



Optimizing Outcomes of Aortic Valve Replacement

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ISBN: 978-94-6361-663-8

Lay-out and printing by Optima Grafische Communicatie (www.ogc.nl)

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Optimizing Outcomes of Aortic Valve Replacement

Verbeteren van uitkomsten van aortaklepperving

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof. dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on
Tuesday 24 May 2022 at 10:30

by

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Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged. Furthermore, financial support by the Erasmus University Rotterdam, the department of Cardiothoracic Surgery Erasmus MC, Krijnen Medical Innovations B.V., ChipSoft B.V. and Stichting ETB-BISLIFE for the publication of this thesis is gratefully acknowledged.

The research described in this thesis was supported by a grant of the Dutch Heart Foundation (DHF 2012B001).

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1

General introduction, aims and outline

SIGNIFICANCE, SYMPTOMS, AND OUTCOMES OF AORTIC VALVE DISEASE

Heart valves have a major role in regulating normal blood flow through the human body. Disorders of the heart valves are common and important causes of cardiovascular morbidity and mortality. Diseases of the aortic valve are one of the most prevalent forms of valvular heart disease worldwide (1). **Figure 1.** summarizes the age-related prevalence of aortic valve disease in the Western population.

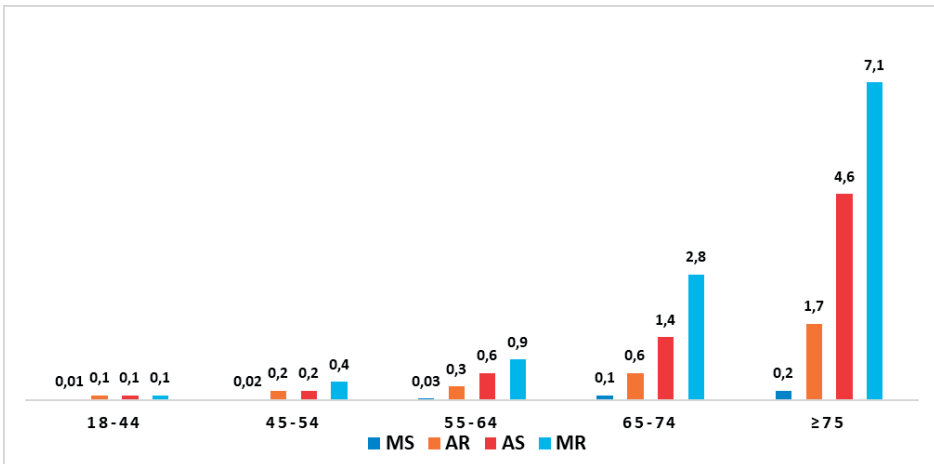


Figure 1. Age-related percentage prevalence of valvular heart diseases – based on Nkomo et al (1)

AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation, MS, mitral stenosis

Aortic valve disease can manifest in three forms: as pure aortic valve stenosis (AS), as pure aortic valve regurgitation (AR), or as the combination of the two. AS, by physically obstructing left ventricular ejection, causes compensatory myocardial hypertrophy leading to relative myocardial ischemia and myocardial remodeling (2). On the contrary, AR results in chronic volume overload of the left ventricle, leading to ventricular dilatation and inducing irreversible histopathological changes in the myocardium (3).

Both AS and AR are seriously limiting diseases, associated with symptoms of dyspnea, chest pain and decreased exercise capacity, severely affecting the quality of life. Both severe AS and AR lead to heart failure and death if not treated timely with aortic valve replacement (4).

Goals of treatment in aortic valve disease and surgical aortic valve replacement

The goals of treatment in aortic valve disease are threefold: to relieve symptoms, to restore quality of life and prolong survival. In case of severe aortic valve disease, these

goals can only be achieved by replacing the diseased valve with a properly functioning substitute.

The invention of cardio-pulmonary bypass and the development of the first surgical heart valve prostheses in the 1960's made surgical replacement of the diseased aortic valve possible (5). During surgical aortic valve replacement (SAVR), the patient is connected to a heart-lung machine and the heart is temporarily arrested. The aorta is opened to excise the diseased valve, which will be replaced with a prosthetic valve. After this, the aorta is closed, and the patient is weaned from the heart-lung machine. Although SAVR is a major surgery with substantial procedure-related morbidity and mortality, it proved to be effective in relieving symptoms and prolonging life and became the "golden standard" of the treatment of aortic valve diseases (6, 7). Refinements in perioperative care, prosthesis design and surgical techniques resulted in gradually improving outcomes over the last decades, and SAVR is currently performed in hundred-thousands of patients annually.

PROSTHETIC VALVE SELECTION FOR SURGICAL AORTIC VALVE REPLACEMENT

Prosthetic heart valves are not perfect substitutes of a healthy native valve. Although valve replacement with a prosthetic valve can effectively eliminate severe valvular stenosis or regurgitation and mitigate their consequences, valve replacement often also means a compromise regarding hemodynamics, durability, or prosthesis-related complications (8, 9). Each valve substitute has a specific profile, which must be weighed against patient characteristics and preference, local resources and expertise, and procedure-related risks. Surgeons and cardiologist are obliged to be familiar with this profile and to take it into account when advising patients or performing valve replacement.

Information regarding prosthetic valve characteristics can be found in the medical literature. These data accumulate since decades and are the primary source of information for clinicians regarding prosthetic valve hemodynamics and durability (10-13). However, these data can be in different publications and is thereby not easy to find, might be incomplete and can be subjected to significant reporting bias.

Another source of information is the data provided by manufacturers. These data are mostly to find in the instruction for use (IFU) leaflets and marketing materials. Among others, IFUs contain information regarding physical dimensions and hemodynamics, and are part of the official product labelling. The quality and quantity of data provided in these booklets are strictly regulated and controlled by regulatory bodies in Europe and the United States (14, 15). These prescriptions frequently use and refer to the applicable technical standards of the International Organization for Standardization (ISO) (16).

Marketing materials, which are the easiest to access, are less strictly regulated and often contain selected data with the primary goal to point out the positive characteristics and increase the market share of the product.

In summary, access to comprehensive information on prosthetic valve characteristics is not optimal, rendering comparison and selection of prosthetic valves difficult (17).

PROBLEMS AROUND SURGICAL HEART VALVE LABELING

Despite the existing regulatory framework, surprising anomalies are present in the labeling of surgical prosthetic valves (SHVs). Dimensions of the aortic annulus vary patient-by-patient and to ensure adequate fit, prosthetic heart valves are provided in different sizes. Labelled valve size of SHV should theoretically indicate the size of the tissue annulus where the specific valve fits (18). One of the most remarkable problems in labeling is that often dramatic differences exist between the dimensions of the sizing tools of similarly labeled valves from different manufacturers (19, 20). This anomaly exists since decades and is a permanent source of confusion in the surgical community (21).

Another major problem is the uncertainty regarding the proper interpretation of prosthetic valve hemodynamics. One of the most important determinants of success in valve replacement is that the implanted prosthesis fulfills the patient's circulatory requirements (22). Current labelling does not offer much help in this regard and labelled size of SHVs is not a direct surrogate of prosthesis hemodynamic performance. To assess hemodynamic compatibility, the term of patient-prosthesis mismatch (PPM) has been introduced in the medical literature (23). Existing PPM definitions are essentially based on the comparison of echocardiographically measured prosthesis effective orifice (EOA) and body surface area (BSA) of the patient (24). Unfortunately, tools provided by manufacturers to assess PPM risk are proven not only to be biased by selecting favorable data (25), but also unreliable to predict hemodynamic compatibility (26-28).

TRANSCATHETER AORTIC VALVE REPLACEMENT AND THE CHANGING LANDSCAPE OF AORTIC VALVE INTERVENTIONS

In contrast to the traditional surgical approach, the concept of transcatheter aortic valve implantation (TAVI) involves deploying a stent-mounted bioprosthetic valve in the aortic position, without excising the diseased valve, utilizing exclusively trans-vascular access and consequently avoiding sternotomy and cardio-pulmonary bypass (29). Fol-

lowing the first successful implants in the early 2000's, TAVI revolutionized the treatment of severe AS in only over a decade (30). Developed for patients with critical aortic stenosis and prohibitive risk for surgery, TAVI proved to be superior not only over medical therapy (31) but also over SAVR in AS patients having high estimated surgical risk (32, 33). Subsequently, the non-inferiority of TAVI in elderly intermediate risk AS patients has been proven (34, 35). Recently, clinical trials have even challenged the ultimate role of SAVR in the treatment of patients with severe AS and low surgical risk (36, 37).

Despite their similarities, SAVR and TAVI are not identical therapies. A fundamental difference is while during SAVR the diseased valve is completely excised and removed, during TAVI the native valve is crushed and pushed aside between the aortic annulus and the stent of the prosthesis. This affects procedure-related risks and complications and prohibits the use of TAVI in an infected environment. Furthermore, most transcatheter prostheses require some degree of valvar calcification to ensure proper anchoring, limiting the use of TAVI in patients with pure AR. Indeed, individual patient characteristics and valve anatomy, expected peri-procedural and long-term complications and prosthesis durability must be considered when choosing between SAVR and TAVI, making the Heart Team even more crucial in providing individualized patient-centered treatment (38-40). The rate of short- and long-term complications and outcomes after TAVI and SAVR are displayed in **Table 1** and **Table 2**, based on landmark randomized controlled trials comparing the two treatment modalities.

Table 1. Periprocedural complications after SAVR and TAVI – based on Durko et al (41)

Trial	Risk category	30-day mortality		Paravalvular AR (≥moderate)		Permanent PM		Stroke or TIA		Major vascular complication	
		TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
PARTNER 1 Cohort B (31)	Extreme	5.0%	2.8%*	12%	NA*	3.4%	5.0%*	6.7%	1.7%*	16.2%	1.1%*
PARTNER 1 Cohort A (32)	High	3.4%	6.5%	12.2%	0.9%	3.8%	3.6%	5.5%	2.4%	11%	3.2%
Medtronic CoreValve® U.S. Pivotal Trial (33)	High	3.3%	4.5%	9.0%	1.0%	19.8%	7.1%	5.7%	6.5%	5.9%	1.7%
PARTNER II Cohort A (34)	Intermediate	3.9%	4.1%	3.7%	0.6%	8.5%	6.9%	6.4%	6.5%	7.9%	5.0%
SURTAVI (35)	Intermediate	2.0%	1.3%	3.4%	0.3%	25.9%	6.6%	3.4%	5.3%	6.0%	1.1%
PARTNER III (36)	Low	0.4%	1.5%	0.8%	0.0%	6.5%	4.0%	0.6%	3.1%	2.2%	1.5%
Medtronic Low Risk Trial (37)	Low	0.5%	0.8%	3.4%	0.4%	17.4%	6.1%	2.6%	2.1%	3.8%	3.2%

*Comparator was optimal medical therapy; AR, aortic regurgitation; PM, pacemaker; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

Table 2. Complication rates in landmark TAVI trials, at the longest available follow-up – based on Durko et al (41)

Trial	Risk category	Longest available follow-up	Mortality		Paravalvular AR (≥moderate)		Stroke or TIA	
			TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
PARTNER 1 Cohort B (31)	Extreme	5 years	71.8%	93.6%*	NR	NR	16.0% ^o	18.2% ^o *
PARTNER 1 Cohort A (32)	High	5 years	67.8%	62.4%	NR	NR	15.9%	14.7%
Medtronic CoreValve® U.S. Pivotal Trial (33)	High	3 years	32.9%	39.1%	5.9%	0%	15.2%	21.0%
PARTNER II Cohort A (34)	Intermediate	2 years	16.7%	18.0%	8.0%	0.6%	12.7%	11.0%
SURTAVI (35)	Intermediate	2 years	11.4%	11.6%	4.9%	0%	10.0%	11.0%
PARTNER III (36, 42)	Low	2 years	2.5%	3.2%	0.5%	0%	3.5%	5.2%
Medtronic Low Risk Trial (37)	Low	1 year	2.4%	2.9%	3.6%	0.6%	5.6%	6.1%

*Comparator was optimal medical therapy; AR, aortic regurgitation; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack

Being less invasive than SAVR and having comparable outcomes, TAVI has drastically changed the landscape of aortic valve interventions in the last decade. The annual number of patients treated for severe AS has been effectively doubled in the recent years and TAVI numbers saw a continuous, dramatic increase in several Western countries (**Figure 2.**) (43, 44).

