T) of 500 patients treated between November 2005 and December 2014 (T1), January 2015 and May 2018 (T2), and June 2018 and April 2020 (T3).

Results Over time, mean age and gender did not change (T1 to T3: 80, 80 and 79 years and 53%, 55% and 52% men, respectively), while the Society of Thoracic Surgeons risk score declined (T1: 4.5 to T3: 2.7%, $p<0.001$). Use of general anaesthesia also declined over time (100%, 24% and 1% from T1 to T3) and transfemoral TAVI remained the default approach (87%, 94% and 92%). Median procedure time and contrast volume decreased significantly (186, 114 and 56 min and 120, 100 and 80 ml, respectively). Thirty-day mortality (7%, 4% and 2%), stroke (7%, 3% and 3%), need for a pacemaker (19%, 22% and 8%) and delirium (17%, 12% and 8%) improved significantly, while major bleeding/vascular complications did not change (both approximately 9%, 6% and 6%). One-year survival was 80%, 88% and 92%, respectively.

Conclusion Over 15 years' experience, patient age remained unchanged but the patient risk profile became more favourable. Simplification of the TAVI procedure occurred in parallel with major improvement in outcomes and survival. Bleeding/vascular complications and the need for pacemaker implantation remain the Achilles' heel of TAVI.

Keywords Aortic stenosis · Transcatheter aortic valve implantation · Survival · Clinical outcomes

INTRODUCTION

Since the first transcatheter aortic valve implantation (TAVI) was performed in a patient with aortic stenosis (AS) at prohibitive surgical risk in 2002, TAVI has evolved into a standardised minimally invasive treatment for high-risk patients [1-3]. Expanding operator experience, improvements in catheter and valve design and progress in peri-procedural patient care have contributed to improved outcomes and have been followed by further simplification of the TAVI pathway (i.e. post-procedural monitoring and recovery on the cardiology ward in lieu of the intensive care unit, early mobilisation and early discharge) [4-7].

As randomised controlled trials (RCTs) showed equivalence between TAVI and surgical aortic valve replacement (SAVR), the European Society of Cardiology updated the guidelines in 2017 by expanding indications for TAVI in patients at intermediate surgical risk [8]. Importantly, a recent RCT showed transfemoral TAVI to be superior to SAVR in low-risk patients [9].

In the context of the above, we sought to analyse whether this development had an impact on the patients that we accepted and treated for TAVI in conjunction with in-hospital outcomes and survival post-discharge of the first 1500 patients that underwent TAVI in our institution between 2005 and 2020.

METHODS

Study population

The study population comprised the first 1500 patients with AS (including 15 patients with aortic regurgitation more severe than stenosis) who underwent TAVI between November 2005 and April 2020 at the Erasmus University Medical Centre (Erasmus MC), Rotterdam, The Netherlands. Patient selection and treatment strategy was based on clinical (i.e. age, comorbidities, surgical risk) and anatomical characteristics (access-site suitability) in the context of available valve technology per studied time period. Self-expanding valves were primarily used during the start-up phase in 2005-2007, after which self-expanding, balloon-expandable and mechanically expanded (the last mentioned since 2013) devices were used in more recent phases of the TAVI programme. In the initial period (November 2005 – October 2010), the final treatment decision was based on arbitrary case discussions primarily between an interventional cardiologist and a thoracic surgeon, complemented with a radiologist with valvular access and closure expertise. From October 2010, patient eligibility for TAVI, choice of treatment

and strategy were decided during a structured weekly meeting of a multidisciplinary heart team consisting of an interventional cardiologist, a cardiac surgeon, a cardiac anaesthetist and an imaging cardiologist [10]. Since October 2013, all patients with AS evaluated at the outpatient cardiology clinic were also seen by the geriatrician who assessed specific pre-defined geriatric domains such as physical function, frailty and cognitive status. This was done in the framework of the TAVI Care & Cure clinical research project and programme, the details of which have been described before [11]. A diagnosis of delirium was based on geriatric assessment as described previously [12]. All other endpoint definitions are in accordance with VARC-2 criteria [13].

The study has been reviewed and approved by the ethics committee of the Erasmus MC (MEC-2014-277) and was conducted according to the Erasmus MC regulations for appropriate use of data in patient-oriented research and the privacy policy of the Erasmus MC. Data on mortality after hospital discharge were collected via the Dutch Civil Registry.

Statistical analyses

For the assessment of changes in patient demographics and clinical outcomes, the study population of 1500 patients was categorised into three chronological tertiles of 500 patients each. Tertile 1 (T1) included all TAVI cases performed between November 2005 and December 2014; tertile 2 (T2) included those treated between January 2015 and May 2018, while tertile 3 (T3) included patients treated between June 2018 and April 2020.

Continuous variables are presented as mean ± standard deviation or median with interquartile range, and differences between the three tertiles were analysed by one-way ANOVA or Kruskal-Wallis test, as appropriate. Categorical variables are presented as numbers and percentages and were analysed by chi-square test or Fisher's exact test, as appropriate. One-year survival was studied with the Kaplan-Meier method; the log-rank test was used to evaluate differences between tertiles. Results are assumed to be statistically significant if $p<0.05$. All data were analysed with SPSS software (SPSS Version 25; IBM Corp., Armonk, NY, USA).

Table 1 Demographics and baseline characteristics

	Total cohort	Tertile 1	Tertile 2	Tertile 3	
Period of admission	Nov 2005–Apr 2020	Nov 2005–Dec 2014	Jan 2015-May 2018	Jun 2018-Apr 2020	
	n=1500	*n*=500	*n*=500	*n*=500	*p*-value
Age, mean ± SD	79.4±7.9	79.8±8.0	79.5±7.8	78.9±7.8	0.17
Male, *n* (%)	797 (53)	263 (53)	273 (55)	261 (52)	0.72
Body mass index, mean ± SD	27.0±5.0	26.5±4.6	27.1±4.9	27.3±5.4	**0.027**
Medical history, *n* (%):					
Stroke	318 (21)	104 (21)	101 (20)	113 (22)	0.63
Myocardial infarction	308 (21)	125 (25)	106 (21)	77 (15)	**0.004**
Peripheral vascular disease	617 (41)	241 (48)	218 (44)	158 (32)	**<0.001**
Percutaneous coronary intervention	439 (29)	146 (29)	161 (32)	132 (27)	0.14
Coronary artery bypass graft surgery	263 (18)	115 (23)	86 (17)	62 (12)	**<0.001**
Previous valve replacement	88 (6)	26 (5)	31 (6)	31 (6)	0.74
Risk factors, *n* (%):					
Diabetes mellitus	460 (31)	150 (30)	159 (32)	151 (30)	0.65
Hypertension	1099 (73)	345 (69)	390 (78)	364 (73)	**0.002**
Chronic renal failure	499 (33)	138 (28)	198 (40)	163 (33)	**0.001**
Chronic obstructive pulmonary disease	306 (20)	133 (27)	93 (19)	80 (16)	**<0.001**
Malignancy					0.47
Curative treatment	263 (18)	76 (15)	96 (19)	91 (18)	
Under treatment or proven metastases	69 (5)	20 (4)	22 (4)	27 (5)	
Clinical characteristics, *n* (%):					
Pacemaker	149 (10)	47 (9)	50 (10)	52 (11)	0.68
LBBB/RBBB, *n/n* (total %)	172 / 137 (21)	69 / 44 (14)	44 / 50 (19)	59 / 43 (20)	0.25

Table 1 Demographics and baseline characteristics (*continued*)

	Total cohort	Tertile 1	Tertile 2	Tertile 3	
Porcelain aorta	42 (3)	15 (3)	16 (3)	11 (2)	0.60
Chronic haemodialysis	32 (2)	16 (3)	11 (2)	5 (1)	0.055
Creatinine, median (IQR)	95 (76-120)	96 (77-123)	96 (75-123)	93 (74-115)	0.057
Haemoglobin, mean ± SD	7.7±1.1	7.7±1.0	7.8±1.0	7.7±1.1	0.14
NYHA class III/IV	1000 (67)	403 (81)	307 (61)	290 (58)	**<0.001**
STS score, median (IQR)	3.9 (2.5-5.8)	4.5 (3.3-6.5)	4.3 (2.9-6.7)	2.7 (1.8-4.2)	**<0.001**
Echocardiographic parameters					
Aortic valve area (cm^2)[a], median (IQR)	0.79 (0.60-0.90)	0.70 (0.60-0.90)	0.74 (0.60-0.90)	0.80 (0.68-0.90)	**<0.001**
Mean aortic gradient (mmHg)[b], median (IQR)	39 (30-49)	41 (30-52)	38 (30-48)	38 (30-48)	**0.010**
AR ≥ moderate, *n* (%)[c]	255 (19)	77 (19)	91 (19)	87 (19)	0.99
MR ≥ moderate, n (%)[d]	308 (23)	79 (20)	130 (27)	99 (21)	**0.015**
Indication for TAVI, *n* (%):					0.061
Severe native AS	1386 (92)	466 (93)	448 (90)	472 (94)	
Severe native AR	15 (1)	4 (1)	7 (1)	4 (1)	
Degenerated surgical bio-prosthesis	37 (2.6)	13 (3)	19 (4)	5 (1)	
Other (i.e. moderate AS, mixed AS/AR)	62 (4)	17 (3)	26 (5)	19 (4)	

LBBB Left bundle branch block, *RBBB* right bundle branch block, *IQR* interquartile range, *NYHA* New York Heart Association, *STS* Society of Thoracic Surgeons, *AR* aortic regurgitation, *AS* aortic stenosis, *MR* mitral regurgitation, *TAVI* transcatheter aortic valve implantation

Data not available in [a])121 patients, [b]) 121 patients, [c]) 170 patients, and [d]) 149 patients

RESULTS

The study results (baseline characteristics, procedural details and in-hospital outcomes and mortality at 30 days) are summarised in Tables 1-3. The first 500 patients were treated in the first 9 years and 2 months (November 2005 – December 2014), while the next two cohorts of 500 patients were treated in the following 3 years and 5 months (January 2015 – May 2018) and 1 year and 10 months (June 2018 – March 2020). In other words, it took almost 10 years to include the first 500 patients but only 3.5 years and less than 2.0 years for the subsequent cohorts.

While age and gender did not change from T1 to T3 (80, 80 and 79 years and 53%, 55% and 52% male gender, respectively), the patient's baseline risk [i.e. Society of Thoracic Surgeons (STS) risk score] dropped from 4.5% to 2.7% (p<0.001) due to a progressive decline in the prevalence of antecedent cardiovascular disease (i.e. myocardial infarction, coronary bypass surgery and peripheral artery disease) (Electronic Supplementary Material, Fig. S1). In addition, the aortic valve area at discharge increased significantly over time (1.60-2.00 cm^2, p<0.001). There was a slight, but significant, increase in the prevalence of atrial fibrillation (31%-35%). The prevalence of hypertension and renal failure fluctuated.

With respect to the TAVI procedure, general anaesthesia was virtually eliminated (100%, 24% and 1% from T1 to T3). Transfemoral TAVI remained the default approach (87%, 94% and 92%) with subclavian being the most common alternative (1%, 0% and 7%) (Electronic Supplementary Material, Fig. S2). Also, there was a decrease in the use of balloon pre-dilatation (84% to 25%, p<0.001), albeit with a higher overall need for balloon post-dilatation (19%-30%, p<0.001). Initially, the self-expanding prosthesis CoreValve (Medtronic, Minneapolis, MN, USA) was the only valve used (later replaced by the Evolut R and Evolut PRO). In 2007, the balloon-expandable Edwards Sapien3 valve (Edwards Lifesciences, Irvine, CA, USA) was introduced into our programme, followed by the mechanically expanded Lotus valve (Boston Scientific, Marlborough, MA, USA) in 2013. Vascular closure was predominantly performed surgically in T1 (78%), while a fully percutaneous approach was used in T3 (97%, p<0.001). Following its introduction in 2013, the use of filter-based cerebral embolic protection (CEP) increased from 26% to 43% (p=0.001). Overall, the median procedure time and contrast volume reduced significantly (186, 114 and 56 min and 120, 100 and 80 ml, respectively). With respect to outcomes, the frequency of 30-day all-cause mortality (7%, 4% and 2%), all stroke (7%, 3% and 3%), new pacemaker implantation (19%, 22% and 8%) and delirium (17%, 12% and 8%) improved significantly. The frequency of major bleeding and vascular complications did not change over time (both approximately 9%, 6% and 6% over the entire study period). One-year survival increased significantly from T1 to T3 (Fig. 1).