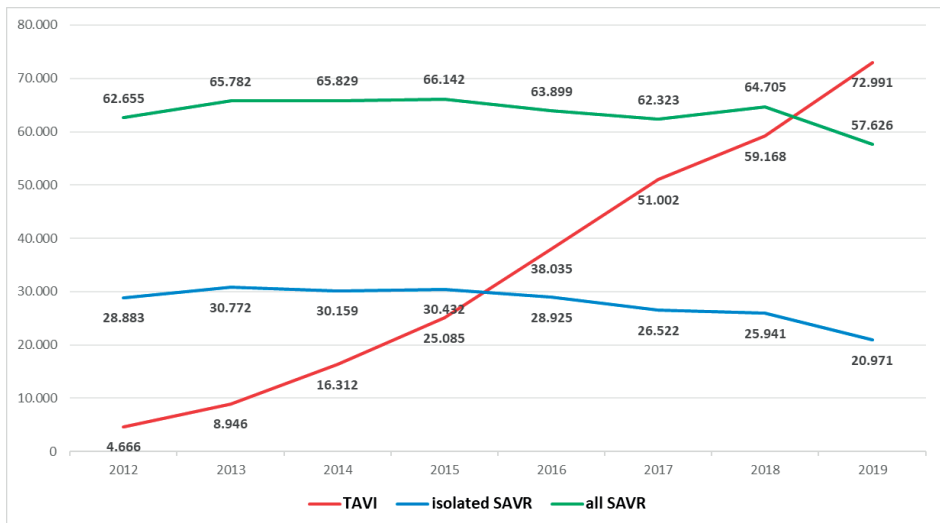


Figure 2. The changing landscape of aortic valve interventions, registry data from the United States – based on Carroll et al. (44)

SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation

These changes in clinical practice make investigating outcomes after SAVR and TAVI ever more important. This information is equally essential for health policy makers and clinicians, who make treatment decisions for the individual patient.

AIMS

The aims of this thesis are twofold. At first, this thesis aims to summarize current challenges around surgical prosthetic heart valve labelling and to provide potential solutions. Adequate information on surgical prosthetic heart valves will aid intraoperative prosthesis selection and the unbiased comparison of prosthetic valves from different manufacturers.

Secondly, it intends to analyze the current state of treatment options in aortic valve disease. Investigating treatment outcomes after SAVR and TAVI and analyzing trends in aortic valve replacement can facilitate informed treatment decisions for the individual patient.

OUTLINE

In the first chapters of this thesis, the current problems of surgical heart valve labelling are investigated, and solutions are proposed to facilitate optimal surgical prosthetic valve selection. These chapters are based on the work of the multi-society EACTS-STSAATS Valve Labelling Task Force. **Chapter 2** describes the framework of the assessment of surgical prosthetic valves, and discusses the current difficulties around informed SHV selection. **Chapter 3** provides comprehensive recommendations on which information is necessary for an optimal SHV choice and on how this information should be presented by valve manufacturers. **Chapter 4** highlights the differences between the novel tool suggested by the Task Force to assess the risk of PPM and the traditional EOAI charts used for this purpose.

The last four chapters are focusing on analyzing the treatment trends and outcomes of surgical and transcatheter aortic valve replacement. **Chapter 5** describes the historical and contemporary trends in the utilization of SAVR in the Erasmus MC. Long-term survival after SAVR is assessed and compared to that of the age-matched general population. **Chapter 6** is a modelling study which estimates the number of patients that could be potential TAVI candidates in various European and Northern American countries soon. Besides mortality, neurological complications are the most important outcomes after SAVR or TAVI and decisive in treatment outcomes. **Chapter 7** investigates the rate and characteristics of neurological complications after SAVR and TAVI in intermediate risk

patients enrolled in the SURTAVI clinical trial. After aortic valve replacement, coronary access for percutaneous coronary interventions (PCI) can be challenging, especially after implantation of a transcatheter prosthesis. **Chapter 8** investigates the incidence and the characteristics of patients requiring PCI after SAVR, to provide insights into the extent of this problem.

Finally, **Chapter 9** discusses the most important findings of this thesis and provides perspectives for future research.

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2

Characteristics of surgical prosthetic heart valves and problems around labeling: a document from the European Association for Cardio-Thoracic Surgery (EACTS) – The Society of Thoracic Surgeons (STS) – American Association for Thoracic Surgery (AATS) Valve Labeling Task Force.

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J Thorac Cardiovasc Surg. 2019 Oct;158(4):1041-1054

Ann Thorac Surg. 2019 Jul;108(1):292-303

ABSTRACT

Intraoperative surgical prosthetic heart valve (SHV) choice is a key determinant of successful surgery and positive postoperative outcomes. Currently, many controversies exist around the sizing and labelling of SHVs rendering the comparison of different valves difficult. To explore solutions, an expert Valve Labelling Task Force was jointly initiated by the European Association for Cardio-Thoracic Surgery (EACTS), The Society of Thoracic Surgeons (STS) and the American Association for Thoracic Surgery (AATS). The EACTS–STS–AATS Valve Labelling Task Force, comprising cardiac surgeons, cardiologists, engineers, regulators and representatives from the International Organization for Standardization (ISO) and major valve manufacturers, held its first in-person meeting in February 2018 in Paris, France. This article was derived from the meeting's discussions. The Task Force identified the following areas for improvement and clarification: reporting of physical dimensions and characteristics of SHVs determining and labelling of SHV size, *in vivo* and *in vitro* testing and reporting of SHV haemodynamic performance and thrombogenicity. Furthermore, a thorough understanding of the regulatory background and the role of the applicable ISO standards, together with close cooperation between all stakeholders (including regulatory and standardsetting bodies), is necessary to improve the current situation. Cardiac surgeons should be provided with appropriate information to allow for optimal SHV choice. This first article from the EACTS–STS–AATS Valve Labelling Task Force summarizes the background of SHV sizing and labelling and identifies the most important elements where further standardization is necessary.

Keywords: Aortic valve replacement • Mitral valve replacement • Prosthetic heart valve • Surgical prosthetic heart valve (SHV) • International Organization for Standardization (ISO) • International standard • Labelling • Sizing • Device approval • Regulation • Valve performance • Prosthesis–patient mismatch (PPM) • Objective performance criteria (OPC)

INTRODUCTION

Intraoperative prosthetic valve selection is a key determinant of surgical success; using the most appropriate surgical prosthetic heart valve (SHV) minimizes the risks of surgery, maximizes haemodynamic performance and optimizes long-term outcomes [1]. The final choice of an SHV, including appropriate size, is typically made in the operating theatre. To facilitate an evidence-based SHV choice, sufficient appropriate information on SHV characteristics is required. Background information from medical literature is not available in the intraoperative setting, so SHV package labels and instructions for use (IFU) booklets are the primary sources of information for the surgeon in the operating theatre.

In both the European Union (EU) and the USA, the quality and quantity of information provided with an SHV are regulated. The International Organization for Standardization (ISO) plays an important role in this process by providing a framework for regulatory bodies [2]. Although the ISO 5840 standard (Cardiovascular Implants—Cardiac Valve Prostheses) provides general conditions for testing SHVs for human implantation and defines operational and labelling requirements, the current labelling situation is not optimal. Simple definitions such as ‘labelled valve size’ are often unclear, and inconsistencies and controversies exist around the sizing and labelling of SHVs in relation to haemodynamic performance [3].

To resolve these issues, the European Association for Cardio-Thoracic Surgery (EACTS), The Society of Thoracic Surgeons (STS) and the American Association for Thoracic Surgery (AATS) set up the EACTS–STS–AATS Valve Labelling Task Force, involving representatives of the 3 surgical societies, cardiologists, engineers, regulatory professionals and representatives from ISO and major valve-manufacturing companies. The discussions during the first in-person meeting of the Task Force (held in February 2018, Paris, France) provided the core content of this article.

This first article of the EACTS–STS–AATS Valve Labelling Task Force is intended to provide an overview of important characteristics of SHVs relating to sizing and labelling, reviews current practices in these areas and identifies where improvements are necessary. This article will be followed by an expert consensus document containing recommendations on SHV sizing and labelling.

REGULATORY ASPECTS AND USE OF STANDARDS IN PROSTHETIC HEART VALVE LABELLING

In the EU and the USA, medical devices must demonstrate conformity to the local legislations before they can be introduced to the market. Assessment of conformity is

defined as the evaluation of whether a certain device is safe and effective according to the applicable regulations. This includes the assessment of the device labelling information, including the IFU and package labels. The ISO standards play an important role in defining these device-specific requirements.

International Organization for Standardization and the prosthetic heart valve standards

Technical standards are formal documents, defining uniform engineering criteria for technical systems. The ISO is an independent, non-governmental organization consisting of national standards bodies [4]. Manufacturers globally use ISO standards during product development and production. In addition, ISO standards are widely utilized by regulatory bodies as a conformity assessment tool for market approval. The ISO standards are periodically revised and updated in line with new innovations.

‘ISO 5840’ is a family of standards developed by a group of professionals from engineering and medical backgrounds, including representatives of the medical device industry, regulators and clinicians. The current 2015 version (ISO 5840:2015, Cardiovascular Implants—Cardiac Valve Prostheses) consists of 3 parts: ‘part 1: general requirements, part 2: surgically implanted heart valve substitutes and part 3: heart valve substitutes implanted by transcatheter techniques’.

‘ISO 5840:2015’ provides recommendations and requirements for preclinical and clinical evaluations of SHVs [2], and it defines valve-related objective performance criteria according to linearized event rates of key safety end points (thromboembolism, valve thrombosis, haemorrhage, paravalvular leakage and endocarditis) [2, 5, 6]. Furthermore, ISO provides guidance on labelling by describing the information that should be available on the product labels and in the IFU, including detailed information on intended use, indications/contraindications and warnings, and physical and performance characteristics [2].

Standards and prosthetic heart valve approval in the European Union

In the EU, the regulatory framework provided by the European Commission sets the general requirements for the whole range of medical devices [7, 8]. More specific requirements are defined within ‘Common Specifications’ or in ‘Harmonized Standards’. The European Committee for Standardization (CEN) cooperates with the ISO, and existing ISO standards can be adopted as ‘Harmonized Standards’ endorsed by the European Commission [9]. Furthermore, technical standards are used as a tool to define the generally acknowledged ‘state of the art’ in a certain field. To define ‘state of the art’, other documents such as consensus documents by professional societies are also taken into account during conformity assessment [8].

In the EU, conformity assessment of medical devices is performed by Notified Bodies. These are independent, third-party organizations appointed by Member States. Notified Bodies can grant the CE (European Conformity) mark, which allows marketing a product within the European Economic Area.