Table 2 Procedural characteristics

	Total cohort	Tertile 1	Tertile 2	Tertile 3	
Period of admission	Nov 2005-Apr/2020	Nov 2005-Dec 2014	Jan 2015-May 2018	Jun 2018-Apr 2020	
	n=1500	*n*=500	*n*=500	*n*=500	*p*-value
Urgent procedure, *n* (%)	52 (4)	15 (3)	15 (3)	22 (4)	0.38
PCI (combined), *n* (%)	158 (11)	45 (9)	49 (10)	64 (13)	0.077
Anaesthesia, *n* (%)[a]					**<0.001**
General anaesthesia	622 (42)	500 (100)	117 (24)	5 (1)	
Local anaesthesia	861 (57)	0	377 (75)	484 (97)	
Conscious sedation	11 (1)	0	6 (1)	5 (1)	
Access, *n* (%)[a]					**<0.001**
Transfemoral	1360 (91)	434 (87)	468 (94)	458 (92)	
Transapical	43 (3)	29 (6)	14 (3)	0 (0)	
Subclavian	44 (3)	6 (1)	1 (0)	37 (7)	
Other (i.e. axillary, aortic)	50 (3)	31 (6)	17 (3)	2 (0.4)	
Cerebral protection device, *n* (%)	604 (40)	129 (26)	260 (52)	215 (43)	**<0.001**
Balloon pre-dilatation, *n* (%)	598 (40)	418 (84)	57 (11)	123 (25)	**<0.001**
Balloon post-dilatation, *n* (%)	381 (26)	93 (19)	138 (28)	150 (30)	**<0.001**
Prosthesis type, *n* (%):[a]					**<0.001**
Self-expanding[b]	827 (55)	354(71)	222 (45)	251 (51)	
Mechanically expanded[c]	208 (14)	41 (8)	118 (24)	49 (10)	
Balloon expandable[d]	460 (31)	105 (21)	159 (32)	196 (40)	
Valve-in-valve, *n* (%)	39 (3)	20 (4)	8 (2)	11 (2)	0.11
Conversion to SAVR, *n* (%)	5 (0.3)	1 (0)	2 (0)	2 (0)	0.80
Vascular closure, *n* (%):					**<0.001**
Surgical	422 (28)	390 (78)	21 (4)	11 (2)	

Table 2 Procedural characteristics (*continued*)

	Total cohort	Tertile 1	Tertile 2	Tertile 3	
Prostar XL	77 (5)	59 (12)	18 (4)	0	
Proglide	318 (21)	43 (9)	131 (26)	144 (29)	
Manta	571 (38)	0	229 (46)	342 (68)	
Other (i.e. TR band, left in situ)	112 (8)	8 (2)	101 (20)	3 (1)	
Fluoroscopy time (min), median (IQR)	15 (11-21)	21 (16-31)	15 (12-20)	13 (10-18)	**<0.001**
Contrast volume (ml), median (IQR)	100 (80-130)	120 (95-170)	100 (80-125)	80 (75-100)	**<0.001**
Procedure time (min), median (IQR)	120 (65-177)	186 (156-224)	114 (80-149)	56 (43-72)	**<0.001**

PCI Percutaneous coronary intervention, *SAVR* surgical aortic valve replacement, *IQR* interquartile range
[a]Due to some (≤6) missing data, totals may not add up to 1500/500
[b]Includes: Medtronic CoreValve, Evolut R, Evolut Pro, Symetis Acurate, Edwards Centera, JenaValve and Portico
[c]Includes: Lotus, Lotus Edge and Lotus Depth Guard
[d]Includes: Edwards XT and Edwards Sapien 3

Table 3 Clinical outcomes

	Total cohort	Tertile 1	Tertile 2	Tertile 3	
Period of admission	Nov 2005-Apr 2020	Nov 2005-Dec 2014	Jan 2015–May 2018	Jun 2018–Apr 2020	
	n=1500	*n*=500	*n*=500	*n*=500	*p*-value
All-cause mortality, n (%)					
30-day mortality	63 (4)	34 (7)	18 (4)	11 (2)	0.001
1-year mortality	201 (14)	100 (20)	62 (12)	39[a]	**<0.001**
3-year mortality	370 (28)	187 (38)	131[b]	52[b]	**<0.001**
In-hospital complications, n (%)					
All bleeding complications (<24 h)	205 (14)	73 (15)	75 (15)	57 (11)	0.19
a. Life-threatening/disabling/major	105 (7)	46 (9)	28 (6)	31 (6)	0.057
Peri-procedural myocardial infarction (<72 h)	13 (1)	4 (1)	3 (1)	6 (1)	0.58
Stroke/transient ischaemic attack	63 (4)	35 (7)	15 (3)	13 (3)	**0.001**
All vascular complications	263 (18)	82 (16)	96 (19)	85 (17)	0.47
a. Major vascular complication	121 (8)	43 (9)	39 (8)	40 (8)	0.35
Delirium	123 (12)	37 (17)	59 (12)	27 (8)	**0.018**
Conduction disorders, *n* (%):					
a. New left bundle branch block	744 (56)	256 (68)	268 (58)	220 (46)	**<0.001**
b. 3rd-degree AV block	147 (10)	46 (9)	65 (13)	36 (7)	**0.007**
c. Temporary pacemaker, *n* (%)	666 (46)	300 (60)	309 (62)	57 (13)	**<0.001**
d. New permanent pacemaker[c], *n* (%)	224 (17)	87 (19)	99 (22)	38 (8)	**<0.001**
Discharge echocardiography[d], mean±SD:					
Aortic valve area (cm^2), median (IQR)	1.80 (1.50-2.20)	1.60 (1.40-2.07)	1.80 (1.50-2.20)	2.00 (1.60-2.30)	**<0.001**
Mean aortic gradient (mmHg), median (IQR)	9.0 (7.0-13.0)	9.0 (7.0-12.0)	9.0 (7.0-13.0)	10.0 (7.0-14.0)	0.20
AR ≥ moderate, *n* (%)	127 (11)	41 (11)	46 (10)	40 (12)	0.73

Table 3 Clinical outcomes (*continued*)

	Total cohort	Tertile 1	Tertile 2	Tertile 3	
MR ≥ moderate, *n* (%)	211 (19)	53 (16)	95 (21)	63 (19)	0.21

AV atrioventricular, *IQR* interquartile range, *AR* aortic regurgitation, *MR* mitral regurgitation

[a]No percentage since cohort 3 did not complete the full 1-year follow-up

[b]No percentage since cohorts 2 and 3 did not complete the full 1- and 3-year follow-up

[c]Percentage is based on number of patients with new pacemaker divided by number of patients without a pacemaker at baseline

[d]Data not available in approximately one-third of the total cohort

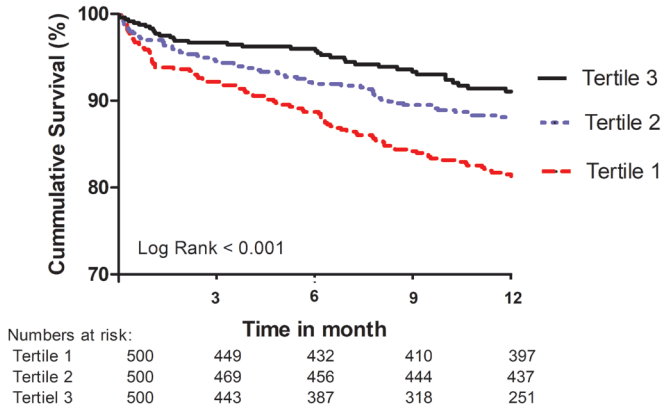

Figure 1 Overall 1-year survival

DISCUSSION

Over our 15 years' experience, we found that the age of patients who received TAVI in our institution (approximately 80 years) did not change, while operative risks dropped from prohibitive/high to intermediate, mainly because of fewer antecedent cardiovascular diseases. In conjunction, the in-hospital complication rates and 1-year mortality improved significantly. Another finding is the exponential growth in TAVI that preceded the publication of the two RCTs assessing the role of TAVI in intermediate-risk patients (2016) [14, 15]. This increase likely reflects the embracement of TAVI by the patients and their relatives, as well as by the medical professionals and institutions, based upon the minimally invasive nature of the procedure (including local anaesthesia) and its sound technical/physiological concept, namely the effective reduction of increased afterload of the left ventricle by the replacement of a stenotic valve similar to surgical replacement.

The reason for improved outcomes is obviously multifactorial and the question as to which factor played a (more) prominent role cannot be answered given the observational nature and time bias of this study. Patient-specific factors but also growing operator experience, refinements in catheter and device technology and procedure simplification will have played a role in reducing risks in favour of better outcomes. These advancements likely played a role in achieving a greater aortic valve area and overall valve performance over time, which is known to favourably influence outcomes. Simplification measures (i.e. abandoning the use of general anaesthesia, use of a femoral approach in almost 100% of cases) likely resulted in significant reductions of delirium and mortality [12]. It has to be acknowledged that the present series stems from an institution that

was an early adopter of TAVI at a time when TAVI was still in an experimental phase with limited experience worldwide, during which general anaesthesia, surgical cut-down and circulatory support were the standard, in addition to the fact that only patients at extreme risk were considered as candidates [16]. Also, the institution played a role in the elimination of circulatory support and the introduction of echo-guided access with a percutaneous closure technique that paved the way for a true percutaneous approach in TAVI [17].

It may be assumed that the combination of the factors described above plus the implementation of TAVI in the true low-risk or so-called surgical candidate will further reduce complication rates and improve outcomes. The incessant improvement of outcomes over time is illustrated by the RCTs that initially recruited extreme-risk (2010) [2, 3] and subsequently intermediate-risk (2017) [14, 15] and most recently (2019) [9, 18] low-risk patients. It is noteworthy that data from the PARTNER III and NOTION trials have contributed to expanding indications for TAVI in the updated European Society of Cardiology guidelines for valvular heart disease, supporting the selection of lower-risk patients based on multidisciplinary heart team consensus [8, 9, 19].

At the commencement of the TAVI programme at our centre, the function and position of the heart team was elementary and foundational in nature. The team initially comprised only a cardiologist and a cardiothoracic surgeon, whereas since 2010 discussions on structural heart disease cases are held on a regulated, weekly basis, using a formalised, multidisciplinary approach, involving cardiologists, surgeons and geriatricians. With the inclusion of geriatricians in the heart team, more specific attention is paid to patient perspectives and preferences, coupled with life expectancy and the influence of the frailty status (i.e. utility vs futility) [10, 20-22].

As we learned by doing and as it became clear that 'fixing the heart' is just one part of the management of the - in general elderly - patient with cardiac disease, the role of the geriatrician became pivotal and led to the creation of the TAVI Care & Cure programme and patient pathway [11], a clinical and scientific programme that started in October 2013 and is approved by the medical ethics committee All patients referred for TAVI are seen at the outpatient clinic of the Departments of Cardiology and Geriatrics, where pre-defined clinical variables are collected that are entered into the electronic medical record and anonymously into a dedicated research database. The main clinical objective was to further improve patient selection by a more refined benefit/risk prediction via a comprehensive patient evaluation followed by the above-mentioned multidisciplinary discussion [11].

During the same time, a rapid transition of TAVI using general anaesthesia to TAVI under local anaesthesia was instituted (first local anaesthesia September 2012) [23, 24]. Other changes in the execution of TAVI were, in chronological order, the use of filter-based CEP beginning in January 2013 and plug-based arterial closure techniques (first application 23 July 2015) as well as the sutured-based techniques, with the easier-to-use Proglide replacing the more complex Prostar closure system (both Abbott Vascular, Santa Clara, California, USA) [25-28]. These changes over time – in addition to improved treatment planning via heart team discussions, experience, and refinement in technology - may have contributed to better outcomes. However, such changes may actually confound outcome in the opposite direction, since their introduction implies a learning curve and, thus, risk upon initiation. Furthermore, notwithstanding the fact that CEP effectively captures debris travelling to the brain during TAVI, only indirect evidence suggests a reduction in stroke incidence [29, 30]. Currently, the Achilles' heel of TAVI remains new conduction abnormalities and the eventual need for a new permanent pacemaker (PPM). We observed a significant reduction in PPM implantation from 22% to 8% from T2 to T3. The question is whether this is a chance finding or a real improvement due to a combination of more appropriate valve selection (e.g. avoidance of mechanically expanded valves in patients at risk of new conduction abnormalities), improved implantation technique (i.e. operator experience) or post-operative management, e.g. by prolonged monitoring instead of quick discharge and low PPM threshold [31-33]. Although the frequency of pre-existing bundle branch block has remained stable over time, it is conceivable that the lower-risk profile of patients in T3 as compared to T2 (STS score 4.3 vs. 2.7, $p<0.001$) played a key role in the lower frequency of PPM in T3. This is in line with the findings of the PARTNER cohort B trial, in which pacemaker rates were equal irrespective of whether TAVI or medical therapy was performed [2]. Also, mechanically expanded prostheses were used less often in T3 as compared to T2, which may in part explain the lower need for pacemakers in T3. In the present series we found no decrease in moderate to severe aortic regurgitation post-TAVR. As experience has invariably increased over time, the absence of a reduction in aortic regurgitation post-TAVR may be related to specific patient-related factors, such as valve anatomy or reduced use of mechanically expanded prostheses – known to be associated with the least amount of residual aortic regurgitation - in T3 [34].

What we have learned from looking back at our data spanning a period of 15-years of experience with TAVI is the pivotal role of innovation. Yet, this comes with a responsibility, since one should not offer treatment because it is available but because the patient is expected to benefit either in terms of survival and/or quality of life. This delicate balance (survival or quality of life) depends on a set of variables that go beyond the standard and easy-to-collect cardiovascular variables and must include a more comprehensive or

holistic approach for which medical specialists such as geriatricians are essential, as they have an understanding of the patient and his/her disease and, hence, the outcome of treatment from a much broader perspective. All too often, we have learned that despite successful treatment, life expectancy or independence of daily living or quality of life were lower than expected. Since 2013, the geriatricians have been playing an active and primordial role in treatment decision making during the heart team discussions, to avoid futility and promote utility.

Limitations

The objective was to report changes in baseline characteristics of patients treated with TAVI since the initiation of our programme in 2005. In addition, we have reported changes in the procedure and also reported on in-hospital outcome and 1-year mortality. With respect to the primary objective, observational bias may have played a role and in particular in the period before the start of the TAVI Care & Cure project. The latter was characterised by the collection of pre-defined variables related to patient characteristics and outcomes via a study protocol approved by the medical ethics committee. Observation bias may also have played a role in the in-hospital outcomes but not in the assessment of mortality, including during follow-up, for which the Dutch Civil Registry was used. The main limitation may be the tertiary referral nature of our institution (generalisability) and the fact that we cannot directly relate outcomes to changes in patient-related, procedure-related or operator-related factors (time bias). With the simplification of the TAVI pathway and a reduction in complication risks, total hospital admission times likely declined over time, although the data confirming this hypothesis were incomplete in this study.

Conclusion

We found that since the initiation of TAVI at our institution in 2005, the age of patients treated with TAVI did not change. Yet, their baseline risk profile improved mainly because of fewer antecedent cardiovascular diseases. Therefore, the patients treated with TAVI remain primarily octogenarians but at intermediate surgical risk. TAVI was associated with significant improvement of outcomes and 1-year survival. Bleeding and vascular complications as well as the need for a pacemaker remain the Achilles' heel of TAVI.

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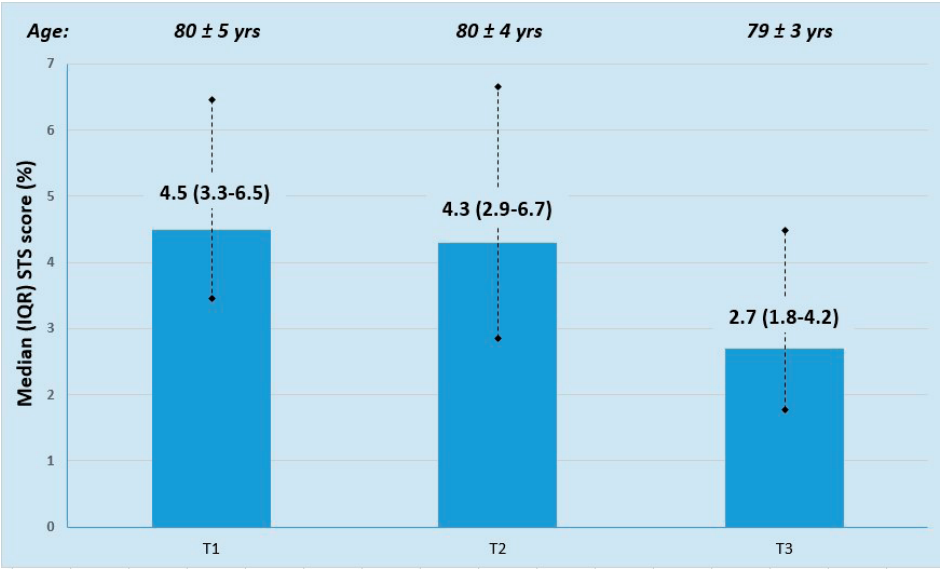
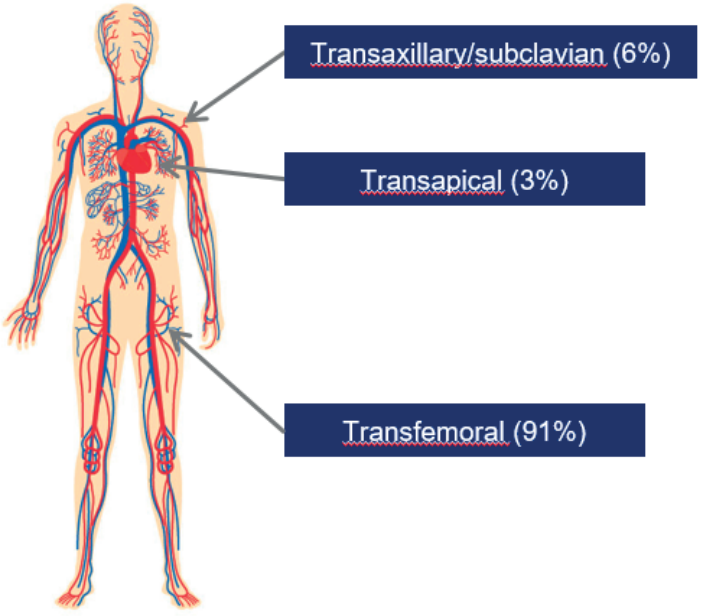
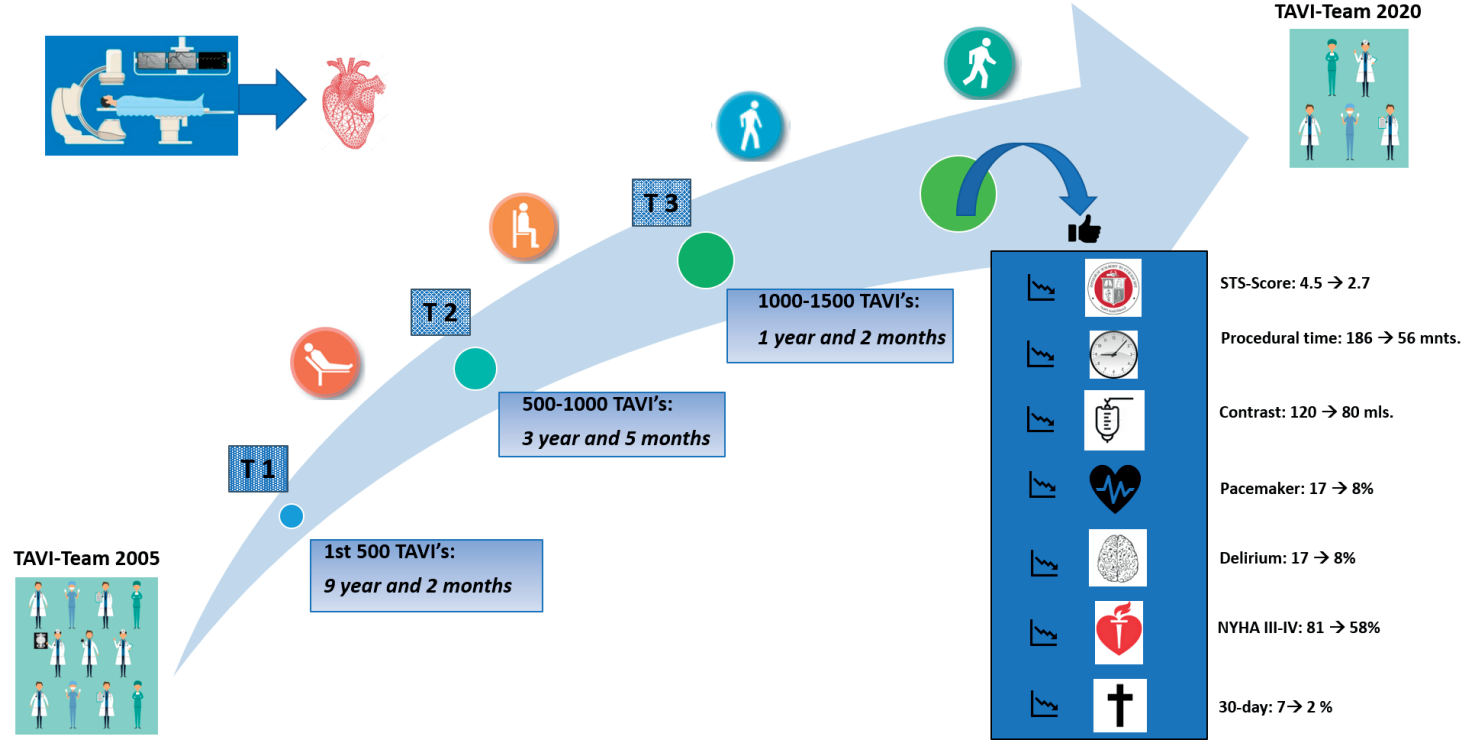
SUPPLEMENTAL MATERIALS



Supplemental Figure S1 Median (interquartile range) STS score and mean (standard deviation) age stratified per Tertile



Supplemental Figure S2 Access options Transcatheter Aortic Valve Implantation



Supplemental Graphical Abstract

11

Setting a Benchmark for Quality of Care

Update on Best Practices in Transcatheter Aortic Valve Replacement Programs

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ABSTRACT

Transcatheter aortic valve replacement (TAVR) is an established therapy for the treatment of severe aortic stenosis. The evolution of technology and procedural approaches has facilitated the development of streamlined clinical pathways to optimize patient care and improve outcomes. The revision of historical practices and the adoption of contemporary best practices throughout patients' journey from referral to discharge create opportunities to drive quality improvement. Nursing expertise and leadership are essential to recalibrate preprocedure, periprocedure, and postprocedure practice to transform the way we care for TAVR, achieve excellent outcomes, and promote high-performing health services for the treatment of valvular heart disease.

Keyword: Aortic stenosis, Transcatheter aortic valve replacement**,** Clinical pathway**,** Minimalist approach**,** Nursing**,** Outcomes

INTRODUCTION

In the first decade of transcatheter aortic valve replacement (TAVR) innovation, clinicians and researchers focused their attention on the development of improved devices, multimodality assessment, case selection, and procedural approaches.[1] These collective efforts resulted in TAVR rapidly becoming established as a safe and effective treatment option for people with symptomatic severe aortic stenosis (AS) with surgical risk profiles ranging from prohibitive to low.[2] Today, TAVR has surpassed surgical aortic valve replacement (SAVR) as the preferred treatment for AS in multiple international jurisdictions.[3] This accelerated success of *"how we do TAVR"* has now enabled a shift to *"how we care for TAVR patients"*. This new focus is driven by early clinical experience, and the pressing need to standardize processes of care to consistently achieve excellent outcomes, patient experiences, and program efficiencies.[4]

In this new clinical context, nurses' expertise in patient-centred care, development of clinical pathways, and change management creates new opportunities for leadership to advance the care of TAVR patients. Nurses are ideally positioned to promote quality improvement initiatives, leverage current evidence, and help recalibrate practices that were often informed by the early era of innovation and surgical blueprints, and are ill-suited to contemporary TAVR.

To reach this goal, and help prepare TAVR programs for the anticipated need for increased capacity and decreased health service resource utilization, quality improvement warrants close scrutiny of all aspects of patients' journey of care, from referral to follow-up. The objective of this review is to outline current evidence that supports the adoption of best TAVR practices, and highlight opportunities for nurses to be champions of change to improve the care of patients with valvular heart disease.

DISCUSSION

The goal of TAVR care is to enable patients to safely return home after a seamless and uncomplicated hospital admission to derive the survival and quality-of-life benefits of the procedure. From patients' perspective, transitions from their preprocedure assessment pathway and procedure planning, to their periprocedure experience, and finally to their postprocedure care represent a single journey of care.[5] As such, the adoption of best TAVR practices must encompass a single clinical pathway inclusive of all time points to improve transitions of care and multidisciplinary collaboration.[1]

Pre-Procedure Best Practices

The Central Role of the transcatheter aortic valve replacement coordinator

The complexity of referral processes and the assessment pathway create unique challenges for patients with AS referred for treatment. Similarly, cardiac programs require efficient processes to manage communication with referring and procedure physicians, facilitate multidisciplinary consultations, diagnostic imaging, and treatment recommendations, support patient education and shared decision-making (SDM), and ensure early discharge and procedure planning.[6] Although titles differ between programs and across international regions, the TAVR Nurse Coordinator has emerged as a pivotal member of the Heart Team to address this issue. Widely endorsed by international guidelines, this role has been integrated unevenly in different regions, with an early adoption in the United States, Canada, United Kingdom and Australia, and growing or emerging interest in European countries and Asia. Nurses are well suited to excelling in the role, given the requirements for comprehensive and cardiac clinical assessment skillset, patient teaching, leadership and communication.[7,8]

Although the responsibilities of the TAVR Nurse Coordinator differ across programs, most clinicians focus their work on program leadership and coordination, facilitation of patient-focused processes of care, and fostering effective communication pathways. For patients, the Coordinator acts as a case manager who can individualize communication, planning and teaching; for programs, benefits span centralized coordination and close collaboration with implanting physicians, diagnostic imaging departments, procedure rooms and in-patient units, research services and administration. Essential competencies and core responsibilities are summarized in Table 1.

Measurement of frailty

The multimodality assessment to inform patients' eligibility and suitability for TAVR requires diagnostic imaging (e.g., transthoracic echocardiography, cardiac angiography, competed tomography), cardiology and cardiac surgery consultations, and specialized referrals (e.g., geriatric medicine, nephrology). Nurses' expertise in the specialized assessment and management of functional and/or cognitive decline and frailty can significantly strengthen a wholistic approach to multidisciplinary treatment recommendation.[9] Frailty is a complex health state that differs from aging; it is an age-related, multisystem syndrome that increases health vulnerabilities when exposed to stressors that increase the risk of functional decline and other adverse events.[10] Frailty is associated with mortality, morbidity, and quality of life after TAVR, and with processes such as length of stay and health service utilization.[11,12] The advanced age of most patients with AS warrants the assessment of frailty and function in higher risk patients who may not

Table 1
Competencies and responsibilities of the transcatheter aortic valve replacement nurse coordinator

Competencies and Core Knowledge	Responsibilities
1. Expertise in cardiovascular care: • Cardiovascular nursing • Specialized knowledge of valvular heart disease • Specialized knowledge of TAVR 2. Specialized knowledge of providing care for patients with aortic stenosis: • Specialized knowledge of patients with complex heart disease, multiple co-morbidities, and frailty 3. Clinical assessment skills: • Comprehensive cardiovascular assessment • Assessment of frailty and functional status 4. Patient and family education: • Assessment of learning needs to individualize teaching • Patient and family teaching skills • Conduct of shared decision-making 5. Coordination of complex processes of care: • Organizational skillset to develop and individualize assessment and procedure planning pathways 6. Clinical leadership: • Leadership skills to contribute to the Heart Team • Administrative leadership to develop program efficiencies	1. Program leadership: • Serves as essential and central member of the Heart Team • Supports and leads TAVR program development • Participates in program evaluation and quality improvement to improve outcomes 2. Facilitation of patient-focused processes of care: • Develops seamless and patient-centred processes and clinical pathways • Develops evaluation pathways, including diagnostic testing and functional assessment • Conducts clinical triage and wait-list management • Case manages urgent in-patients • and interhospital referrals • Facilitates referrals to sub-specialty consultants • Facilitates and contributes to multidisciplinary, treatment decision-making • Coordination of procedure planning, admission and follow-up 3. Development of communication pathways: • Conducts patient and family education, and promotes shared decision-making • Leads communication with the Heart Team • Facilitates communication with administration for planning purposes

derive the benefits of TAVR, who may require a more in-depth geriatric assessment, and/or when the anticipated procedure planning and recovery trajectory presents significant challenges to achieve a good outcome.

There is no consensus on the standardized measurement of frailty in patients with AS.[13] Upward of 20 tools are available and utilized across programs; the most commonly used instruments in TAVR programs are outlined in Table 2.

Patient education

Most programs can be classified as "procedure-focused" programs; patients are referred by their cardiologist, internist or other health care provider for assessment of eligibility; episodic care focuses on the short period of admission and ends at the time of follow-up. To match this mandate, the following outlines some key components of the patient education imperatives for TAVR patients:

Table 2
Commonly used instruments to measure frailty in patients with aortic stenosis

Instrument	Details of Measurement
Fried Scale[43]	*Captures core phenotypic domains:* • Slowness • Weakness • Low physical activity • Exhaustion • Shrinking (unintentional weight loss)
Short Physical Performance Battery[44]	*Captures slowness, weakness and balance; measured by timed physical performance tests:* • Gait speed • Chair rises • Tandem balance
Essential Frailty Toolset[12]	*Developed to predict mortality after SAVR/TAVR using phenotypic domains:* • Chair rises • Cognitive status (MiniCog: short term memory and orientation; clock drawing test) • Hemoglobin • Albumin
Clinical Frailty Scale[45]	*Captures clinicians' assessment of accumulated deficits including:* • Presence of terminal illness • Activities of daily living • Instrumental activities of daily living • Chronic health conditions • Patient-reported health status and activities
Rotterdam Frailty Index[46]	*Captures clinicians' assessment of 38 accumulated deficits including:* • Functional status • Health conditions • Cognition • Mood

1. Shared decision-making (SDM): SDM is a bidirectional process between patients and clinicians that enables an information exchange, and treatment decisions that consider patients' informed preferences and allows them to participate in choosing the right treatment option. It is not solely patient education. SDM acknowledges equally important forms of expertise to achieve quality decisions: the clinician's expertise, based on knowledge of the condition, prognosis, treatment, options and possible outcomes, and the patient's expertise, informed by the impact of their health condition on their daily life, values, and preferences for the possible outcomes.[14] Increasingly, TAVR programs are embracing SDM to ensure patients can make a high-quality decision, especially in light of the emerging equipoise between SAVR and TAVR.[15] Patient decision aids (PDAs) are tools to support SDM; PDAs for AS have been published by American and European agencies to strengthen the adoption of SDM and patient empowerment to participate in their treatment decision.