Standards and prosthetic heart valve approval in the USA

In the USA, the medical device market is centrally regulated by the Food and Drug Administration (FDA) through review and approval of applications for new devices [10]. During the process of approving new SHVs, the use of 'Consensus Standards' by the FDA is voluntary [11]. The ISO 5840 standards are recognized by the FDA and could serve as a guidance for manufacturers when submitting their applications for approval to the FDA [12].

DESIGN AND CHARACTERISTICS OF SURGICAL PROSTHETIC HEART VALVES

Design and materials

The design and component materials of an SHV should: cause minimal harm to endothelial tissue and blood cells; pose minimal chances for platelet and thrombus deposition; be resistant to structural wear and tear, mechanical failure and degradation; be biochemically inert in a physiological milieu; and be suitable for sterilization [13]. Mechanical valve leaflets and their supporting frames are composed mostly of pyrolytic carbon. Bioprosthetic valves, however, have more variation in their component materials: both native valves from animals and valves manufactured from animal pericardium are used (Table 1). Preparation techniques used for biological tissues aim to reduce immunogenicity [14], cross-link collagen and prevent calcification to delay valve degeneration [15]. Polymeric heart valves might offer a relatively inexpensive alternative to biological tissues, but their safety and effectiveness in the clinical setting are yet to be proved [16, 17]. Differences in long-term outcomes with various prostheses have been identified, which may relate to specific design features [18, 19].

Materials used for the supporting frames of bioprosthetic valves vary in composition (Table 1), which is potentially relevant for subsequent valve-in-valve transcatheter procedures, when bioprosthetic valve frame fracture could enable insertion of a larger transcatheter prosthesis [20]. Importantly, some bioprosthetic SHVs are equipped with an expandable band, which is intended to facilitate controlled expansion of the valve support structure when subjected to radial force. Many SHVs are equipped with radiopaque markers or have an intrinsically radiopaque support structure. This is useful when a valve-in-valve procedure is planned, as it aids in positioning of the transcatheter

valve and provides information about the proximity of the SHV strut to the coronary ostia. Currently, there is a considerable variety in radiopaque marking of bioprosthetic SHVs [21].

The ‘ISO 5840:2015’ standard contains recommendations on reporting the magnetic resonance imaging (MRI) safety designation of the prosthesis in the accompanying IFU. However, it does not require detailed reporting of the materials used for SHV manufacturing.

Table 1: Component materials in stented surgical prosthetic heart valves

	Stented bioprostheses	Mechanoprostheses
Leaflets	Native porcine valve and bovine pericardium	Pyrolytic carbon
Supporting frame/stent	Titanium, Elgiloy ^a and Delrin ^b	Pyrolytic carbon and titanium
Sewing ring	Silicone rubber and Dacron ^c	Dacron and Teflon ^d

^aCobalt–chromium–nickel–molybdenum alloy.

^bAcetal homopolymer.

^cPolyethylene terephthalate.

^dPolytetrafluoroethylene.

Physical dimensions

Physical dimensions of SHVs are closely related to their performance, safety and ease of use, and can influence the choice of prosthesis and the implantation technique. Dimensions are defined in ‘ISO 5840:2015’ and should be provided in the IFU [2]. However, reporting of these measurements in terms of dimensional definitions is not consistent, and the relationship between SHV physical dimensions and the ‘labelled valve size’ is unclear, creating confusion in the surgical community [3].

Axial dimensions

The fundamental axial dimensions of an SHV are the overall ‘profile height’ and ‘outflow tract profile height’, the latter being the maximum distance that the heart valve substitute extends axially into the outflow tract, measured from the valve structure’s intended annular attachment, according to ‘ISO 5840:2015’ (Figs 1 and 2) [2].

Horizontal dimensions

The ISO-defined horizontal dimensions of an SHV are the ‘internal orifice diameter’ and the ‘external sewing ring diameter’ (Figs 1 and 2). According to ‘ISO 5840:2015’, ‘internal orifice diameter’ is ‘the minimum diameter within a surgical heart valve substitute through which blood flows’ [2], making it one of the most relevant physical dimensions characterizing SHV performance.

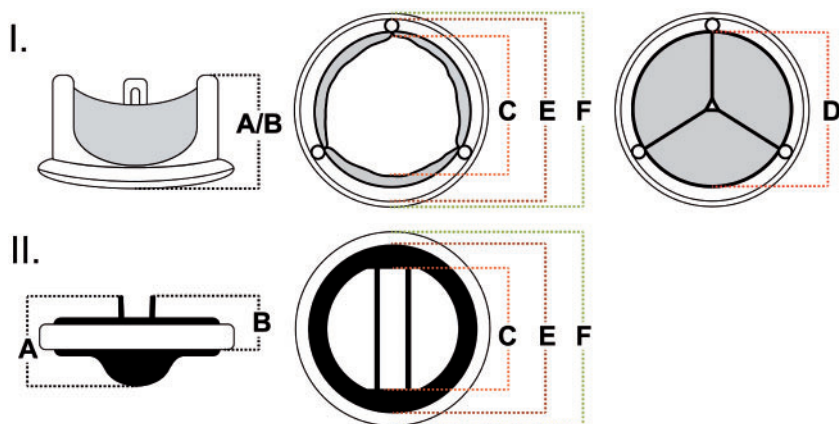


Figure 1: Physical dimensions of surgical prosthetic heart valves, aortic position. (I) Typical tissue valve. (II) Typical bileaflet mechanoprosthesis. (A) Overall profile height; (B) outflow tract profile height; (C) internal orifice diameter; (D) internal diameter/internal stent diameter; (E) external stent/housing diameter; (F) external sewing ring diameter.

A widely used parameter when selecting a transcatheter prosthesis during a valve-in-valve procedure is the ‘true internal diameter’ (true ID) of the surgical bioprosthesis. This ‘true ID’ is measured by passing a Hegar dilator through the bioprosthetic orifice and therefore closely corresponds to the ISO-defined ‘internal orifice diameter’ [22]. Of note, manufacturers often report ‘internal diameter (ID)’ or ‘stent internal diameter (stent ID)’, which is the ID of the stent (label F in Figs 1 and 2). Importantly, this ‘stent ID’ does not account for the space occupied by the prosthetic leaflets in the orifice of a bioprosthetic valve (e.g. the difference between labels C and D in Figs 1 and 2).

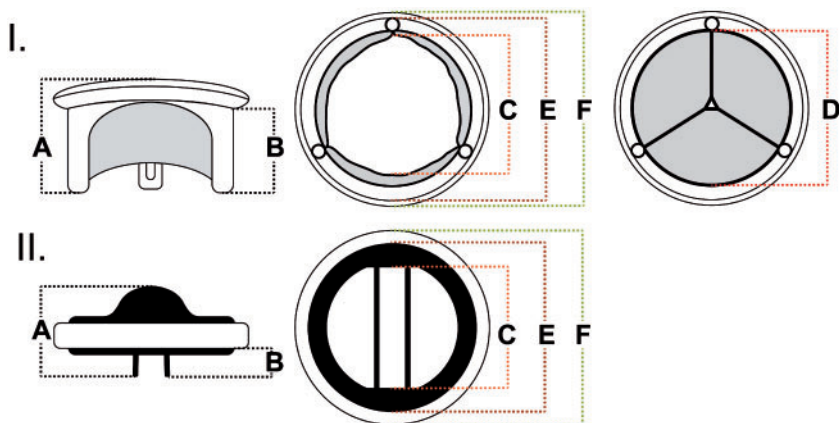


Figure 2: Physical dimensions of surgical prosthetic heart valves, mitral position. (I) Typical tissue valve. (II) Typical bileaflet mechanoprosthesis. (A) Overall profile height; (B) Outflow tract profile height; (C) Internal orifice diameter; (D) Internal diameter/internal stent diameter; (E) external stent/housing diameter; (F) external sewing ring diameter.

Labelled valve size

Importantly, rather than being a strictly valve-related physical parameter, labelled 'valve size', according to 'ISO 5840:2015', is an indicator of the 'tissue annulus diameter of the patient into whom the surgical heart valve substitute is intended to be implanted' [2]. In other words, the labelled 'valve size' is not based on any single valve-related physical dimension, according to ISO definitions. This is a source of profound confusion in the cardiac surgical community [23].

Another problem is the common erroneous perception of a direct relationship between labelled valve size and haemodynamic performance [24].

Sewing ring

The sewing ring enables an SHV to be secured to the patient's tissue annulus. Sewing rings must be biocompatible and capable of sustaining expected in vivo loading.

Intra- and supra-annular positioning

The sewing ring determines the position of the SHV in relation to the patient's tissue annulus. According to 'ISO 5840:2015', a supra-annular sewing ring is a 'sewing ring designed to secure the valve "wholly above" the patient's tissue annulus', while an intra-annular sewing ring is a 'sewing ring designed to secure the surgical heart valve "wholly or mostly within" the patient's tissue annulus' [2]. Although there is some controversy surrounding exact definitions of intra-annular and supra-annular positions of the valve (Fig. 3), this information is sometimes displayed on product labels or used in marketing materials. Despite the design of an SHV, surgeons can implant most valves in either intra- or supra-annular positions using specific suturing techniques.

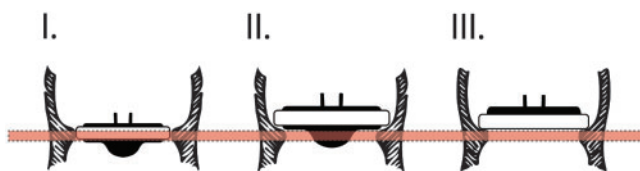


Figure 3: Possible positions of a prosthetic heart valve in relation to the aortic annulus (red line). (I) The valve is positioned in the annulus—'intra-annular'. (II) The valve 'partially' extends into the level of the annulus—unclear situation. (III) The valve is 'wholly' above the annulus—'supra-annular'.

Sewing ring shape and suture markers

Sewing rings can be designed as completely flat structures or can have a curvilinear form that aims to provide alignment with the patient's non-planar anatomical annulus. Suture markers on the sewing ring are intended to facilitate implantation and correct orientation of the SHV. Currently, there is a considerable variety in the number and position of suture markers.

Implantation aids

Several implantation aids are provided with an SHV, including handles, rotators or systems to prevent inadvertent suture looping and/or facilitating knot-tying. According to 'ISO 5840:2015', the use of these implantation aids should be described in the IFU.

Intraoperative sizing

The goal of intraoperative sizing is to determine the labelled size of the SHV that can be safely implanted into the patient. This information, together with easy access to information about the relevant properties (e.g. haemodynamic performance, durability, thrombogenicity, etc.) of the particular SHV that would fit, makes optimal intraoperative valve choice possible.

Sizers

Manufacturers provide a set of valve-related sizers for each SHV model. Sizers are numbered according to the labelled sizes of the corresponding SHVs. Typically, sizers have 2 ends: a cylindrical end (barrel) to measure the annulus and guide SHV selection based on the labelled valve size, and a replica mimicking the configuration of the prosthesis (Fig. 4). Sizing with a replica after suture placement is particularly useful because both the patient's anatomy and the surgeon's suturing technique influence the SHV's final position and affect ultimate sizing [25, 26].

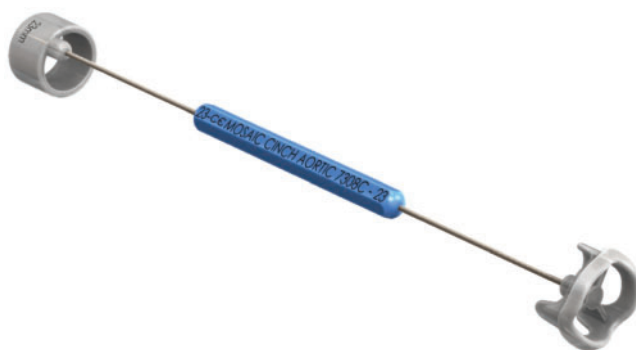


Figure 4: Typical 2-ended valve sizer.

Sizers and the labelled valve size

Given that the numbering of sizers follows the labelled valve size, the sizer barrel should determine the diameter of the patient's tissue annulus. Indeed, size measured using the sizer barrel is not intended to provide direct information regarding the physical dimensions of the corresponding SHV [27]. However, numerous publications have demonstrated significant differences between labelled valve size and the actual dimensions of the valve-related sizer barrel, causing confusion in the surgical community [3, 28–30].

During labelling, the manufacturer determines which valve is recommended for a measured tissue annulus, which is reflected in the labelled valve size. However, clinical sizing can vary depending on the extent of annular debridement or surgeon aggressiveness when entering the sizer to the annulus. These variabilities make it challenging for manufacturers to determine which valve to recommend for implanting into a specific tissue annulus diameter (i.e. to determine the labelled valve size). Although the actual tissue annulus diameter is easily determined using a Hegar dilator or a similar circular sizing tool, these inconsistencies and challenges mean that optimal sizing is currently best performed using the set of sizers provided by the manufacturer with the valve selected for implantation.

HAEMODYNAMIC PERFORMANCE OF SURGICAL PROSTHETIC HEART VALVES

In vitro hydrodynamic performance testing

In vitro hydrodynamic testing is intended to assess the ability of an SHV to enable forward flow and prevent reverse flow and is required for device approval. Although steady flow testers allow manufacturers to measure forward flow and reverse flow (leakage) across the SHV under controlled conditions, the testing environment is very different from physiological conditions. 'ISO 5840:2015' provides guidance for *in vitro* hydrodynamic performance testing and defines flow hydrodynamic acceptance criteria for pulsatile testing based on valve size and implant position [2].

Pulsatile testing

Pulsatile testing enables SHV performance to be assessed under physiological flow and pressure conditions that are similar to those in which it is intended to function. Pulsatile testing enables measurement of flow and pressure drop (pressure gradient), calculation of the *in vitro* effective orifice area (EOA) and total regurgitant volume and fraction. *In vitro* EOA is derived from the mean pressure difference and forward flow measured across the open valve, while regurgitant fraction is the volume of fluid that flows retrograde through the test valve as a percentage of forward flow. These parameters are defined in 'ISO 5840:2015' [2]. *In vitro* EOA is calculated using the following equation:

$$\text{in vitro EOA} = \frac{q_{V \text{ RMS}}}{51.6 \times \sqrt{\frac{\Delta p}{\rho}}},$$

where EOA is measured in cm^2 , $q_{V \text{ RMS}}$ is the root mean square of forward flow (ml/s), Δp is the mean pressure difference (mmHg) and ρ is the test fluid density (g/cm^3).

Pulse duplicator

Pulsatile testing is performed in a test apparatus commonly known as a 'pulse duplicator'. 'ISO 5840:2015' provides specifications for pulsatile testing to reduce variability in testing and reporting methods between testing centres. These include specifications for the test apparatus (pulse duplicator), measurement equipment accuracy and test procedures [2]. However, pulse duplicators are not perfect substitutes for human anatomy and the physiological conditions in which the SHV is intended to be used. Currently used pulse duplicators vary between test centres and range from simple to sophisticated systems with different degrees of mimicking of the human anatomy. These subtle differences in test environments have a profound effect on the results of pulsatile testing. An inter-laboratory round-robin study of SHV *in vitro* pulsatile testing demonstrated considerable differences in results of hydrodynamic performance measures in different test centres evaluating the same reference valves, using a common ISO-derived protocol. In this study, measures of both forward (EOA) and backward flow (regurgitant fraction) were found to be subject to this effect [31]. Results of EOA and regurgitant fraction measurements in the participating 6 centres are displayed on Fig. 5, for a 25-mm bileaflet mechanical (St. Jude Medical, St. Paul, MN, USA) and for a 25-mm tissue reference valve (Edwards Lifesciences, Irvine, CA, USA). This variation in *in vitro* haemodynamic performance measurements mandates improved standardization of investigational protocols to increase the reproducibility of test results across different centres.

In vivo haemodynamic performance testing

The haemodynamic performance of most SHVs is inferior to that of native healthy valves. Hence, the majority of normally functioning SHVs cause some degree of obstruction to blood flow, depending on the model and size of the SHV as well as the patient's cardiac function. Furthermore, several models of SHVs harbour some degree of 'physiological' transprosthetic regurgitation, which may be considered as part of washing the valve. Doppler echocardiography is the primary imaging modality used to assess SHV haemodynamic function *in vivo* [32, 33], although cardiac catheterization may also be used.

Assessment of forward flow haemodynamics

Transprosthetic velocity and pressure gradients

Transprosthetic gradients (ΔP) are measured using Doppler echocardiography and the simplified Bernoulli formula:

$$\Delta P = 4 \times V_{\text{PrV}}^2$$

where V_{PrV} is the maximal transprosthetic velocity obtained using continuous-wave Doppler echocardiography.

The peak velocity across the prosthesis is to some extent related to valve size, with smaller SHVs having higher velocities. However, in the case of normally functioning aortic SHVs, V_{PrV} is low, and in high cardiac output or when the left ventricular outflow tract (LVOT) is narrow, the velocity in the LVOT may not be negligible. In these cases, the pressure gradient is more accurately estimated by integrating the velocity proximal to the prosthesis in the following Bernoulli equation:

$$\Delta P = 4 \times (V_{PrV}^2 - V_{LVOT}^2)$$

Overestimation of the gradients may occur in the presence of significant pressure recovery in any SHV, or in cases of localized high velocities in mechanical SHVs, as discussed later in this section.

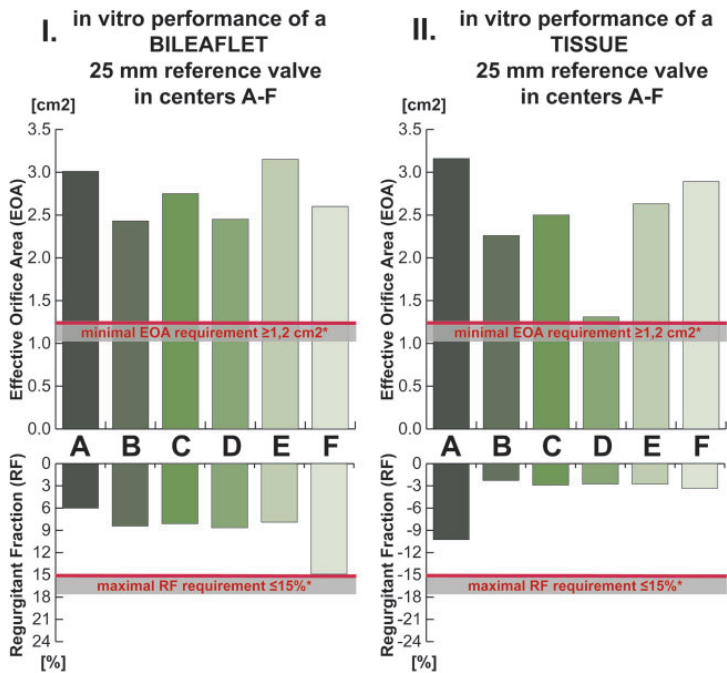


Figure 5: In vitro round-robin testing results. (I) EOA and regurgitant fraction results of a 25-mm bileaflet mechanical reference valve (St. Jude Medical, St. Paul, MN, USA), determined by in vitro pulsatile testing in 6 different centres [(A–F) coded from light to dark shades of green]. (II) EOA and regurgitant fraction results of a 25-mm tissue reference valve (Edwards Lifesciences, Irvine, CA, USA), determined by in vitro pulsatile testing in 6 different centres [(A–F) coded from light to dark shades of green]. *Minimum performance requirements, as defined in the International Organization for Standardization 5840:2005 standard. Data from J Heart Valve Dis 2017;26:72–80, by Retta et al. Reproduced by permission. EOA: effective orifice area; RF: regurgitant fraction.

Valve geometric and effective orifice areas

The geometric orifice area (GOA) of the SHV is the area between the free edges of the open leaflets of a bioprosthetic valve, or the area created by the open spaces between the valve ring and leaflet(s) for a mechanical SHV. The GOA represents the area theoretically available for flow. Importantly, GOA should not be mistaken for the internal orifice area, which is the area calculated from the ID of the SHV stent/housing. Typically, the GOA is smaller than the internal orifice area, because internal orifice area does not account for the space occupied by the leaflets in the SHV orifice (Fig. 6).

Similarly, the *in vivo* EOA is smaller than the GOA, as it corresponds to the smallest area of the flow jet passing through the prosthesis as it exits the valve (Fig. 6). The flow contraction coefficient (i.e. the ratio EOA/GOA) varies from 0.70 to 0.90. From a pathophysiological perspective, transvalvular pressure gradients are more closely related to EOA than to GOA.

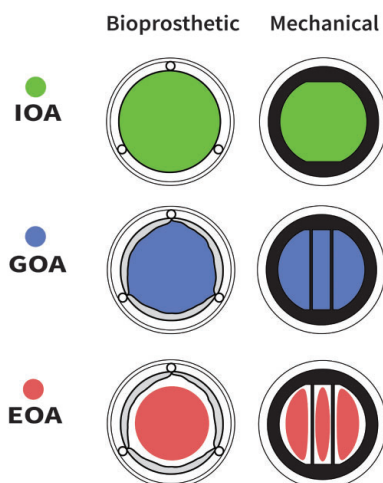


Figure 6: IOA, GOA and EOA in bioprosthetic and mechanical valves. EOA: effective orifice area; GOA: geometric orifice area; IOA: internal orifice area.

The *in vivo* EOA is less flow-dependent than the transprosthetic velocity or gradient, and is thus often a better metric of intrinsic valve haemodynamic performance. For both aortic and mitral SHVs, the EOA is calculated using the continuity equation method incorporating the stroke volume measured in the LVOT using pulsed-wave Doppler echocardiography:

$$\text{in vivo EOA} = \frac{\text{CSA}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}}}{\text{VTI}_{\text{PV}}},$$

where CSA_{LVOT} is the cross-sectional area of the LVOT, calculated from the ID of the LVOT, measured just proximal to the apical border of the SHV stent/sewing ring; VTI_{LVOT} is the velocity–time integral (VTI) of blood flow in the LVOT measured using pulsed-wave Doppler echocardiography in the LVOT just proximal to the apical border of the SHV stent/sewing ring; and VTI_{PrV} is the VTI through the SHV obtained using continuous-wave Doppler echocardiography. It should be noted that each of these parameters (CSA_{LVOT} , VTI_{LVOT} and VTI_{PrV}) may be subject to certain measurement errors [32, 34]. In particular, the CSA_{LVOT} might be underestimated by transthoracic echocardiography because the cross-section of the LVOT is often elliptic and transthoracic echocardiography measures the smaller diameter of the ellipse. Some studies therefore suggested to use 3D imaging modalities (e.g. 3D transoesophageal echocardiography or multidetector computed tomography) to measure CSA_{LVOT} for EOA calculations [35]. However, this approach did not demonstrate any incremental prognostic value compared to standard EOA calculations based on transthoracic echocardiography measurements [36, 37].

The normal reference values of EOA depend on the SHV model and size. Therefore, to confirm that an SHV has a normal function, the *in vivo*-obtained EOA should be compared with the normal *in vivo* EOA value reported for the same model and size of SHV [32]. Normal SHV function is defined as an *in vivo* EOA that is within ± 1 standard deviation (SD) of normal value for the corresponding model and size of SHV [32, 38]. A difference of more than 2 SDs between the normal reference value and the *in vivo* EOA measured in the patient suggests prosthetic valve stenosis [32].