2. Streamlined assessment pathway: Information about the TAVR assessment pathway must include information about the sequence, scheduling and details of diagnostic imaging requirements, and the expected consultations. The COVID-19 pandemic forced and accelerated the adoption of virtual health platforms to minimize patients' exposure to the hospital environment, and further highlighted the imperative need for a streamlined assessment pathway.[4] Additional education may be required to prepare patients for telemedicine consultations, including coaching to successfully connect, accommodations in the case of auditory, visual or other impairments, and clarity of expectations. Importantly, there may be opportunities to streamline assessment requirements based on clearly defined risk criteria to accelerate access to timely and efficient care. **Fig. 1** illustrates components of the accelerated and routine assessment pathways implemented to facilitate the transition to virtual care in TAVR programs.
3. Preparing for the TAVR clinical pathway: Successful safe and early discharge home hinges on early discharge planning and consistent communication about goals of care from all health care providers at every contact time with patients. This "united front" of uniform communication, inclusive of written resources and clinical interactions with nursing and medicine, is pivotal to avoid confusion, help patients and families prepare "their" discharge plan and availability of social support, manage expectations, and anticipate the important role they play as partners to optimize their outcomes. Key messages for patient and family education must reflect these stated goals (**Box 1**).
4. Early discharge planning: The TAVR Nurse Coordinator plays an important role in coaching patients to prepare for discharge. Effective individualized discharge planning begins before admission to ensure safe transition home. Although the TAVR trajectory of care is standardized and highly predictable,[16] patients who present with unique health vulnerabilities and social determinants of health may benefit from the development of an adapted discharge plan to improve their outcomes and experiences.

Key take-away messages to adopt preprocedure best practices

- The TAVR Nurse Coordinator plays a pivotal role to optimize patients' pathway, communication and program efficiencies.
- The standardized measurement of frailty augments assessment findings and informs treatment decisions.
- A comprehensive patient education strategy is essential to establish a close partnership with patients.
- Early discharge planning is an effective intervention to facilitate early and safe transition home.

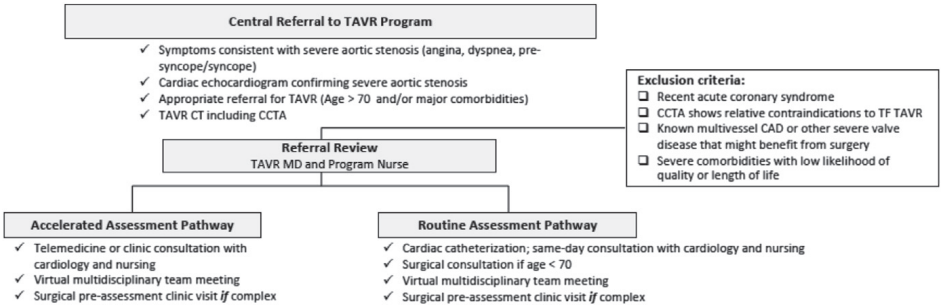

Figure 1. Vancouver accelerated TAVR assessment pathway adapted for COVID-19.[4] CAD, coronary artery disease; CCTA, Coronary Computed Tomography Angiography; CT, computed tomography; TF, Transfemoral.

Box 1
Key messages for transcatheter aortic valve replacement preprocedure patient and family education

Goal #1: Maximize patients' pre-TAVR conditioning and reduce risks of complications
- Importance of mobilization and physical functioning
- "Stay as active as you can. Ask your regular doctor about what level of activity is best for you."
- Individualized medical referrals
- "The TAVR Clinic nurse or doctors may want you to see other medical specialists."
- Discharge planning: Endocarditis prophylaxis
- "Book an appointment with your dentist."

Goal #2: Develop a discharge plan before admission and set patient/family expectations
- The TAVR journey of care is predictable; standard/goal of care is safe next-day discharge home
- "Our Goal is for you to go home the day after your procedure".
- Early mobilization and avoidance of deconditioning are priority activities while in hospital
- "Our Goal is for you to walk and do basic activities on the day of your procedure, and to go home the next day".
- Discharge planning requires family coordination
- "Speak with your family about your Going Home Plan."

Goal #3: Facilitate seamless admission and patient safety on day of procedure
- Set expectations of same-day admission.
- "Most people come to hospital the morning of the procedure. We let you know what time you should arrive."

Goal #4: Set expectations about periprocedure experience
- TAVR is a minimalist procedure that is more akin to a "big angiogram" than open heart surgery
- The default anesthesia strategy is local anesthesia with light sedation
- TAVR is a short procedure

Goal #5: Set expectations about postprocedure experience and early mobilization
- Post-procedure mobilization after 4-hour bedrest
- Importance of early and frequent mobilization
- "Our Goal is for you to have two short walks on the evening of the procedure".
- Patient comfort and avoidance of opioids
- "Most people who have TAVR do not have a lot of pain. We will check with you to make sure you are comfortable."

Goal #6: Set expectations for next-day discharge and safe transition home
- Target length of stay is next-day discharge
- Safe transition home
- "Once at home, your priorities are to recover safely, rest, get back to your regular activities, and do a bit more every day."

Periprocedure Best Practices

The arc of the development and refining of the TAVR procedure started with the earliest innovation days in the cardiac catheterization laboratory with "interventional cardiology-like" practices.[17] Early clinical trial practices evolved to the adoption of a surgical template to promote patient safety and anticipate the "*what ifs*" complication scenarios. Most recently, there is increasing that the early vision of a truly minimally invasive and standardized approach is safe, feasible and efficient.[16] Peri-procedure best practices include the adoption of a streamlined approach matched to contemporary technology and evidence, and the development of nursing competencies that are uniquely adapted to the needs of TAVR patients.

Minimalist transcatheter aortic valve replacement

The transition from historical practices primarily informed by cardiac surgery models to more streamlined contemporary TAVR practices continues to evolve. The definition of what constitutes a minimalist approach remains disputed.[18] Important aspects include procedure location, anaesthesia strategy and use of invasive equipment.

1. Procedure location: The rapid expansion of the availability of hybrid operating rooms equipped with high-quality imaging and hemodynamic monitoring equipment provided operators with an effective environment to achieve excellent periprocedure outcomes. This tailored space was endorsed in early guidelines as the optimal setting, and became a standard of care in most North American programs and other international programs. Increasingly, the cardiac catheterization laboratory is becoming an appropriate or even preferred space for most TAVR procedures. Careful planning, staff training and emergency preparedness through simulation training, can enable programs to significantly increase their peri-procedure capacity, reduce the intensity of operating room resource use, and decrease costs without compromising patient safety.[19] In addition, the intrinsic "nimbleness" of the cardiac catheterization laboratory to accommodate the scheduling of urgent in-patients, and its integration in cardiac service lines offer important operational advantages to improve access to care.
2. Anaesthesia strategy: There is clinical interest in selecting an anaesthesia strategy that aligns with goals of care of contemporary TAVR.[20] In light of current evidence, these goals include the following:

- Patient comfort and experience;
- Capacity to easily communicate with patients during the procedure as required;
- Hemodynamic stability;
- Readiness for mobilization within 4-6 hours after the end of the procedure;
- Post-procedure transfer of a consistently stable patient with a predictable recovery.

To this end, the use of local anaesthesia with or without light sedation, or conscious sedation has been reported as safe and effective options for most TAVR patients.[21] Potential advantages of the avoidance of general anaesthesia include minimal disruptions to hemodynamic status, improved ability to detect early warnings of complications, prevention of delirium, accelerated reconditioning and predictable time to mobilization, and shorter procedure times. An open visual field between the patient, the anaesthesiologist and the implanting team is particularly effective to promote communication.

To maintain patient safety, periprocedure must retain the ability to convert to general anaesthesia, obtain periprocedure imaging within 5 minutes, or to initiate femoral-femoral hemodynamic support within 10 minutes. Collaboration consensus agreements between medical and nursing disciplines and regular multidisciplinary simulation training exercises can promote a culture of quality and patient safety, while recalibrating practices to improve care.

3. Best use of invasive onitoring lines: In contemporary TAVR, the avoidance of central venous or urinary catheters in widely accepted across multiple programs and regions.[22] Patient skin preparation and draping aligned with interventional cardiology practice instead of the more extensive practices of cardiac surgery are in keeping with contemporary TAVR. These practices also convey an important message to the patient that the team is conducting a minimalist procedure, and not cardiac surgery. The avoidance of surgical draping and the systematic opening of cardiac surgery instruments have significant cost savings implications. Implanting physicians' systematic use of ultrasound-guided sheath insertion technique and the monitoring of activated clotting time with partial reversal of anticoagulation at the end of the procedure can significantly improve post-procedure hemostasis and contribute to early mobilization. Last, the timely removal of the temporary pacemaker if used at the time of valve deployment in the absence of new conduction delays can further facilitate a rapid return to baseline status and reduce the requirements for post-procedure critical care.

Periprocedure models of nursing care

Multiple factors influence the models of peri-procedure nursing staffing models, including procedure room location (operating room or cardiac catheterization laboratory), primary implanting physicians' specialty (interventional cardiology or cardiac surgery), program historical practice, and competing hospital demands. The expertise of operating room nurses prioritizes the asepsis imperatives of valve implantation, assistance with anaesthesia, and management of emergency strategy. Similarly, the expertise of the cardiac catheterization team with transcatheter techniques and invasive hemodynamic

monitoring, and their competencies in the setting of emergency percutaneous coronary intervention are well suited to the needs of a safe TAVR procedure. The required ratio of distribution of these skillsets remains disputed; nevertheless, TAVR increasingly requires a "hybrid model of staffing" to ensure the availability of the required competencies.[23] The contributions of operating room and interventional cardiology nursing competencies to augment the unique requirements of peri-procedure TAVR nursing, and an example of peri-procedure staffing model, are illustrated in **Fig. 2**.

Importantly, change in management strategies, communication, education and training, and practice leadership is essential to achieve role clarity and satisfactory selective crosstraining of competencies and attend to the challenges of "merging" distinct areas of nursing practice and expertise.[24] Careful attention to equipping nurses to participate in emergency intervention planning and simulation training should focus on emergency vascular repair, percutaneous coronary intervention, management of severe hemodynamic instability and pericardial tamponade, and conversion to open heart surgery.

Key take-away messages to adopt periprocedure best practices

- TAVR can be safely performed in a cardiac catheterization laboratory with close scrutiny of all aspects of the procedure.
- The selection of anaesthesia strategies for TAVR should reflect the goals of care.
- The avoidance of invasive lines, the adoption of best practices to avoid vascular injury and the rapid removal of the temporary pacemaker when appropriate are effective strategies to prepare patients for rapid reconditioning.

Postprocedure Best Practices

TAVR can be defined as a procedural success when the patient returns home safely and early, without sustaining any in-hospital complications or need for readmission, to enjoy the survival and quality of life benefits of their new valve. To this end, postprocedure nurses play an essential role in the TAVR clinical pathway to facilitate patients' rapid reconditioning and safe discharge.[25] The early recognition of potential complications associated with TAVR, and the significant risks associated with the hospitalization of the primarily older AS patient population warrant a standardized post-procedure pathway to achieve these goals of care.

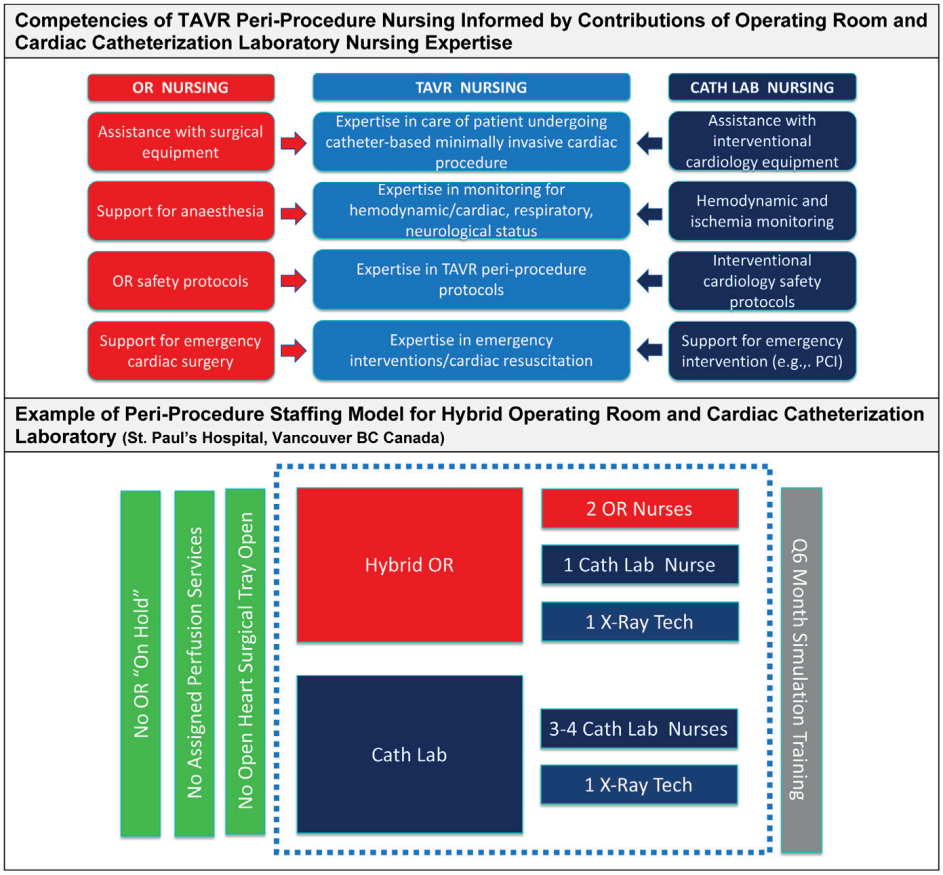

Figure 2:
Conceptual illustration of periprocedure TAVR nursing competencies and example of staffing model. CATH LAB, cardiac catheterization laboratory; OR, operating room; PCI, percutaneous coronary intervention.