Doppler velocity index (or dimensionless ratio)

For aortic SHVs, the Doppler velocity index (DVI) is calculated as the ratio of the VTI in the LVOT to the transprosthetic flow VTI:

$$DVI = \frac{VTI_{LVOT}}{VTI_{PrV}}$$

For mitral SHVs, the DVI is calculated as the ratio of the transprosthetic flow VTI to the LVOT VTI:

$$DVI = \frac{VTI_{PrV}}{VTI_{LVOT}}$$

The DVI is ≥ 0.30 for a normally functioning aortic SHV and < 2.2 for a normally functioning mitral SHV. The DVI has the advantage over the EOA of being less subject to measurement variability and less dependent on SHV size.

Pressure recovery and localized high gradient

In patients with an aortic SHV and small aorta relative to the valve EOA, a substantial proportion of the pressure generated by the left ventricle might initially be lost between the LVOT and the vena contracta of the SHV flow, but may be recovered downstream to the vena contracta (Fig. 7). This phenomenon is called pressure recovery and may occur with both native and prosthetic valves.

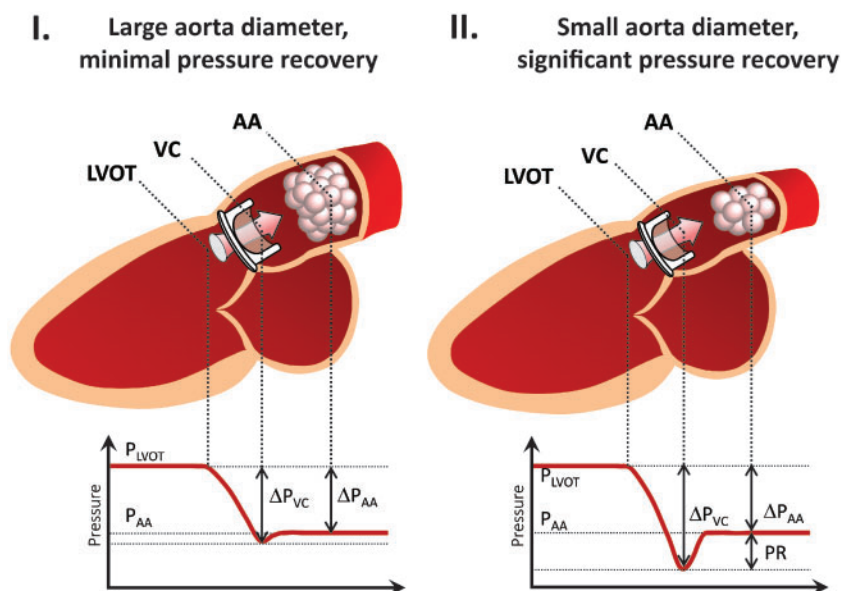


Figure 7: Pressure recovery. (I) Large aorta diameter, minimal pressure recovery. Pressure gradients between the LVOT and VC, and between the LVOT and AA are similar. (II) Small aorta diameter, significant pressure recovery. Pressure gradients between the LVOT and VC, and between the LVOT and AA are different. AA: ascending aorta; LVOT: left ventricular outflow tract; P_{AA} : ascending aortic pressure; P_{LVOT} : left ventricular outflow tract pressure; PR: pressure recovery; ΔP_{AA} : pressure gradient between the LVOT and the ascending aorta; ΔP_{VC} : pressure gradient between the LVOT and the vena contracta; VC: vena contracta.

Given that Doppler echocardiography measures the highest V_{PV} and thus transprosthetic gradient at the level of the vena contracta, and that cardiac catheterization measures the aortic pressure and gradient downstream of the vena contracta (and thus downstream of the pressure recovery phenomenon), Doppler echocardiography may yield higher values of gradients and smaller values of EOA compared with catheterization (Fig. 7). Failure to take 'pressure recovery' into account may lead to overestimation of the transprosthetic gradient and underestimation of the EOA using Doppler echocardiography, especially in patients with an ascending aortic diameter <30 mm. It is possible to correct the EOA for the extent of pressure recovery by calculating the energy

loss coefficient (ELC). The ELC adjusts the Doppler EOA for the size of the ascending aorta in order to account for the extent of pressure recovery:

$$ELC = \frac{EOA \times AA}{AA - EOA},$$

where AA is the cross-sectional area of the aorta measured about 1 cm downstream of the sinotubular junction [39]. The ELC, in fact, provides an estimate of the EOA measured by catheterization.

In bileaflet mechanical valves, a localized high velocity may be recorded using continuous-wave Doppler echocardiography through the central orifice of the valve, which is often smaller than the 2 lateral orifices. This may yield an overestimation of the transvalvular gradient (by an average of 5–15% compared with cardiac catheterization) and underestimation of the EOA [40].

Assessment of physiological prosthetic heart valve regurgitation

All mechanical SHVs have a regurgitant volume (2–10 ml) that includes a closing volume (necessary for closing the occluders) and/or a washing/leakage volume (through the components), which contribute to the prevention of blood stasis and thrombus formation. Normal leakage backflow jets are narrow at their origin, often symmetrical, and have a homogeneous colour without significant aliasing (Fig. 8). Of note, trace (<1 ml) central leakage may also occur in normally functioning bioprosthetic valves. It is important to separate physiological from pathological prosthesis regurgitation.

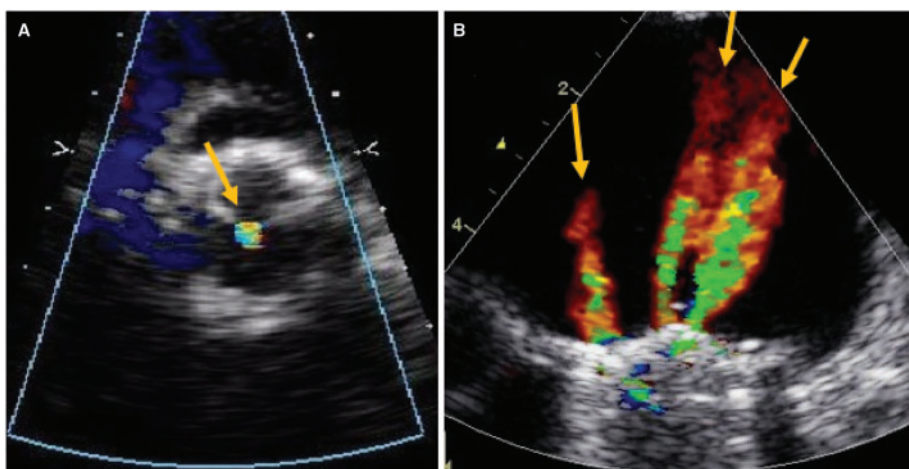


Figure 8: Normal regurgitant jet in bioprosthetic and mechanical valves. Normal ‘physiological regurgitant’ jets (orange arrows) in a stented bioprosthetic aortic valve (A) and in a bileaflet mechanical mitral valve (B).

The approach for detecting and grading SHV regurgitation is similar to that for native valves and involves colour Doppler imaging in multiple views and planes as well as measurement of several Doppler echocardiographical parameters [32, 41]. There are limited data on the application and validation of semiquantitative and quantitative parameters such as width of the regurgitant jet or of the vena contracta, the effective regurgitant orifice area, and the regurgitant volume and fraction in the context of prosthetic valves [42]. Given that all parameters of SHV regurgitation have important limitations and may be subject to measurement errors, a comprehensive, multiparametric integrative approach is recommended [32, 41]. Cardiac MRI using phase-contrast sequences may be helpful to quantitate SHV regurgitation [43].

Prosthesis–patient mismatch

Prosthesis–patient mismatch (PPM) after surgical aortic valve replacement (SAVR) occurs when a patient receives an SHV that has insufficient EOA relative to cardiac output requirements.

After indexing EOA to the body surface area (BSA), PPM after SAVR is considered to be ‘moderate’ if the indexed EOA is $0.66\text{--}0.85\text{ cm}^2/\text{m}^2$, and ‘severe’ if indexed EOA is $\leq 0.65\text{ cm}^2/\text{m}^2$ [32]. In obese patients [body mass index (BMI) $\geq 30\text{ kg}/\text{m}^2$], it is recommended to use lower cut-off values of indexed EOA to define ‘moderate’ and ‘severe’ PPM ($0.56\text{--}0.70$ and $\leq 0.55\text{ cm}^2/\text{m}^2$, respectively) [32, 44]. In a meta-analysis of 34 studies on PPM after SAVR, the rates of moderate and severe PPM were 34.2% and 9.8%, respectively [1]. Predictors for PPM are female sex, larger BSA, larger BMI, diabetes, hypertension and renal failure [45]. Mechanical valves generally have a slightly larger EOA than bioprosthetic valves with the same labelled size, and they are associated with lower PPM rates [46].

The presence of PPM results in higher postoperative residual transvalvular gradients, which have been associated with less left ventricular mass regression, worse functional class and quality of life, higher risk of hospitalization due to heart failure and higher short- and long-term mortality rates after SAVR [1, 47]. Furthermore, studies have suggested that structural valve degeneration is accelerated if PPM is present [48]. In summary, PPM after SAVR impacts prognosis at various follow-up stages, and prevention of PPM should be a priority, especially in young, active patients and those with left ventricular systolic dysfunction.

A tool for predicting PPM after SAVR is available: multiplying the patient’s BSA by 0.85 calculates the minimum EOA value required to prevent PPM, thus allowing surgeons to select an appropriate SHV to obtain the desired EOA [49]. In cases where the aortic annulus is too small to fit an acceptable valve, aortic annulus or root enlargement may be considered to facilitate implantation of a larger prosthesis. Reliable data on EOA are critical to the success of this strategy.

Valve manufacturers have provided valve-specific charts that can be used intraoperatively to predict PPM. Ideally, comparing these charts would allow the surgeon to select the optimal valve for the patient to avoid PPM. However, accurate prediction of severe PPM using these charts has been reported to be as low as 59% [50]. Moreover, these charts have been severely criticized for lack of uniformity: different cut-offs were used to define PPM; in some instances, in vitro data were used to determine EOA and in vivo echocardiographical studies were occasionally selected to include those with the largest EOA values. Furthermore, even normal reference values of SHV haemodynamic performance reported in the literature are derived mostly from single-centre studies without core laboratory evaluation of SHV function [32]. These issues render effective prevention of PPM challenging.

THROMBOGENICITY OF PROSTHETIC HEART VALVES

The risk of bleeding and thromboembolic events after SHV implantation depends on the type and anatomical position of the prosthesis, anticoagulation strategy and patient-related risk factors, such as haematological disorders, arrhythmias and cardiac chamber dilatation or function. 'ISO 5840:2015' defines objective performance criteria for bleeding and thromboembolic events for the clinical evaluation of SHVs [2, 5, 6].

North American and European clinical practice guidelines provide recommendations on postprocedural anticoagulation after mechanical and bioprosthetic valve replacement [51, 52]. In contrast to bioprosthetic SHVs, mechanical valves require lifelong anticoagulation with vitamin-K antagonists. Treatment with vitamin-K antagonists carries certain risks and demands rigorous patient compliance. To date, no viable alternative to vitamin-K antagonists in this setting has been identified [53, 54], but numerous studies have been performed to investigate the safety of a lower international normalized ratio (INR) target in patients with mechanical valves in the aortic position [46, 55]. In the EU, 2 mechanical SHVs have received regulatory approval for reduced anticoagulation, if used in the aortic position in patients with low risk for thromboembolic events [54, 56]; this information is often displayed on the device packaging and used in marketing materials. However, there are no comparisons among currently used valves, so it cannot be concluded whether a lower INR is safe in only those 2 valves or also in others [46]. Indeed, clinical practice guidelines categorize mechanical SHVs on the basis of their thrombogenicity, with most contemporary mechanical valves falling into the 'low thrombogenicity' category [51, 52], and several studies with the use of mechanical valves not specifically approved for lower INR ranges have also shown improved safety and similar efficacy with lower INR ranges [46, 55].