"The Big 5" – Monitoring for Potential Complications after Transcatheter Aortic Valve Replacement

Contemporary TAVR patients achieve outstanding outcomes, including rapid and significant improvement in quality of life, and risk of 30-day mortality that is as low as less than 0.5%. Device modification, lower profile systems, use of computed tomography sizing, and increased operator experience have contributed to substantial reduction in most complications.[26] Nevertheless, clinical awareness of these adverse outcomes and close monitoring remain essential to mitigate risks and ensure patients have the best possible outcomes.[27] The following important, albeit increasingly infrequent, complications require early recognition and timely and effective treatment (**Figs. 3 and 4**).

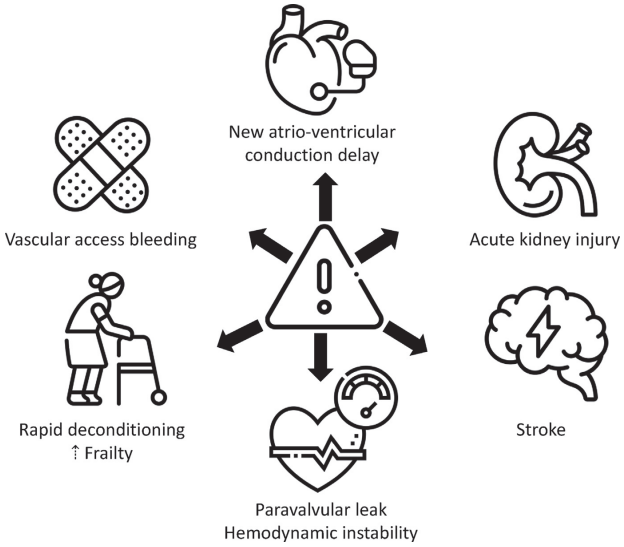

Figure 3.
Major in-hospital complications associated with TAVR (From Grube E, Sinning JM. The "big five" complications after transcatheter aortic valve replacement: do we still have to be afraid of them? *JACC Cardiovasc Interv 2109;12(4):370 to 372)*

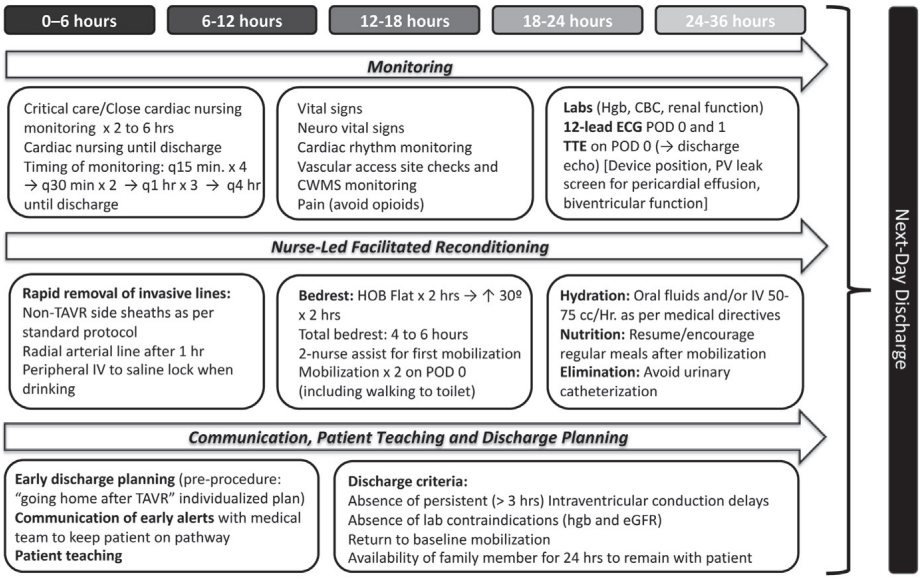

Figure 4.
Summary of TAVR postprocedure nursing protocol.[25] CBC, complete blood count; CWMS, colour, warmth, movement and sensitivity; ECG, electrocardiogram; Hgb, hemoglobin; HOB, head of bed; IV, intravenous; POD, post-operative day; PV, paravalvular; TTE, transthoracic echocardiogram. (*From* Lauck SB, Sathananthan J, Park J, et al. Post-procedure protocol to facilitate next-day discharge: Results of the multidisciplinary, multimodality but minimalist TAVR study. *Catheterization and Cardiovascular Interventions.* 2020;96(2):450 to 458. https://onlinelibrary.wiley.com/doi/abs/10.1002/ccd.28617. https://doi.org/10.1002/ccd.28617.)

Stroke

Different mechanisms and potential contributing factors, including patients' demographics, clinical characteristics and procedural factors. Early stroke is considered to be related to particle embolization.[28] Embolic neurological events can range from a minor transient ischemic attack to a major event causing permanent disability or death. Overall, recent clinical trials and large registry observational studies report stroke rates that continue to decrease.[29] The use of cerebral embolic protection devices remains under evaluation to reduce the risk of stroke.[30] A comprehensive neurological assessment on admission, and in conjunction with vital signs and vascular access checks should screen patient for (1) facial symmetry or changes from baseline when smiling, (2) speech characteristics and presence of slurring, and (3) asymmetrical weakness, numbness and/or drift when arms are raised. The acronym FAST (Face drooping; Arm weakness; Speech difficulty; Time to call for help) is an easy guiding reference to conduct a preliminary standardized assessment.

Paravalvular leak

As the native or failed surgical valve is not removed in TAVR, suboptimal placement of the device with incomplete sealing of the annulus, incomplete apposition of the valve stent frame due to the calcification of the annulus and/or leaflets, and under-sizing of the device can cause the onset of paravalvular leak between the device and the annulus.[31] This can cause severe aortic regurgitation and hemodynamic instability. Nurses should anticipate the need for urgent echocardiography and possibly angiography to confirm device function and establish a plan of care. Vasoactive or mechanical support may be needed in the setting of severe instability.

Acute kidney injury

Although there is increasing awareness and strategies to limit periprocedure contract dye exposure, some TAVR patients remain at higher risk for acute kidney injury (AKI) because of their pre-existing renal dysfunction, atherosclerotic vascular disease, advanced age, and/or high frailty.[32] The onset of AKI is associated with significant morbidity and mortality.[33] Close monitoring of renal function and rapid resumption of normal hydration can effectively reduce patients' risk and promote an accelerated return to baseline renal function.

New conduction delay

The close proximity between the aortic valve and the conduction system is the primary reason the TAVR device can cause a mechanical insult to the conduction tissue, including various degrees of edema, hematoma, and ischemia.[34] The subsequent development of high degree atrioventricular block may require the implantation of a new permanent

pacemaker, while the new onset of a left bundle branch block may be associated with increased mortality and need for pacemaker.[35] In the immediate postprocedure period, TAVR patients require continuous cardiac monitoring as nurses stay alert for the risk of electrocardiographic changes, especially in atrio-ventricular conduction (i.e., measurement of P-R interval). Increasingly, TAVR programs are endorsing continuity of medical care and the adoption of standardized approaches to the management of new conduction delays to improve outcomes and reduce the risks of pacemaker without compromising patient safety.[25]

Bleeding

The incidence of vascular injuries continues to improve with the availability of smaller sheath sizes, flexible delivery systems, computed tomography imaging of the peripheral vasculature, and operator experience.[36] In addition, periprocedure best practices described in the previous section significantly increase the likelihood that most patients will have a predictably stable vascular access site and will achieve timely hemostasis. Standardized and expert assessment of potential bleeding (including in the retrosternal location) is an essential nursing intervention to ensure early identification and treatment. There are on-going efforts to define and measure the range of bleeding and vascular injury complications to drive quality improvement.[37]

Standardized postprocedure clinical pathway

The post-procedure care of TAVR patients evolved from earlier protocols informed by cardiac surgery to the increasing adoption of contemporary standardized and streamlined practices based on new evidence. In most programs, TAVR nursing care is now well established and integrated in practice; given the low rates of complications and the predictability of patients' journey, this group of patients has become somewhat "less special" over time, and now requires substantially fewer health care resources during their early in-hospital recovery. Research supports the transition of historical postprocedure admission to a critical care unit to the preferred use cardiac telemetry ward for most patients, and the safety and feasibility of next-day discharge home.[38]

This recalibration of nursing practices and resources continues to warrant excellent cardiovascular nursing care, albeit not always critical care nursing, that focuses on close monitoring, nurse-led accelerated reconditioning, and communication, patient teaching, and criteria-driven safe discharge home. A standardized TAVR postprocedure clinical pathway provides guidance for nurses to focus on priorities of care.[25]

Monitoring

The assessment of vital signs, cardiac rhythm, neurological status, vascular access site, and pain/discomfort requires an intensive period of close observation in the immediate post-recovery period, followed by routine cardiovascular care. Immediate post-procedure assessment of hemoglobin and renal function, as well as serial 12-lead electrocardiograms can effectively identify the onset of complications. The documentation of postimplantation echocardiography, completed either at the end of the procedure or prior to discharge, provides necessary information to determine procedural success and inform long-term follow-up.

Nurse-led accelerated reconditioning

In the absence of post-procedure complications, the focus of care shifts to ensuring patients return to their baseline status as soon as possible, and prepare for safe discharge home. With a goal of next-day discharge, every hour counts to accelerate this reconditioning. Nurse-led early mobilization is a central component of post-procedure care. The progressive steps include (1) bedrest flat x 2 hours, (2) bedrest with head of bed elevated to 30 degrees x 2 hours, (3) assistance for first mobilization with progression from sitting at side to walking to toilet in the absence of complications, and (4) goal of mobilization x 2 on procedure day, including up in chair for evening meal. In addition, rapid resumption of oral fluids and nutrition plays a pivotal role in reducing the risks of deconditioning.[25]

Communication, patient teaching and discharge

All post-procedure efforts should be focused on maintaining patients on the clinical pathway and address potential complications early and effectively. This requires seamless communication between nursing and the implanting team that enables nurses to raise their concerns in a timely way. In-hospital communication with the patient and their family should build on early discharge planning, with confirmation of the individualized planning for safe transition home, and the availability of social support for the first days at home as required. Patient teaching focused on vascular access site care, medications, progressive activity protocol, when to seek help, and follow-up instructions can be provided in a streamlined format using standardized resources. Last, confirmation of readiness for next-day or subsequent discharge can be guided by the following criteria:

1. Absence of persistent (>3 hours) intraventricular conduction delay
2. Absence of diagnostic contraindication (i.e., stable hemoglobin and renal function)
3. Return to baseline mobilization
4. Availability of family member for 24 hours to remain with patient

Importantly, patients should hear consistent messages, from every health care provider, at every encounter from referral to discharge to achieve safe and early discharge home. The key messages outlined in **Box 1** must be repeated and endorsed by all providers to clarify expectations and carry individualized discharge planning.

Last, there is growing interest in accelerating physical functioning in the early recovery period. The health benefits of exercise after TAVR are well documented and represent the foundation of cardiac rehabilitation.[39,40] Cardiac rehabilitation in patients after TAVR is safe, reduces mortality, and improves quality of life and exercise tolerance.[41] The 2019 Canadian Cardiovascular Society Position Statement recommends cardiac rehabilitation as a component of long-term management.[42] To date, cardiac rehabilitation has been dramatically underused, and different methods for its delivery (eg, centered-based, home-based, telehealth) have been explored to overcome the presence of barriers to utilization, including referrals and adherence. Regardless of method of delivery, systematic and standardized referrals, combined with patient education regarding the importance of cardiac rehabilitation in the postprocedure recovery, are evidence-based interventions that aim to improve outcomes.

CLINICS CARE POINTS

- Complications after transcatheter aortic valve replacement are increasingly rare; nevertheless, nurses need to be vigilant to identify stroke, hemodynamic instability, acute kidney injury, new conduction delay, and bleeding.
- There is strong evidence that a standardized clinical pathway that prioritizes close monitoring, accelerated nurse-led reconditioning, communication, patient teaching, and criteria-driven discharge is effective to facilitate safe next-day discharge home after transcatheter aortic valve replacement.

SUMMARY

The adoption of best practices along the preprocedure, periprocedure, and postprocedure components of TAVR care is informed by contemporary evidence on how to best care for this patient population. It also reflects the essential need to "get it right, for every patient, at every touch point" to ensure TAVR continues to offer the best possible outcomes, irrespective of individual risk profiles. Nurses are increasingly developing the specialized competencies to support patients' journey of care, and play an essential role to reach these goals and help patients achieve outstanding outcomes. The close scrutiny

of the care of TAVR patients offers new opportunities to leverage this evidence across cardiac and other patient populations, and to pursue nurses' collective goal of improving outcomes and efficient health services.

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General discussion and summary

GENERAL DISCUSSION AND SUMMARY

Aortic valve stenosis is a frequently occurring disease in the western hemisphere and is found predominantly in older patients over the age of 75. Until 2002 Surgical Aortic Valve Replacement (SAVR) was the treatment of choice for patients with severely symptomatic Aortic Valve Stenosis (AS) although a significant number of these patients did not meet the treatment criteria for SAVR due to high surgical risk and the presence of co-morbidities. However, in 2002 Prof. A. Cribier initiated a potential new option by treating the first patients with severe AS using an aortic heart valve implanted percutaneously through the groin approach; a trans-catheter aortic valve implantation (TAVI). In the following years, across the world, many more surgical high-risk patients (inoperable patients) were treated successfully using this percutaneous technique. The positive results of international randomized trials have led to an expansion in the indications for TAVI to include not only inoperable patients but also patients with AS and an acceptable surgical risk. Long term outcomes are important for patients with a low and medium surgical risk, as they often have a longer life expectancy than the high-risk patients. A recent study described that degeneration of an aortic valve prosthesis occurs more often in patients with severe symptomatic AS treated with a surgical bio-prothesis compared to those treated with a self-expandable trans-catheter valve. Although TAVI, due to its minimally invasive characteristics, offers many advantages compared to open heart surgery there are still some risks involved. At the start of the use of the technique these were mostly bleeding events, vascular complications, pacemaker implants, peri-valvular leaks and sometimes even deaths during or shortly after the procedure. These procedure related complications have been significantly reduced over time with the increased experience of the Multidisciplinairy Heart Team and operators combined with the continuous innovation of the technique and equipment, resulting in an improvement in outcomes of TAVI. The procedure itself has been technically significantly simplified over time, with it now taking place under local anesthetic with a minimally invasive access site resulting in quicker mobility and recovery and when possible, a shorter hospital stay.

Together with these clinical and technical improvements, TAVI has also become a popular subject for scientific studies, contributing to the above-mentioned improvements. This thesis aims to also contribute to that.

The aim of this thesis is to provide an overview of the evolution of TAVI in the Erasmus MC since the first procedure in 2005, the implementation of the TAVI Care and Cure Program and the consequences on daily clinical practice. Central to this is the holistic approach to the individual patient with Aortic Valve stenosis, to determine the best treatment strategy for the patient taking into account the balance between risks and

benefits to meet the patient's expectations and outcome on quality of life after treatment. I have been actively involved in the setting up and further development of the percutaneous, Transcather Aortic Valve replacement (TAVI) program since the introduction and implementation of the first TAVI procedure in November 2005 in the Erasmus MC in Rotterdam, the Netherlands. Due to this, I have learnt a lot, both as a nurse and on a human level.

We started small with one procedure in 2005, the first TAVI procedure in the Netherlands (patient number 16 worldwide with a CoreValve implant). For this case we had discussions on a multi-disciplinarily level, with close co-operation between interventional cardiologists, cath lab staff (nurses and technicians), cardio-thoracic surgeons, cardio-perfusionists, anesthetists, interventional radiologists and vascular surgeons on the one hand and the industry technical and support team on the other. Introducing a percutaneous heart valve through the groin sounded futuristic. We didn't really had an idea on what this new technology would bring, especially for the patients we were planning to treat. At the time there was no written handbook for the procedure, so colleagues from the cath lab created one together with the CoreValve team. The nursing staff on the ward, who were to take care of the patient pre- and post-procedure were closely consulted on this.

It also proved to be of vital importance to ensure that all sterile and unsterile material was available, of which a critical element was a second, correctly sized valve implant with all accessories in case there was a complication during the procedure. For example, occlusion balloons to stop unexpected, major bleeds and gain time to stabilize the patient and treat any other complications. In addition, for these first pioneering procedures, Prof dr. P.J de Jaegere prepared a detailed script that was sent to all TAVI team members so that everyone was aware of his or her responsibilities and at which point in the procedure specific material was required. This script was also discussed with the team prior to the TAVI procedure and can be seen as the precursor to the current Time-Out procedure (see the picture below). An experienced proctor was always present during the first TAVI's to perform the procedure together with the Erasmus MC team. Nowadays our intervention cardiologists are experts at the procedure and take on the role of proctor for less experienced centers.

At the time, my interest as a cath lab manager and as a nurse in the specific complexities of and around TAVI inspired and challenged me to start this thesis project in 2013. An important aspect of this was the need for more structure and policy as the TAVI procedures at Erasmus MC took a more prominent and frequent role in the treatment of these vulnerable patients. The initial TAVI plan of care was written and developed on

Fig: Briefing prior to a TAVI (2005). Seated front left to right M de Ronde (Chief Nurse), Dr de Jaegere, Dr Kappetain, Professor Serruys. Standing behind Professor Serruys; Dr Klein (anesthetist). Refer to the script where referenced i.e. the description of the procedure, required material, individual tasks and responsibilities, all in chronological order during the procedure

a multi-disciplinarian level to better align the internal and later the external chain of care. Alongside the technical execution of the valve replacement there was also more attention paid to the expected improvement of the patients' Quality of Life (QoL) and their expected return to their home environment. In the beginning period there was little to no information available on the somatic, psychological and social effects on the outcome of TAVI, both in the short (30 days) and long term (1 year). This resulted eventually in the initiation and implementation of the TAVI Care and Cure programin the Erasmus MC with a focus on a more careful patient selection, including a more active role and close collaboration with the geriatric team.

As part of the TAVI Care and Cure program, a database was built to include a large number of variables for all following TAVI patients. In 2004 a dedicated student team was established for this. A useful by-effect of this student team was that it provided the basis for numerous doctoral theses (in the meantime several of the student members of this team are in the process of, or have completed their doctoral theses in the department of Cardiology).

The (co) authorship of the chapters in this thesis, the research itself, my participation in the weekly heart valve meetings and also the many conversations with patients during weekly outpatient clinics have provided me with many insights in the disease itself, the associated signs and symptoms and not to forget the many limitations these patients experience in their daily life both before and sometimes after the procedure. If we focus on the chapters in this thesis, chapters 2 and 4 discuss the era since the first TAVI in 2002, including the role of different clinical experts and visionaries in the field, from the pre-clinical phase to the first procedure in the Netherlands in 2005. Differing factors have contributed to this successful introduction and implementation, including the establishment of a dedicated heart center with multi-disciplinary teams, an optimal patient selection, protocol-based procedures and complication management.

Chapter 3 describes the setting up and implementation of the TAVI Care and Cure program, a prospective, observational study in which the focus was on, not only the procedural and functional aspects of the case but also on the cognitive function of the elderly patients for whom TAVI was indicated. The increase in the number of patients that were meeting the inclusion criteria for TAVI in the Erasmus MC resulted in a larger treatment capacity being established in the hospital. At the same time, this resulted in the establishment of a standardized multi-disciplinary program with a major emphasis on a systematic geriatric-based evaluation during the TAVI pre- and post-procedure phase. The majority of these patients are more than 80 years of age and have therefore an increased risk of post-operative delirium (POD) associated with a higher mortality rate.

Chapters 5, 6 and 7 report on which factors were important in the changes over time whereby the collection of specific datasets, both cardiology and geriatric, provided valuable information. The data showed that in the majority of patients, complaints due to aortic valve stenosis after TAVI were reduced and the patient's quality of life improved. However, the data also showed that in a number of patients the positive affects of TAVI were limited or not present. This represents a vulnerable population in which as well as pathological factors, also frailty and independence can be an indication of a deterioration in quality of life resulting in a diminishing clinical function for the patient. This is the basis on which we conclude that it is of importance for the patient that the clinical geriatrician screens and assesses for eventual vulnerability and that this is used with established scoring systems (EuroSCORE and STS score) to make a balanced assessment for best treatment options. The expansion of the TAVI options for treatment have also brought the surgical risk down from a mid to high risk to a low risk procedure and because of this a larger number of patients treated with TAVI at Erasmus MC required a more streamlined discharge procedure.

In addition to transfer to a referring hospital for further recovery from TAVI for a select group of patients, we also studied the safety and efficacy of the treatment on a group of patients with AS and a low surgical risk who were discharged early from hospital (> 3 days) (Chapter 8). Of importance for this were a number of discharge criteria (for example, hemodynamic stability, a successful TAVI procedure, no procedural complications, no indication for a temporary pacemaker, the presence of logistical support from the referring center and a home support network). Also critical to early discharge was the simplification of the TAVI procedure by, for example, the use of local instead of general anesthetic and the use of less invasive lines which meant that the patient did not require monitoring post-procedure on an ICCU.

Chapter 9 details the introduction of pacing using alligator clamps on the left ventricle guidewire instead of positioning a temporary pacemaker lead in the right ventricle using a venous sheath. Due to this simplification, the use of an additional venous sheath was no longer necessary in most patients. The use of an extra venous sheath and a temporary pacemaker lead is only required in cases with a high grade atrio-ventricular block occurring during the TAVI procedure. This strategy proved to be safe and feasible in the majority of TAVI cases and resulted in a reduced procedure time.

The development, experience, and progress of TAVI in Erasmus MC, from the first successful TAVI procedure in 2005 up to and including those in 2020 which are simpler and less burdensome for the patient, is described in Chapter 10. While the average age for patients with AS remained at 80 years for 15 years, the patient risk profile improved due to a reduction in baseline cardio-vascular co-morbidities, a reduction in indication for a permanent pacemaker and an improved left ventricle function due to an effective afterload reduction post TAVI procedure. Despite procedural simplifications, improved in-hospital outcomes and 1 year morbidity, focus on TAVI related complications such as bleeding events, vascular complications and conduction disorders remain essential.

Due to activities of the above-mentioned research and my activities as TAVI coordinator I was able to gain more insight on the expectations of the patient prior to the TAVI procedure; what will the future hold, what if complications happen, what could those be and also will my quality of life improve? Despite the patient being well informed about the treatment, it's limitations and eventual risks, many patients are more often choosing TAVI over SAVR. My combined role as nursing TAVI coordinator and doctoral candidate appears since 2016 to have developed into a specialist role in which the organization of and around TAVI planning, the organization of the pre-peri and post-operative phase, advising and informing the patient and family are central.

That also international collaboration is a relevant topic for this thesis is highlighted in Chapter 11. This chapter discusses the evolving role of the assisting nursing staff in TAVI procedures to a multi-functional role as a TAVI coordinator with quality improvement as a result. Certainly, this role as a central point of communication for the patient throughout the treatment is of essential importance. This has proven to have an impact on the expectations and overall experience for the patient and family. Further optimalization of the TAVI care program is a 'continuing journey' from hospital admission to discharge, from referral to follow-up, from patient selection to treatment strategy, in which optimalization and standardization of care and patient safety and quality of life are central. In this the TAVI coordinator plays a unique and prominent role which makes a demonstrated difference to patient orientated care for this specific vulnerable population. It is advisable to formalize this role further to ensure continuous improvement in treatment for these elderly patients. The number of patients with an indication for TAVI is increasing annually, both countrywide as in Erasmus MC. To guarantee continued inclusion of this role within the cardiology department, there needs to be a focus on specific training for these dedicated professionals. With this, I include experienced colleagues in interventional cardiology with areas of expertise in TAVI and structural heart who follow an additional course, for example a Master Advance Nursing Practice (MANP) or a course for Physician Assistant (PA). With this it is important to mention that the role and position of a TAVI coordinator associated with the structural heart program of a heart center, also has visibility internationally. With the inclusion in the most recent ESC-EACTS guidelines (2021), in which the role of a nurse with cardio-vascular expertise in the multi-disciplinary heart team is mentioned as an important addition, it would to be expected that in the future this would be formalized with a dedicated competency profile for the tasks and role of the TAVI coordinator.

In light of the afore mentioned, I have had the great privilege to be part of the TAVI program at the Erasmus MC since the very beginning and have witnessed it's impressive clinical innovation. I am thankful to be part of this team of experts and professionals that has been responsible for the development, initiation and implementation of the Rotterdam TAVI Care and Cure program; the basis of this thesis.

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Discussie en samenvatting Nederlands

DISCUSSIE EN SAMENVATTING

Aortaklepstenose is een vaak voorkomende hartklep-aandoening in de Westerse landen en komt het meest voor bij de oudere patientenpopulatie boven de 75 jaar. Tot aan 2002 was een chirurgische aortaklepvervanging (SAVR) de standaard behandeling voor patienten met ernstige symptomatische aortaklepstenose (AS) hoewel een aanzienlijk deel van de patiënten niet in aanmerking komt voor SAVR vanwege een verhoogd operatierisico en voorkomende comorbiditeiten. In 2002 echter werd door Prof. A. Cribier een nieuwe weg ingeslagen door de eerste patient met ernstige AS succesvol te behandelen via een percutane hartklepimplantatie via de lies, een transcatheter aortic valve implantation (TAVI). In de hieropvolgende jaren zijn wereldwijd steeds meer patienten met een hoog risico voor een chirurgische aortaklepvervanging (inoperabele patienten) behandeld via deze percutane techniek. De positieve resultaten van internationale gerandomiseerde studies hebben geleid tot een uitbreiding van de indicaties voor TAVI bij niet alleen inoperabele patienten maar ook bij patienten met AS en een aanvaardbaar operatierisico. Voor patienten met een gemiddeld en laag operatierisico, die vaak een langere levensverwachting hebben dan de hierbovengenoemde hoogrisico patienten, zijn de lange termijn uitkomsten (≥10 jaar) van belang. Een recente studie beschrijft dat degeneratie van een aortaklepprothese vaker voorkomt bij patiënten met ernstige symptomatische aortastenose die worden behandeld met een chirurgische bioprothese in vergelijking met degenen die met een zelfexpanderende transkatheter-hartklepbehandeld worden. Hoewel TAVI door het minimaal invasieve karakter vele voordelen biedt ten opzichte van een openhart operatie, zijn er echter ook procedure gerelateerde risico 's. In de begintijd waren dit voornamelijk bloedingen, vasculaire complicaties, pacemaker implantaties, para-valvulaire lekkage en soms ook peri-procedureel of het kort na de procedure overlijden. Inmiddels hebben de opgebouwde ervaring van de hartteams en de operateurs in combinatie met een voortdurende innovatie van deze techniek en materialen tot een significante afname van complicaties en verbetering van de uitkomsten van TAVI geleid. De procedure zelf is door de jaren heen technisch vereenvoudigd en wordt inmiddels uitgevoerd onder lokale anesthesie met een minimum aan invasieve toegangswegen met als gevolg versnelde mobilisatie, een voorspoedig herstel, en indien mogelijk een verkorte opnameduur. Parallel met deze ontwikkelingen in de klinische praktijk, bleek TAVI tevens een dankbaar onderwerp voor wetenschappelijk onderzoek, hetgeen een belangrijke bijdrage heeft geleverd aan bovenstaande ontwikkelingen. Ook dit proefschrift hoopt hieraan een bijdrage te leveren.

Het doel van dit proefschrift is om een beschrijving te geven van de evolutie van TAVI in het Erasmus MC sinds de eerste TAVI in 2005, de implementatie van het TAVI Care and Cure programma en de gevolgen voor de dagelijkse klinische praktijk. Centraal hierbij

staat een holistische benadering van de individuele patient met aortaklepstenose om doormiddel van een optimale balans tussen risico's en baten de beste behandelingstrategie vast te stellen die voldoet aan de de verwachtingen van de patient en de invloed op de kwaliteit van het leven na de behandeling.