In bioprosthetic valves, the issue of subclinical leaflet thrombosis has been raised recently [57, 58] and clearly deserves further study. It remains unclear whether bioprosthetic valve thrombosis occurs more frequently with some valves compared with others or why the rate is lower in SHVs than in transcatheter valves [58]. Comparative studies are needed to differentiate thrombotic risk among various valves. These should be carefully evaluated before statements are made on anticoagulation for bioprostheses, which would have possible ramifications for labelling.

DISCUSSION

Sizing and labelling of SHVs are complex issues that span the domains of clinical practice, engineering and product manufacturing, and have important regulatory aspects. Currently, many unanswered questions surround intraoperative sizing and labelling of SHVs, making optimal intraoperative SHV selection challenging. These include:

1. non-uniform or incomplete reporting of SHV materials and physical dimensions in the IFU;
2. unclear definition of labelled valve size and inconsistencies between size dimensions and labelled valve size;
3. non-uniform marking of SHV support structures;
4. lack of robust information on in vivo haemodynamic performance in the IFU, and no information available regarding haemodynamic performance on package labels;
5. lack of uniform tools backed by solid evidence to prevent PPM; and
6. lack of good-quality, robust clinical data on SHV thrombogenicity.

This situation has persisted for decades and has received many calls for action, but no uniform solution has been achieved to date.

Determining the right amount of information for intraoperative decision-making requires finding a delicate balance. Although currently available parameters on the package labels provide incomplete information regarding the most important characteristics of the SHV, the inclusion of redundant or irrelevant information would similarly create confusion in the surgical community.

Complex issues are best prioritized and solved through concentrated efforts from all critical stakeholders [59]. The EACTS–STS–AATS Valve Labelling article Project has been initiated with this intention. The medical community requires clarity and should work together with valve manufacturers, regulatory bodies and the ISO group to achieve an optimal solution. This article has summarized the most important characteristics of SHVs and the background of SHV labelling and is intended to pave the way for an EACTS–STS–

AATS Expert Consensus Document that will include recommendations on SHV sizing and labelling.

CONCLUSION

This joint EACTS–STS–AATS Labelling Task Force has identified several issues related to SHV sizing and labelling. These issues should be addressed to ensure that surgeons are provided with sufficient, appropriate and standardized information required for optimal SHV choice.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the help of Rianne Kalkman (EACTS Office) in coordinating the Task Force activities.

FUNDING

This work was supported by the European Association for Cardio- Thoracic Surgery (EACTS). We acknowledge the financial support from the Netherlands Cardio Vascular Research Initiative: the Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences.

Conflict of interest

Vinayak Bapat served as a consultant for Edwards Lifesciences, Medtronic and 4Tech Inc.; Filip P.A. Casselman served as a consultant for Edwards Lifesciences and Medtronic; Edward P. Chen served as a consultant for CryoLife and as a proctor for Medtronic; Philippe Pibarot has received research grant support from Edwards Lifesciences and Medtronic for echocardiography core laboratory analyses in transcatheter heart valves; Giordano Tasca reports speaker fees from St. Jude Medical; Marco Stijnen is an employee of LifeTec Group; Ruggero De Paulis served as consultant for Edwards Lifesciences and Medtronic. All other authors declared no conflict of interest.

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APPENDIX: TASK FORCE MEMBERS

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3

Essential information on surgical heart valve characteristics for optimal valve prosthesis selection: Expert consensus document from the EACTS-STS-AATS Valve Labelling Task Force.

Durko AP, Pibarot P, Atluri P, Bapat V, Cameron DE, Casselman FPA, Chen EP, Dahle G, Ebels T, Elefteriades JA, Lancellotti PA, Prager RL, Rosenhek R, Speir A, Stijnen M, Tasca G, Walther T, De Paulis R; EACTS–STS–AATS Valve Labeling Task Force.

Eur J Cardiothorac Surg. 2021 Jan 4;59(1):54-64.

J Thorac Cardiovasc Surg. 2021 Feb;161(2):545-558.

Ann Thorac Surg. 2021 Jan;111(1):314-326.

ABSTRACT

Comprehensive information on the characteristics of surgical heart valves (SHVs) is essential for optimal valve selection. Such information is also important in assessing SHV function after valve replacement. Despite the existing regulatory framework for SHV sizing and labelling, this information is challenging to obtain in a uniform manner for various SHVs. To ensure that clinicians are adequately informed, the European Association for Cardio-Thoracic Surgery (EACTS), The Society of Thoracic Surgeons (STS) and American Association for Thoracic Surgery (AATS) set up a Task Force comprised of cardiac surgeons, cardiologists, engineers, regulatory bodies, representatives of the International Organization for Standardization and major valve manufacturers. Previously, the EACTS–STS–AATS Valve Labelling Task Force identified the most important problems around SHV sizing and labelling. This Expert Consensus Document formulates recommendations for providing SHV physical dimensions, intended implant position and haemodynamic performance in a transparent, uniform manner. Furthermore, the Task Force advocates for the introduction and use of a standardized chart to assess the probability of prosthesis–patient mismatch and calls valve manufacturers to provide essential information required for SHV choice on standardized Valve Charts, uniformly for all SHV models.

Keywords: Labeling • ISO • Prosthesis-patient mismatch; PPM • Prosthetic heart valve • PHV • Regulation

INTRODUCTION

Comprehensive and reliable information on the characteristics of surgical heart valves (SHVs) is essential for optimal valve selection. This information is also important in assessing SHV function after valve replacement. Despite the existing regulatory framework [1, 2] and the efforts by the International Organization for Standardization (ISO) [3], the amount and quality of currently available information on SHV characteristics provided by manufacturers is not optimal and often not uniform, rendering intraoperative SHV selection challenging.

To ensure that clinicians are provided with the necessary information, the European Association for Cardio-Thoracic Surgery (EACTS), The Society of Thoracic Surgeons (STS) and American Association for Thoracic Surgery (AATS) established the EACTS–STS–AATS Valve Labelling Task Force, composed of cardiac surgeons, cardiologists, engineers, regulatory professionals and representatives of major valve manufacturing companies.

The first document of the Task Force addressed the following issues around SHV sizing and labelling: (i) non-uniform or incomplete reporting of SHV materials and physical dimensions; (ii) non-uniform marking of SHV support structures (e.g. sewing rings); (iii) unclear definition of labelled valve size and inconsistencies between size dimensions and labelled valve size; (iv) lack of robust information to reliably predict SHV haemodynamic performance; (v) lack of uniform tools to predict and prevent prosthesis–patient mismatch (PPM); and (vi) lack of good-quality, robust clinical data on SHV thrombogenicity [4].

This second Expert Consensus Document of the Task Force provides recommendations on the information that should be provided together with an SHV, to ensure consistent comparability of different SHVs and to facilitate optimal intraoperative SHV selection.

PHYSICAL DIMENSIONS OF SURGICAL HEART VALVES

Defining uniform, standardized physical dimensions is necessary to objectively compare various SHVs. Current ISO standards for cardiac valves provide definitions only for ‘internal orifice diameter’, ‘profile height’ and ‘outflow tract profile height’ [3], and manufacturers often use non-uniform terminology to describe the physical dimensions of their SHVs. Furthermore, it is not always easy to find detailed information on the physical dimensions of an SHV [5].

The Task Force recommends that manufacturers provide the physical dimensions of SHVs using the terminology listed in Tables 1 and 2. Physical dimensions should be provided in millimetres, with preferably at least 1 decimal place precision. In addition, a

pictogram of the SHV should be presented, clearly indicating the corresponding physical dimensions. Example tables and pictograms for standardized displaying of the physical dimensions of stented biological and mechanical SHVs in the aortic and mitral position are provided in Figs 1 and 2.

Table 1: Physical dimensions of mechanical SHVs

Physical dimension	Definition	Label on Fig. 1	Reference
Overall profile height	Maximal axial dimension of an SHV in the open or closed position, whichever is greater	A	[3]
Outflow profile height	Maximum distance that the SHV extends axially into the outflow tract in the open or closed position, whichever is greater, measured from the valve structure intended to mate with the top (atrial or aortic/pulmonic side) of the patient's annulus	B	[3]
Minimum internal diameter ^a	The smallest diameter within an SHV orifice, which is theoretically available for flow	C	[3]
External housing diameter	The largest external diameter of the supporting frame (housing)	D	^b
External sewing ring diameter	The largest diameter of the uncompressed sewing ring	E	^b

^aDefined in the ISO 5840:2015 as 'internal orifice diameter'.

^bNot defined in the ISO 5840:2015.

ISO: International Organization for Standardization; SHV: surgical heart valve.

Table 2: Physical dimensions of bioprosthetic SHVs

Physical dimension	Definition	Label on Fig. 2	Reference
Overall profile height	Maximal axial dimension of an SHV in the open or closed position, whichever is greater	A	[3]
Outflow profile height	Maximum distance that the SHV extends axially into the outflow tract in the open or closed position, whichever is greater, measured from the valve structure intended to mate with the top (atrial or aortic/pulmonic side) of the patient's annulus	B	[3]
Minimum internal diameter ^a	The smallest diameter within an SHV orifice, which is theoretically available for flow	C	[3]
Internal stent diameter ^b	The smallest internal diameter of the supporting frame (stent), without fabric covering	D	^c
External stent diameter ^b	The largest external diameter of the stent, with fabric covering	E	^c
External sewing ring diameter ^b	The largest diameter of the uncompressed sewing ring	F	^c

^aDefined in the ISO 5840:2015 as 'internal orifice diameter'.

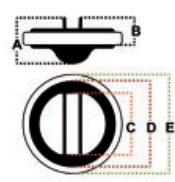
^bNot applicable for stentless bioprosthetic SHVs.

^cNot defined in the ISO 5840:2015.

ISO: International Organization for Standardization; SHV: surgical heart valve.

A Mechanical valves, aortic position

Labelled valve size	Physical dimensions				
	Overall profile height	Outflow profile height	Minimum internal diameter	External housing diameter	External sewing ring diameter
	(A)	(B)	(C)	(D)	(E)



B Mechanical valves, mitral position

Labelled valve size	Physical dimensions				
	Overall profile height	Outflow profile height	Minimum internal diameter	External housing diameter	External sewing ring diameter
	(A)	(B)	(C)	(D)	(E)

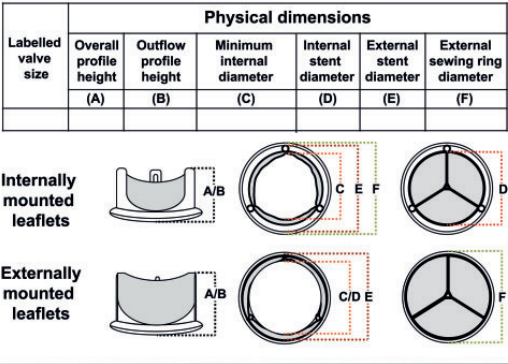


Figure 1: Standardized approach to present surgical heart valve physical dimensions: mechanical valves in the aortic (A) and mitral (B) position. The Task Force suggests that manufacturers use a complete, standardized set of physical dimensions and a standardized pictogram when describing their surgical heart valves.

Although defined in the ISO 5840 standard [3], ‘internal orifice diameter’ (the minimum diameter within an SHV through which blood flows) is difficult to determine for certain bioprosthetic SHVs [6] and some manufacturers have refrained from reporting it. In specific bioprosthetic SHV designs, the orifice available for flow is encircled by the prosthetic leaflets and it is smaller than the internal stent diameter (Fig. 2A). Furthermore, the uneven surface created by the leaflets makes exact measurements difficult. Considering the inconsistency in the use and reporting of ‘internal orifice diameter’, the Task Force advocates the use of ‘minimum internal diameter’ to define the smallest diameter theoretically available for flow within an SHV orifice.

The minimum internal diameter of a bioprosthesis, also termed as ‘true internal diameter (true ID)’, is important when a valve-in-valve procedure is planned [6]. Some have tried to determine this dimension of bioprosthetic SHVs by manually passing a circular sizing tool through the orifice of the SHV in 0.5mm increments [6]. However, these results might not be always accurate since the force used for passing the sizers through the orifice is not standardized. A standardized method for determining ‘minimum internal diameter’ during bench testing should be developed, and this dimension should be made available by the manufacturers, for all bioprosthetic SHV models and sizes, along with the other physical dimensions of the prosthesis. It is important that these determinations of this dimension are calculated in a similar standardized manner across all manufacturers with accepted protocols with reproducibility amongst laboratories.

A Bioprosthetic valves, aortic position



B Bioprosthetic valves, mitral position

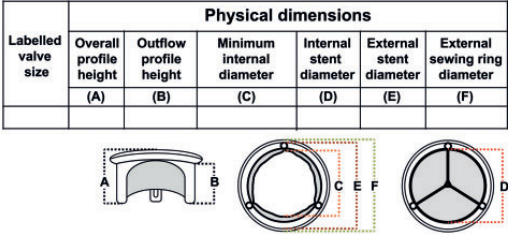


Figure 2: Standardized approach to present surgical heart valve physical dimensions: bioprosthetic valves in the aortic (A) and mitral (B) position.

POSITION OF SURGICAL HEART VALVES RELATIVE TO THE ANNULUS

The intended position of an SHV related to the patient tissue annulus has important implications on the surgical technique and more importantly on the haemodynamic performance of the SHV following implantation [7, 8]. Manufacturers should provide clear guidance regarding the intended implant position of an SHV. Currently, the terminology and definitions provided by the ISO 5840:2015 standard (Table 3) are used for this purpose [3]. However, this terminology has certain shortcomings since it is unclear how certain aortic SHVs, primarily seated above but with partial extension into the annulus, should be classified [4].

An easy way to overcome the ambiguity of the current ‘supra-annular’ and ‘intra-annular’ terminology is that manufacturers provide a standardized pictogram, clearly indicating the intended position(s) of the SHV after implantation, related to the tissue annulus of the patient. Example pictograms indicating the position of an aortic SHV related to the annulus are provided in Fig. 3 for aortic and in Fig. 4 for mitral mechanical and bioprosthetic valves.

Table 3: Current terminology used to describe annular attachment of SHVs, according to the ISO 5840:2015 standard

Term to describe sewing ring configuration	Definition provided in the ISO 5840:2015 standard [3]
Intra-annular sewing ring	Sewing ring designed to secure the SHV ‘wholly or mostly’ within the patient’s tissue annulus
Supra-annular sewing ring	Sewing ring designed to secure the valve ‘wholly’ above the patient’s tissue annulus

ISO: International Organization for Standardization; SHV: surgical heart valve.

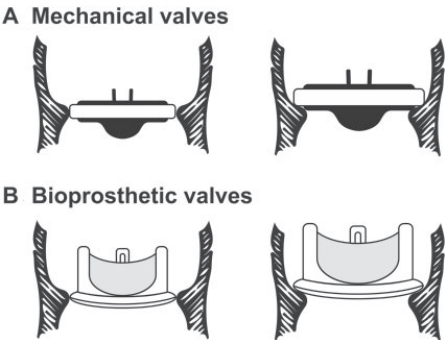


Figure 3: Example of standardized pictograms indicating the intended implant positions of mechanical (A) and bioprosthetic (B) surgical heart valves (SHV) in the aortic position. Considering the ambiguity of the current terminology used to describe the annular position of SHVs, the Task Force suggests that manufacturers use standardized pictograms to indicate the ‘intended position(s)’ of their SHVs related to the tissue annulus of the patient.

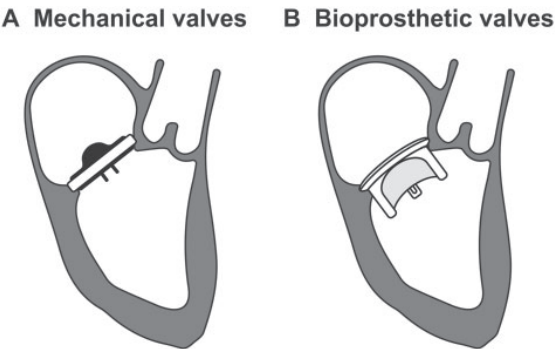


Figure 4: Example of standardized pictograms indicating the intended implant positions of mechanical (A) and bioprosthetic (B) surgical heart valves in the mitral position. Knowing the intended implant position of mitral surgical heart valves is important as these valves can potentially interfere with the mitral subvalvular apparatus, the left ventricular wall or the left ventricular outflow tract.

LABELLED VALVE SIZE AND INTRAOPERATIVE SIZING

The proper interpretation of 'labelled valve size' is one of the most challenging issues around SHV labelling, causing the most confusion in the surgical community [9]. Labelled valve size is defined as the 'tissue annulus diameter of the patient into which the SHV is intended to be implanted' in the ISO 5840:2015 standard [3]. In other words, labelled valve size reflects the manufacturer's recommendation into which annulus an SHV can be safely implanted. To emphasize that the actual meaning of 'labelled valve size' is 'patient tissue annulus diameter', manufacturers should always present 'labelled valve size' as a separate variable when presenting the physical dimensions of SHVs. Surgeons should similarly realize that the corresponding valve size is simply a label, and not a true measure of the valve size.

It is not possible to design valves for each annulus size. Therefore, labelled valve sizes are practically representing tissue annulus diameter ranges, where a specific SHV is recommended to be implanted according to the manufacturer [10, 11]. These ranges are defined by the valve-related tubular sizers. The lower margin of this range is the diameter of the largest valve-related tubular sizer that fits the annulus. The upper margin of this range is indirectly bordered by the diameter of the sizer 1 size larger (the sizer that does not fit).

It is sensible that the actual (numerical) labelled size of an SHV falls within these margins (Fig. 5) [12]. However, as the margins of these tissue annulus ranges were not defined in the corresponding ISO standards [3], they can vary for different SHV models having the same labelled valve size (Fig. 6). This historical lack of standardization renders the direct comparison of different SHVs based on labelled valve size impossible, precludes the exclusive use of a universal sizing tool, limits standard sizing and ultimately causes confusion in the surgical community [13].

Redefining these 'tissue annulus ranges' belonging to specific labelled sizes would demand major changes in existing SHV designs. For transparency, however, it is necessary to disclose the margins of these 'tissue annulus ranges'. This can easily be ends of the valve-related sizers and would clarify into which patients a specific SHV is 'intended to be implanted'.

Besides sizing with the cylindrical end of the valve-related sizer, the replica end of the sizer helps to determine the final fit and position of the SHV. Of note, the size of the replica can slightly differ from the actual dimensions of the corresponding SHV. This is due to the different properties of the sizer and SHV materials (mainly different flexibility, with a stiff sizer corresponding to a flexible SHV), and this should be considered during intraoperative sizing.

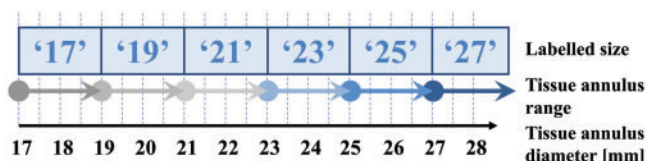


Figure 5: Ideal situation: well-defined, uniform relationship between labelled sizes and tissue annulus ranges. Comparing different surgical heart valve (SHV) models starts with selecting the valves that can be fitted into the same tissue annulus. A well-defined, uniform relationship between 'labelled valve size' and the 'tissue annulus range' where an SHV fits would allow direct comparison of SHVs based on labelled valve size.

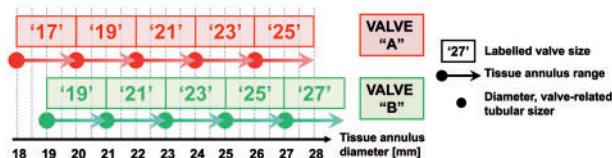


Figure 6: Actual situation: the margins of 'tissue annulus ranges' belonging to specific labelled valve sizes are not defined. The margins of 'tissue annulus ranges' are not standardized and can be different for similarly labelled surgical heart valve models. This lack of standardization precludes direct comparability based on labelled valve size and the use of a universal sizing tool.

PROVIDING INFORMATION ON PREDICTED HAEMODYNAMIC PERFORMANCE

Accurate and reliable information regarding the haemodynamic performance of an SHV after implantation is an important factor in optimal SHV choice. Also, comparison of measured and reference transprosthetic gradients and effective orifice area (EOA) values are used to assess SHV function during follow-up [14].

Information on SHV haemodynamic performance can be obtained by benchtop *in vitro* measurements, by *in vivo* large animal studies and by using *in vivo* data from reference patient populations. Benchtop mock circulatory loops used for *in vitro* testing and animal models are not perfect substitutes of the human circulation, and results can be influenced by differences in experimental protocols [15, 16]. Hence, *in vitro* hydrodynamic data or data from animal experiments should not be used to characterize or predict haemodynamic performance of SHVs in a clinical setting. *In vivo* data, derived from Doppler echocardiography measurements, performed in a reference patient population, should be the primary source to predict the haemodynamic performance of an SHV after implantation [4, 17].

Transprosthetic gradients and EOA do not solely depend on the physical features of an SHV. Doppler echocardiography measurements are influenced by the anatomy (upstream and downstream of the prosthesis) and the physiological state (heart rate,

myocardial function or cardiac output) of the individual patient receiving an SHV implant. Furthermore, surgical implantation technique and the timing between surgery and echocardiography [18, 19] can also potentially affect Doppler parameters [8], introducing variability into the results. In vivo EOA reference values follow a normal distribution (Fig. 7) [20] and should always be described with a mean value and its standard deviation (SD). Theoretically, the variability (described by the SD of the mean) can be reduced by increasing the number of patients, standardizing Doppler echocardiography protocols and performing measurements in independent reference laboratories (core laboratories).

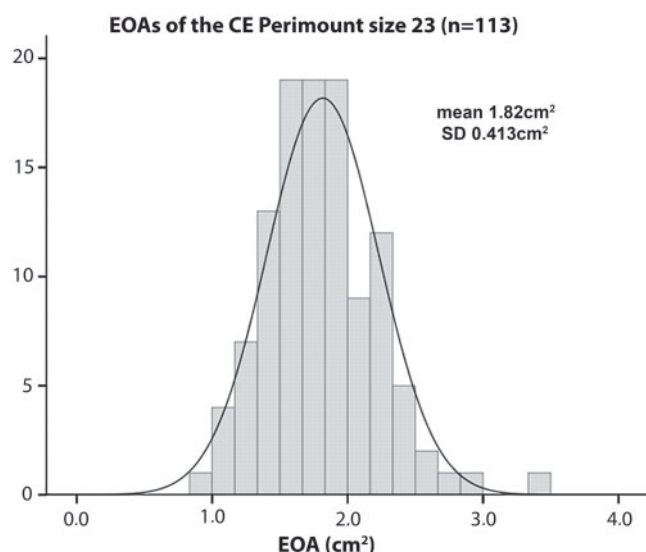


Figure 7: Distribution of the ‘reference EOA’ of a 23-mm bioprosthesis valve. In vivo reference EOAs of surgical heart valves (SHVs) are determined in reference patient populations and are influenced not only by SHV characteristics but also by patient anatomy and physiology. Reference EOAs have a normal distribution, described by a mean EOA and its SD. Reproduced from Ref. [20] with permission from BMJ Publishing Group Ltd. EOA: effective orifice area; SD: standard deviation.