Sinds de introductie en uitvoering van de eerste percutane aortaklep vervanging (TAVI) in November 2005 in het Erasmus MC Rotterdam, Nederland, was ik actief betrokken bij deze het opzetten en verder doorontwikkelen van het TAVI programma en heb hier als verpleegkundige en mens veel van geleerd. We zijn kleinschalig gestart, in 2005, met 1 TAVI procedure, de 1ste in Nederland (patient no 16 wereldwijd met een CoreValve klep), waaraan diverse besprekingen op multi-disciplinair niveau in nauwe samenwerking tussen enerzijds, interventiecardiologen en cath. lab medewerkers (verpleegkundigen, technici), cardiothoracale chirurgen, cardioperfusionisten, anesthesiologen, interventieradiologen, vasculair chirurgen en, anderzijds, het technisch en ondersteunend team van de fabrikant van de hartklep aan vooraf gingen. Een percutane hartklep inbrengen via "de lies", het klonk futuristisch, we hadden er nog niet echt een idee van wat deze nieuwe technologie ons en met name de patienten, die we zouden gaan behandelen, zou gaan brengen. Er was destijds nog geen beschreven werkwijze voorhanden, deze hebben de interventiecardiologen in samenwerking met de collega's van het Cathlab team en de firma CoreValve opgesteld. De verpleegafdelingen die de zorg hadden voor de patient tijdens de pre-en post operatieve fase werden hier ook nauw bij betrokken. Verder bleek het van groot belang om alle materialen (steriel en onsteriel) in stock te hebben, waarbij een 2de hartklep van de juiste maat niet mocht ontbreken en tevens alle materialen die nodig zouden kunnen zijn in geval van een complicatie tijdens de ingreep, in het bijzonder vasculaire bloedingsproblemen (bijv. occlusie-ballonnen om onvoorziene en belangrijke bloedingen te kunnen stelpen waardoor niet alleen stabilisatie van de patient maar ook extra tijd om deze complicatie vervolgens op te lossen). Daarnaast werd in deze pioniersfase elke individuele TAVI procedure terdege voorbereid door Prof.dr. Peter de Jaegere middels een script, dat het TAVI-team per mail ontving zodat iedereen wist waarvoor hij of zij verantwoordelijk was, op welk moment van de ingreep en welke materialen op dat ogenblik nodig waren. Dit script werd voorafgaand aan de TAVI nogmaals met alle betrokkenen doorgenomen en kan gezien worden als de voorloper van onze huidige Time-Out procedure (zie foto hieronder). Bij de eerste TAVI's was er altijd een ervaren proctor aanwezig, die samen met het team van het Erasmus MC de procedure uitvoerde. Inmiddels zijn onze interventiecardiologen zeer ervaren en zijn zelf als proctor bij TAVI's aanwezig in minder ervaren hartcentra.

Mijn interesse als leidinggevende van het cathlab destijds en als verpleegkundige in de specifieke problematiek van-en rondom TAVI heeft mij blijvend geinspireerd en

Fig. Briefing voorafgaand aan TAVI (2005). Zittend vooraan van links naar rechts M. de Ronde (hoofdverpleegkundige), Dr. de Jaegere, Dr. Kappetein, Professor Serruys. Staand achter Professor Serruys: Dr. Klein (anaesthesioloog). Zie het script waarin opgenomen i.e. de beschrijving van de procedure, benodigde materialen, taken en verantwoordelijkheden van ieder, alles in chronologische volgorde tijdens de ingreep.

uitgedaagd met als gevolg dat ik dit promotietraject in 2013 ben gestart. Een belangrijk gegeven hierbij was de behoefte aan meer struktuur en beleid door de steeds prominentere rol die TAVI procedures innamen binnen het Erasmus MC voor deze de kwetsbare groep patiënten en het sterk toenemende aantal TAVI's. Het eerste TAVI-zorgpad werd geschreven en ontwikkeld op multi-disciplinair niveau om de interne en later hieropvolgend de externe ketenzorg beter op elkaar af te stemmen. Naast factoren als technische uitvoering van de klepvervanging en overleving kwam er ook meer aandacht voor de verwachte verbetering van de kwaliteit van leven (QoL) van de patienten en terugkeer naar de eigen woon-en leefomgeving. Er was in die begintijd weinig tot geen informatie over de effecten van somatische, mentale en sociale omstandigheden op de uitkomst van TAVI op zowel korte (30 dagen) als langere termijn (1 jaar). Dit heeft uiteindelijk geleid tot de initiatie en implementatie van het TAVI Care and Cure programma in het Erasmus MC met het accent op een zorgvuldigere patient selectie met een hieraan toegevoegd een actieve rol en nauwe betrokkenheid van de afdeling Geriatrie.

Als onderdeel van het TAVI Care and Cure programma werd een database gebouwd waarin een groot aantal variabelen werd geregistreerd en alle opeenvolgende TAVI-patiënten werden geïncludeerd. Hiervoor werd in 2014 een dedicated Studententeam opgericht.

Een mooi neveneffect van dit Studententeam bleek de vruchtbare voedingsbodem voor promotietrajecten (imiddels zijn meerdere van deze studenten al gepromoveerd of nog bezig met een promotietraject op de afdeling Cardiologie).

Het (mee)schrijven van de hoofdstukken uit dit proefschrift, het doen van onderzoek, mijn deelname aan de wekelijkse hartkleppen-besprekingen en niet in het minst, de vele gesprekken met de patiënten tijdens de wekelijkse poliklinische spreekuren hebben mij veel inzichten gebracht in het ziektebeeld zelf, het daarbij behorende klachtenpatroon en niet te vergeten de dagelijkse beperkingen die deze patienten ervaren voor en soms ook na de procedure. Wanneer we inzoomen op de hoofdstukken van dit proefschrift, wordt in hoofdstuk 2 en 4 het tijdperk sinds de eerste TAVI in 2002 beschreven inclusief de rol van de diverse klinische experts en visionairs op dit gebied tijdens de preklinische fase tot aan de 1ste TAVI in november 2005 in Nederland. Verschillende factoren waaronder het ontstaan van gespecialiseerde hartcentra met ervaren multidiciplinaire hartteams, een geoptimaliseerde patientenselectie, geprotocolliseerde procedures en complicatiemanagement hebben geleid tot een succesvolle introductie en klinische toepasbaarheid van TAVI in Nederland.

Hoofdstuk 3 beschrijft de opzet en implementatie van het TAVI Care and Cure programma, een observationele en prospectieve studie waarbij de focus niet alleen op de procedurele en functionele kant van de procedure lag, maar ook het accent kwam te liggen op de cognitieve functie van de oudere patienten die in aanmerking komen voor TAVI. De toename van het aantal patienten dat in aanmerking kwam voor een TAVI in het Erasmus MC had een uitbreiding van capaciteit tot gevolg. Dit was mededе aanleiding tot de realisatie van een gestandaardiseerd multi-disciplinair programma met als belangrijke toevoeging de systematische applicatie van een geriatrische beoordeling tijdens de pre-en post TAVI fase. De meerderheid van deze patienten zijn immers ouder dan 80 jaar en hebben hierdoor een verhoogd risico op post-operatief delirium (POD) dat geassocieerd is met een verhoogde mortaliteit.

In hoofdstuk 5, 6 en 7 is onderzocht, welke factoren belangrijk waren voor de veranderingen door de tijd heen, waarbij het verzamelen van een specifieke dataset van zowel cardiologische als geratrische variabelen essentieel was. De resultaten laten zien dat bij de meeste patienten de klachten ten gevolge van aortaklep stenose na TAVI verminderen en de kwaliteit van leven verbetert. Echter, ook blijkt een aantal patienten een beperkt of geen positief effect van de TAVI te ervaren. Het betreft immers een kwetsbare patientenpopulatie waarbij naast pathologische factoren, ook factoren als kwetsbaarheid (frailty) een onafhankelijke voorspeller blijken te zijn van een verslechtering van de kwaliteit van leven en resulteren in een afname van de reservecapaciteit van de patiënt.

Het is daarom dat wij concluderen dat het van belang is deze patienten te screenen en identificeren op hun eventuele kwetsbaarheid door een klinisch geriater om naast de bestaande scoringssystemen (EuroSCORE en STS-score) een goede afweging te maken om tot de juiste keuze van behandeling te komen. Daarnaast heeft de uitbreiding van de indicatie voor TAVI van een hoog en gemiddeld operatierisico naar laag risico en daardoor toename van het volume van het aantal TAVI's in het Erasmus MC geleid tot het stroomlijnen van de ontslagroutes post-TAVI om een goede balans te houden tussen vraag en aanbod.

Naast een overplaatsing naar een verwijzend ziekenhuis voor verder herstel na TAVI is bij een selecte groep van patienten met AS en een laag operatierisico een vervroegd ziekenhuis-ontslag beleid (>3 dagen) met behoud van veiligheid en haalbaarheid onderzocht (hoofdstuk 8). Van belang hierbij blijken een aantal ontslag-criteria (o.a. heamodynamische stabiliteit, een succesvolle TAVI, geen procedurele complicaties, geen indicatie voor tijdelijke pacemaker, aanwezigheid van logistieke support verwijzende centra en aanwezigheid van sociale support na thuiskomst). Daarnaast blijken simplificatie van de TAVI door o.a. toepassing van locale i.p.v. algehele anesthesie waardoor geen observatie post-TAVI nodig is op een ICCU en reductie van het aantal invasieve lijnen belangrijke criteria die een eventueel vervroegd ontslag mogelijk maken. I

In hoofdstuk 9 is de implementatie van pacing via de linker ventrikel guidewire met gebruik van krokodillenklemmen in plaats van positionering van een tijdelijke pacemakerdraad in het rechter ventrikel via een veneuze sheath onderzocht en beschreven. Door deze vereenvoudigde procedure bleek een extra veneuze sheath niet meer nodig bij de meerderheid van de patiënten. Alleen bij het optreden van een hoog-gradig atrio-ventriculair blok tijdens TAVI is een extra pacemakerdraad via een extra veneuze sheath nodig. Deze strategie blijkt veilig toepasbaar bij het grootste deel van de TAVI-procedures en laat een reductie zien van de proceduretijd.

In hoofdstuk 10 is de ontwikkeling, ervaring en verandering beschreven vanaf de 1ste succesvolle TAVI in 2005 tot en met 2020 in het Erasmus MC, Rotterdam waarbij de initiele procedure over de jaren heen versimpeld en aangenamer is geworden voor de patient. Terwijl de gemiddelde leeftijd van de patienten met AS 80 jaar bleef in 15 jaar, verbeterde het risicoprofiel door een afname van cardio-vasculaire aandoeningen tijdens baseline, nam de indicatie voor een permanente pacemaker af en verbeterde de linker ventrikelfunctie door een effectieve afterlaodreductie post-TAVI. Naast procedurele simplificaties, verbeterde klinische uitkomsten en 1-jaars mortaliteit blijft aandacht voor complicaties gerelateerd aan TAVI zoals bloedingen, vasculaire complicaties en geleidingsstoornissen essentieel.

Door de actieve rol bij bovenstaande onderzoeken en mijn rol als TAVI coördinator kreeg ik meer inzicht op gebied van de verwachtingen die een patient had voor de periode ná de TAVI-ingreep; wat brengt de toekomst, wat als er complicaties onstaan en welke, maar ook of de kwaliteit van leven zal verbeteren? Ondanks het feit dat patienten goed op de hoogte te zijn van de behandeling, beperkingen en eventuele risico's, geven ze steeds vaker aan dat ze liever een TAVI dan SAVR ondergaan. Mijn gecombineerde rol als verpleegkundig TAVI-coördinator en promovendus blijkt zich, vanaf 2016, te hebben ontwikkeld tot een specialistische rol waarbij de organsatie van-en rondom de TAVI-planning, de organisatie tijdens de pre-peri- en post operatieve fase, alsmede een adviserende en informatieve rol naar de patient en diens familie toe centraal staan.

Dat ook internationale samenwerking een relevant onderdeel van dit promotietraject was blijkt uit hoofdstuk 11. Hierin komt de evolutie van asssisterend verpleegkundige bij TAVI procedures naar een multifunctionele rol van TAVI-coördinator aan bod als een belangrijke kwaliteitsimpuls. Zeker diens rol als vast aanspreekpunt voor patienten is hierbij van groot belang, inclusief de hieruit volgende communicatie. Dit blijkt een grote invloed te hebben op het verwachtingspatroon en de beleving van patiënten en hun naasten. Het verder optimaliseren van het TAVI-zorgpad is een "continuous journey", van ziekenhuisopname tot ontslag, van verwijzing tot follow-up, van patientenselectie tot behandelstrategie, waarbij optimalisatie en standaardisatie van zorg, patientveiligheid en kwaliteit van leven centraal staan.

Hierin speelt de TAVI-coördinator een unieke en prominente rol en maakt het verschil met oog voor patient gerichte zorg voor deze specifieke en vaak kwetbare patientenpopulatie. Het verdient de voorkeur om deze rol verder te formaliseren om ook in de nabije toekomst de zorg voor deze kwetsbare groep patiënten te blijven optimaliseren. Het aantal patienten dat in aanmerking komt voor een TAVI blijft immers jaarlijks toenemen, zowel landelijk als binnen het Erasmus MC. Om deze specifieke rol en bijbehorend taakgebied te borgen binnen de afdeling Cardiologie zal er aandacht moeten zijn voor het opleiden van "dedicated professionals" die hier de juiste invulling aan weten te geven. Hierbij denk ik aan ervaren medewerkers interventiecardiologie met als aandachtsgebied TAVI en Structural Heart die een aanvullende opleiding volgen zoals bijvoorbeeld een Master Advanced Nursing Practice (MANP) of de opleiding tot Physician Assistant (PA). Hierbij is het niet onbelangrijk te noemen dat de rol en positie van een TAVI-coördinator verbonden aan het Structural Heartprogramma van een Hartcentrum ook op internationaal niveau momenteel in de belangstelling staat.

Naast de toevoeging in de meest recente ESC-EACTS richtlijnen (2021) waarin de rol voor een verpleegkundige met cardio-vasculaire expertise in het Multi Disciplinair Hartteam

als een belangrijke toevoeging wordt genoemd, ligt het in de lijn der verwachtingen ligt dat er op termijn een formalisatie zal volgen door middel van een dedicated competentieprofiel voor de taken en rol van een TAVI-coördinator.

In het licht van bovenstaande heb ik het grote voorrecht gehad om aan de wieg van het TAVI programma in het Erasmus Medisch Centrum Rotterdam te staan en getuige te zijn van deze indrukwekkende klinische innovatie. Ik ben dankbaar om deel uit te maken van het uiterst deskundige en professionele team dat verantwoordelijk was en is voor de initiatie, ontwikkeling en implementatie van het Rotterdamse TAVI Care and Cure programma, de basis van dit proefschrift.

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List of publications

LIST OF PUBLICATIONS

1. Peter de Jaegere, Arie Pieter Kappetein, Marco Knook, Ben Ilmer, Dries van der Woerd, Yvon Deryck, **Marjo de Ronde**, Ricardo Boks, G Sianos, Jurgen Ligthart, Jean-Claude Laborde, Ad Bogers, Patrick W Serruys *Percutaneous aortic valve replacement in a patient who could not undergo surgical treatment. A case report with the CoreValve aortic valve prosthesis.* **Eurointervention** (2006)
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PhD Portfolio

Name PhD Candidate:	Maria Josephina Agnes Gerarda (Marjo) de Ronde-Tillmans
Department:	Interventional Cardiology
PhD Period:	Jan 2013 - Dec 2022
Title thesis:	Transcatheter Aortic Valve Implantation; From an academic pioneering project to a multidisciplinary patient-centered clinical and scientific program
Promotor:	Prof. dr. P.P.T. de Jaegere Prof. dr. F.U.S. Mattace-Raso
Co promotor:	Dr. M.J. Lenzen
Date defense:	December 7th 2022

	Year	Workload (ECTS)
General skills & academic courses		
EMC - EndNote workshop	2013	0.20
Literature search Medical Library	2013	0.20
Literature research course Medical Library	2013	0.20
EGSL - Academic Integrity	2019	2.00
Ercathan: Functional and Applied Clinical Anatomy of the Heart	2013	0.30
EMC - Biostatistics and Research Methods = NIHES or MolMed	2019	0.45
Biomechanics of Atherosclerotic Plaque: Site, Stability and in vivo M	2013	0.10
Coronary and cranial Thrombosis	2013	0.10
Cardiovascular Medicine	2013	0.60
Courses		
Erasmus MC - BROK® (Basic course Rules and Organization for Clinical researchers	2020	1.50
Course WMO Good Clinical Practice	2021	0.20
TAVI in de Lage landen: Webinar	2021	0.10
Large bore management in contemporary TAVI Webinar	2021	0.10
Presentations		
CoreValve TAVI course Erasmus MC (Rotterdam, NL) "Essential Materials and Devices for successful Percutaneous Aortic Valve Replacement"	2008	0.50
EuroPCR (Paris, France); "TAVI in the Hybrid Lab, Patient Pathway"	2017	0.50
EuroPCR (Paris, France); "TAVI – Anatomy, Diagnostics, Treatment and Heamodynamics"	2017	0.50
International TVT Nurse Symposium (Copenhagen, Denmark) "Does Quality of Life improve after TAVI?"	2017	0.50

	Year	Workload (ECTS)
GISE, (Milan, Italy) Discussant/Chair of workshop " Europe in Italy, Italy in Europe"	2017	0.50
GISE (Milan, Italy) "The Netherland clinical case: embolic protection during TAVI"	2018	0.50
Refereeravond afdeling Geriatrie: "Trans Aortic Valve Implantation (TAVI)"	2019	0.50
GISE (Milan, Italy); NOVITA' DALL'EUROPA-SESSION; "Short Stay Protocol in TAVI"	2019	0.50
EuroHeartCare, Annual Congress of the Association of Cardiovascular Nursing and Allied Professions (Milaan, Italy); "TAVI without Anesthesia, what is the Plan?"	2019	0.50
Cardiology meets Geriatrics: TAVI Care & Cure, The patient journey	2022	0.50
ACNAP Lecture; Measuring patient vulnerabilities: the value of assessing frailty (Madrid, Spain)	2022	0.50
1th National TAVI-symposium (Veenendaal, The Netherlands)	2022	0.50
Other activities		
Voorzitter Werkgroep Interventiecardiologie Nederlandse Vereniging voor Hart- en Vaatverpleegkundigen (NVHVV)	2007-current	
Voorzitter DRES-Cathlab Symposium Commissie	2015-current	
Voorzitter Werkgroep WIL: Hoofden Cathlab' s Nederland	2015-current	
Committee member of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Nurses and Allied Professionals (NAP)	2022-2024	
Coördinator TAVI-studententeam Erasmus MC	2013-current	
Member of the Edwards Benchmark Program Global Faculty	2021-current	
Reviews		
Reviewer for the European Journal of Cardiovascular Nursing (EJCN) on regular basis (frequency: 8)	2019-currently	1.00
(Co-)author		
"Beroepscompetentieprofiel Medewerker HCK"; Nederlandse Vereniging voor Hart- en Vaatverpleegkundigen (NVHVV)	2019	2.00
"Trans Catheter Aortic Valve Replacement; a Guide for the Heart team"	2019	0.60
"Beroepscompetentieprofiel Medewerker HCK Diagnostisch; Nederlandse Hartfunctie Vereniging (NHV) en Nederlandse Vereniging voor Hart- en Vaatverpleegkundigen (NVHVV)	2021-2022	2.00
"Heart Failure and Transcatheter Aortic Valve Replacement" Critical Care Nursing Clinics	2022	0.20

	Year	Workload (ECTS)
National and International conferences		
Euro PCR (Paris, France)	2013	1.20
CarVasZ, Faculty (Ede, The Netherlands)	2013	0.60
TCT Congress (San Francisco, USA)	2013	1.20
Euro PCR (Paris, France)	2014	1.20
CarVasZ, Faculty (Ede, The Netherlands)	2014	0.60
London Valve meeting (London, UK)	2014	0.60
Trans catheter Heart Therapies, from Niche to Mainstream, Erasmus MC, (Rotterdam, The Netherlands)	2014	0.10
Cathlab symposium DRES, Faculty (Nijkerk, The Netherlands)	2015	0.60
CarVasZ , Faculty (Ede, The Netherlands	2015	0.60
Euro PCR (Paris, France)	2016	1.20
Cathlab symposium DRES, Faculty (Nijkerk, The Netherlands)	2016	0.60
London Valve (London, UK)	2016	0.60
GISE (Genua, Italy)	2016	1.00
CarVasZ , Faculty (Ede, The Netherlands)	2016	0.60
Euro PCR, Faculty (Paris, France)	2017	1.20
European TVT nurse specialist symposium (Kopenhagen, Denmark)	2017	1.20
Cathlab symposium DRES, Faculty (Nijkerk, The Netherlands)	2017	0.60
CarVasZ, Faculty (Ede, The Netherlands)	2017	0.60
Euro PCR, Faculty (Paris, France)	2019	1.50
GISE Congress, Faculty (Milano, Italy)	2019	2.00
London Valve meeting (London, UK)	2019	0.60
CRES Congress (Willemstad, Curacao)	2019	0.60
Cathlab Symposium DRES, Faculty (Nijkerk, The Netherlands)	2021	1.50
Euro PCR (Paris, France)	2022	1.20
ACNAP–EuroHeartCare Congress, Faculty (Madrid. Spain)	2022	1.00
Symposium Geriatrics Meets cardiology (Rotterdam, The Netherlands)	2022	0.50
Cathlab symposium DRES, Faculty (Nijkerk, The Netherlands)	2022	0.60
TAVI Network-day VS and PA-working group (The Netherlands)	2022	0.60
1th National TAVI-Symposium, Faculty (Veenendaal, The Netherlands)	2022	1.00
TAVI Cathlab day Structural Heart, Faculty and Chair(Utrecht, The Netherlands)	2022	0.60
Teaching activities/Supervising		
Education program Interventional cardiology course (Erasmus MC, Rotterdam, The Netherlands)	2019	0.60
Education TAVI for Interventional cardiology students, Erasmus Academy, (Rotterdam, The Netherlands)	2020	1.00

	Year	Workload (ECTS)
TAVI Education (Erasmus MC, Rotterdam, The Netherlands)	2021	1.00
Education program BMH-students; "TAVI evolution in EMC" (Erasmus MC, Rotterdam, The Netherlands)	2021	1.00
Education program department of Cardiology (Erasmus MC, Rotterdam, The Netherlands)	2021	0.60
Supervision of third year medical student in writing thesis (Erasmus University, Rotterdam, The Netherlands)	2020-2021	2.50
Supervision of 5th year master-student (TU Delft)	2021-2022	3.00
Education students ICCU and OR (EPA)	2022	0.50
Total		**54.00**

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About the author

Marjo de Ronde Tillmans was born in 1958 in Maastricht, Limburg, The Netherlands. She graduated from Henric van Veldeke High School in Maastricht in 1975. She started her nursing training at St. Annadal Hospital in Maastricht in 1975 and qualified in 1978. Following this, she worked as a graduate nurse on the Cardiology Ward for two years, during which time she became interested in cardiology and completed the training for a Coronary Care Unit Nurse in 1981. In April 1982, after she moved with her husband, Jaap de Ronde, to Spijkenisse, she started as a nurse in the Cardiac Cath Lab in the Thoraxcenter in Dijkzigt Hospital, nowadays the Erasmus Medical Center in Rotterdam. Supervisors of the Cath Lab Department were Mrs. Susan Veldhof for the Nursing Staff and Dr. Marcel J.B.M. van den Brand as Medical Chief.

In 1986 Marjo graduated in the *Management in Hospitals and Institutions Course* at the IBW Institution for Business Studies, followed by a post HBO-study *Healthcare Management for Unit Managers in Healthcare* at the Transfer Group in Rotterdam. From 1982-1992 she worked as a Senior Cath Lab Nurse in the Interventional Cardiology Department. Following this, she took the position of Chief Nurse of the Interventional Cardiology Department from 1992 until 2016.

In 2010, in co-operation with the Erasmus MC Healthcare Academy, Marjo developed and implemented an annual education program for Cath Lab Nurses and Technicians in The Netherlands which has been accredited by the Dutch Association for Cardiovascular Nurses (NVHVV). In 2012 she set up, also in cooperation with the Erasmus MC Academy, a 2-year trainee program for nurses with a Bachelor's Degree for Nursing (HBOV) to graduate as a Interventional Cardiology Cathlab nurse.

In 2013 she started her PhD titled *"Transcatheter Aortic Valve Implantation; From an Academic Pioneering Project to a Multi-disciplinary Patient Centered Clinical and Scientific Program".* (Promotors Prof. dr F. Zijlstra, Prof. dr P.P.T. de Jaegere, Prof. dr F.U.S. Mattace Raso replacing Prof. dr F. Zijlstra as promotor in 2022 and co-promotor Dr. M.J. Lenzen). In addition she initiated a clinical TAVI-pathway, the TAVI Care & Cure program, to improve the treatment and care of patients with aortic stenosis undergoing a TAVI. To collect all the related data during the outpatient visits, she setup and coordinates a medical student team accompanying the TAVI-cardiologists during the outpatient clinic and entering collected variables into a dedicated database.

Some other projects to which she contributed were the implementation of a Time Out Procedure for patient safety protocols, a Lean Management Project and inter-clinical healthcare pathways with referring hospitals for patients undergoing a percutaneous coronary intervention (PCI) in the Erasmus Medical Center. In close collaboration with the Erasmus MC Academic education department she developed and initiated an education program for nurses and allied health professionals, working on a interventional cardiology ward in the Netherlands. From 2015 to 2018 she was the assisting project manager for the transfer of the Interventional Cardiology and Electrophysiology Departments to the new location in the OR Department in the re-built hospital. Implementation of the new electronical patient dossier (HiX) for the Cath Lab Health Professionals was one of the main goals. One of the latest projects she contributed to is the development and implementation of a dedicated TAVI information-box, including a virtual QR-coded animation, which will be send to all patients before their TAVI-intervention,.

In addition, Marjo fulfills different positions outside of the Erasmus MC. Since 2006 she is chair of the Dutch Interventional Cardiology Working Group at the NVHVV. Since 1995 she is a member of the Working Group for Interventional Leaders (WIL) and holds the chair of the WIL since 2015 until the present. In 2014, she initiated, together with Caroline van Kouwen (member of the WIL), the Cath Lab Symposium in collaboration with the Dutch Revascularization and Electrophysiology Summit (DRES). Marjo is still the chair of the (yearly) Cath Lab Symposium Committee.

On an international level she has been a member of the EuroPCR Nurses and Allied Professions (NAP) Committee from 2012 to 2016; a member of the Program Committee for the annual PCR Nurse-and Technicians Program and currently for the period of 2022 to 2024 a member of the EAPCI NAP's Committee as chair of the Research Sub-committee. In 2019 she was co-author (with Ank Adan from Amphia Hospital, Breda) of the competence profile for Cath Lab Health Professionals (Employees HCK Intervention Cardiology NVHVV). This competence profile is officially recognized and accredited by the College of Health Care Education (CZO). Furthermore, she is co-author of the Competence Profile for Diagnostic Cath Labs (in close collaboration with Danny Verbunt, Chair of the Dutch Heart Function Association (NHV). From November 2016 to the present day, she fulfills the position of Transcatheter Aortic Valve Implantation (TAVI)-Coordinator of the Structural Heart program at the Erasmus Medical Center, Rotterdam, the Netherlands.

Marjo married Jaap de Ronde (†2015) in 1982. Their two children were born in 1982 and 1991 respectively, William René de Ronde and Louisa Christine de Ronde.

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Acknowledgements / Dankwoord

Inleiding

Mijn promotietraject begon in 2013, ik was destijds nog fulltime hoofd van het cathlab, gaf leiding aan de teams en draaide mee in de bereikbaarheidsdiensten. Een drukke baan maar toch was ik op zoek naar een nieuwe uitdaging naast mijn functie, om mijn kennis te verbreden en meer te kunnen betekenen in het zorgproces voor met name de oudere patiënten, die vanwege ernstige aortaklepstenose een TAVI in het Erasmus MC krijgen. Ik heb het grote voorrecht gehad om samen met Prof. Patrick Serruys en Prof. Peter de Jaegere en vele andere collega's, o.a. van de afdelingen OK-Thorax, cardiochirurgie, anesthesie, perfusie, echocardiografie en imaging aan de wieg te hebben gestaan bij de allereerste TAVI in Nederland. Vele mijlpalen op gebied van TAVI volgden waarvan ik getuige mocht zijn en waaraan ik heb mogen meewerken. Inmiddels is het TAVI-structurele hartprogramma in het Erasmus MC een van de belangrijkste pijlers van ons zorgaanbod met een uitgebreide regionale verantwoordelijkheid en samenwerking met aan ons verwijzende omliggende ziekenhuizen

Beste **Professor de Jaegere**, beste Peter, ik zie het nog steeds als een groot voorrecht dat ik bij u mijn promotietraject heb mogen volgen en dat u mijn begeleider en leermeester heeft willen zijn. Vanaf het eerste uur hebben wij samengewerkt aan TAVI Care & Cure, een interklinisch zorgpad voor deze kwetsbare en oudere patiëntenpopulatie. De gedachte van u om bij dit project de geriaters actief te betrekken was een uniek initiatief, dat zijn waarde reeds ver grensoverschrijdend bewezen heeft. Vanaf 2013 hebben de geriaters een belangrijke rol gekregen in de TAVI-patientjourney, die niet meer weg te denken valt in onze dagelijkse klinische praktijk en de kwaliteit van onze (keten-)zorg. Ik heb veel van u geleerd, het waren wijze lessen met soms met een humoristische inslag en soms ook levenslessen, die wij tegenkomen in ons dagelijks leven, die ons hebben gevormd zowel op persoonlijk vlak als in ons werkzame leven en nog deels onze keuzes in het leven bepalen. Veel dank hiervoor!

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