To characterize the haemodynamic performance of a specific SHV model, ‘mean transprosthetic gradients’ and ‘EOAs’ determined by Doppler echocardiography should be used. Echocardiography used to determine normal reference values should be performed between 30 days and 1 year after implantation and in a minimum of 30 patients for each labelled size. Data should be presented as mean \pm SD for each SHV model and labelled size, along with source study details [e.g. study characteristics, number of patients investigated, mean \pm SD age, mean \pm SD body mass index (BMI) and mean \pm SD body surface area (BSA) of patients, per labelled size], indicating whether the measure-

ments were performed in an independent core laboratory or not. Whenever possible, only core laboratory adjudicated data should be used.

PREDICTING THE PROBABILITY OF PROSTHESIS-PATIENT MISMATCH AFTER AORTIC VALVE REPLACEMENT

PPM is manifested by high transprosthetic gradients through an otherwise normally functioning SHV. PPM results from the orifice of the implanted SHV being too small to fulfil the patient's cardiac output requirements [21]. The size of the SHV orifice relative to the patient is characterized by the 'indexed EOA', which is calculated by dividing the EOA of the SHV by the BSA of the patient:

$$\text{Indexed EOA (cm}^2\text{/m}^2\text{)} = \frac{\text{EOA (cm}^2\text{)}}{\text{BSA of the patient (m}^2\text{)}}.$$

PPM is associated with a higher risk of poor outcomes after aortic valve replacement [22, 23], and its prevention is of paramount importance when selecting an SHV for implantation [24]. Cut-off levels of indexed EOA have been introduced to define moderate and severe PPM after aortic valve replacement [14].

To predict PPM after SHV implantation, valve manufacturers provide 'indexed EOA charts'. The main principle of these charts is that by using a 'reference EOA' and the BSA of the patient, the 'expected indexed EOA' after implantation can be calculated and compared to the pre-defined PPM cut-off levels.

$$\text{Expected indexed EOA (cm}^2\text{/m}^2\text{)} = \frac{\text{Reference EOA (cm}^2\text{)}}{\text{BSA of the patient (m}^2\text{)}}.$$

Theoretically, this would make the selection of a large enough SHV, and thereby the prevention of PPM, possible. In 'indexed EOA charts' provided by valve manufacturers, expected indexed EOA values are typically colour-coded as follows: 'green—above PPM cut-off level', 'yellow—moderate PPM' and 'red—severe PPM'. However, PPM charts provided by valve manufacturers have been severely criticized for their inaccuracy [25]. Due to the lack of standardization, the use of different PPM cut-offs and the questionable quality of their reference EOAs, these charts are regarded by many as marketing tools rather than useful clinical assets [26].

Standardized PPM charts, however, would (i) help surgeons in objectively assessing the probability of PPM before SHV implantation; (ii) facilitate optimal SHV choice; and (iii) prevent biased comparisons between different SHVs [26]. Therefore, the Task Force proposes that manufacturers provide standardized charts for their aortic SHVs to predict the probability of severe PPM after implantation.

To create a 'standardized PPM chart', the following is required: (i) high-quality reference EOA values for all SHV models and sizes from a reliable source; (ii) the use of uniform PPM cut-off levels; and (iii) a tool to accurately predict the probability of PPM after SHV implantation.

The use of reliable, high-quality reference EOA values is of paramount importance. In PPM charts, reference EOA values derived from large prospective multicentre clinical studies with standardized core laboratory echocardiography assessment should be used, if possible. Data from at least 30 patients should be available to determine the mean \pm SD reference EOA, for each SHV model and labelled size. In addition, the following study details should be provided on the standardized PPM chart: sample size per labelled SHV size, study characteristics (prospective or retrospective, period of patient inclusion, single or multicentre, regulatory study or not) and whether echocardiography was assessed in a core laboratory.

The use of uniform indexed EOA cut-offs is mandatory to define PPM after aortic valve replacement. Recent guidelines advocate adjusting PPM cut-offs for the BMI of the patient [14]. In the standardized charts, the following PPM cut-off values should be used: for non-obese (BMI $<30 \text{ kg/m}^2$) patients, severe PPM should be defined as an indexed EOA of $<0.65 \text{ cm}^2/\text{m}^2$; while for patients with BMI $\geq 30 \text{ kg/m}^2$, severe PPM should be defined as an indexed EOA of $\leq 0.55 \text{ cm}^2/\text{m}^2$ [14].

Instead of classifying PPM simply into a 'yes/no' (binary) variable, knowing the exact probability of severe PPM is more useful in clinical decision-making. The standardized PPM chart should therefore provide the 'probability of severe PPM' for a given patient in percentages, based on the reference EOA of the corresponding SHV (described as mean \pm SD) and on the BMI and BSA of the patient.

Expected indexed EOAs are derived from reference EOAs. Hence, expected indexed EOA values follow the same distribution as reference EOA values. When applying the abovementioned severe PPM cut-offs to this distribution, the exact probability of PPM can be calculated (Fig. 8). Dividing the area under the curve below the PPM limit by the area under the curve of the whole 'expected indexed EOA distribution' gives us the probability of severe PPM:

$$\text{PPM probability} = \frac{\text{AUC 'below PPM limit'}}{\text{AUC 'expected indexed EOA distribution'}}.$$

In standardized PPM charts, the probability of PPM should be provided using this method. PPM probability should be provided in percentages, for BSA ranges between 1.3 and 2.6 m^2 , in 0.1 m^2 increments [27].

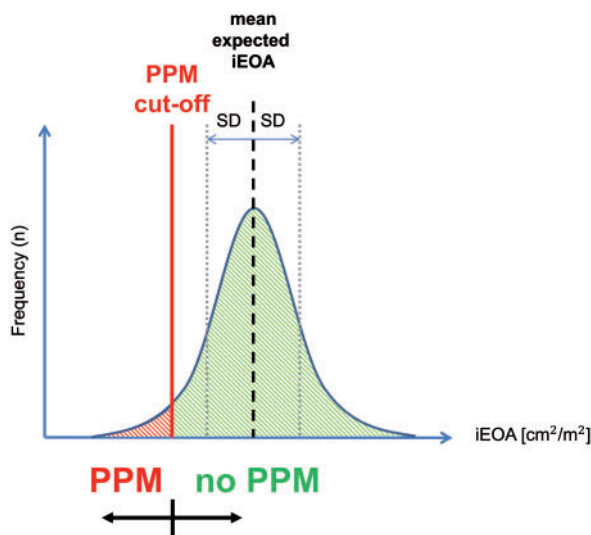


Figure 8: Applying PPM cut-off to the 'expected indexed EOA' distribution, to calculate PPM probability. Applying a PPM cut-off value to the 'expected indexed EOA' distribution helps assessing the 'percentage probability' of PPM after surgical heart valve implantation. This method can provide a better understanding of the actual PPM risk and avoid the shortcomings of classifying predicted PPM into a 'yes/no' binary variable. iEOA: indexed effective orifice area; PPM: prosthesis–patient mismatch; SD: standard deviation.

To emphasize that PPM after aortic valve replacement is not only dependent on the characteristics of the SHV or on the BMI and BSA of the patient, the standardized PPM chart should contain the following disclaimer: 'This chart is a support tool to estimate the probability of PPM in patients undergoing aortic valve replacement with a particular prosthetic heart valve, but the actual risk further depends on specific patient characteristics and operative technique'. An example of the proposed standardized PPM chart is provided in Fig. 9.

Probability of severe*													
Prosthesis-Patient Mismatch													
"MANUFACTURER" - "VALVE MODEL"													
Labelled valve size		19		21		23		25		27		29	
Patient BMI [kg/m ²]		<30	≥30	<30	≥30	<30	≥30	<30	≥30	<30	≥30	<30	≥30
Patient BSA [m ²]	1.2	9%	3%	7%	4%	4%	3%	2%	1%	1%	1%	0%	0%
	1.3	16%	7%	12%	7%	7%	4%	3%	2%	2%	1%	0%	0%
	1.4	25%	12%	18%	10%	11%	7%	6%	3%	3%	2%	0%	0%
	1.5	34%	18%	24%	15%	15%	10%	8%	5%	5%	3%	0%	0%
	1.6	43%	25%	29%	19%	19%	13%	12%	8%	7%	5%	0%	0%
	1.7	51%	31%	35%	24%	23%	16%	15%	10%	10%	7%	0%	0%
	1.8	58%	38%	40%	28%	28%	20%	19%	13%	13%	9%	0%	0%
	1.9	64%	44%	45%	33%	32%	23%	23%	16%	15%	11%	0%	0%
	2.0	69%	50%	50%	37%	35%	27%	27%	19%	18%	14%	1%	0%
	2.1	74%	55%	54%	41%	39%	30%	30%	22%	21%	16%	1%	0%
	2.2	77%	60%	58%	45%	42%	33%	34%	25%	24%	18%	2%	1%
	2.3	80%	64%	61%	48%	45%	36%	37%	28%	27%	21%	3%	1%
2.4	83%	68%	64%	51%	48%	39%	40%	31%	30%	23%	4%	2%	
2.5	85%	71%	67%	54%	51%	41%	43%	34%	32%	25%	6%	3%	
Study details	EOA, mean±SD [cm ²]	1.1 ± 0.2		1.3 ± 0.3		1.6 ± 0.4		1.8 ± 0.4		2.2 ± 0.5		2.8 ± 0.3	
	Patients per valve size (n)	25		52		79		65		43		32	
	Prospective	yes		yes		yes		yes		yes		yes	
	Centers per valve size (n)	3		3		3		3		3		3	
	Pooled data	no		no		no		no		no		no	
	Regulatory	no		no		no		no		no		no	
	Echo core lab	yes		yes		yes		yes		yes		yes	
	Period of data collection	2012 - 2014		2012 - 2014		2012 - 2014		2012 - 2014		2012 - 2014		2012 - 2014	
Timing of postop echo	3 months		3 months		3 months		3 months		3 months		3 months		
*severe PPM is defined as iEOA: ≤0.65 cm ² /m ² , in patients with BMI <30 kg/m ² ; and as iEOA: ≤0.55 cm ² /m ² in patients with BMI ≥30													
COLOR CODING: yellow indicates that the percentage probability of severe PPM is greater than or equal to 50%, meaning that the mean indexed EOA is below the severe PPM cutoff level.													
DISCLAIMER: This chart is a support tool to estimate the probability of PPM in patients undergoing surgical aortic valve replacement with a particular valve, but the actual risk further depends on specific patient characteristics and operative technique.													

Figure 9: Standardized PPM chart for surgical heart valves in the aortic position. Standardized PPM charts provide the percentage probability of severe PPM after implantation of an aortic surgical heart valve into a specific patient. Different cut-offs of severe PPM are used for non-obese (BMI) and obese (BMI) patients. The probability of severe PPM is calculated using the distribution of 'reference EOAs', 'patient BSA' and the 'BMI-adjusted severe PPM cut-off'. The yellow colour indicates that the 'mean expected indexed EOA' is under the PPM cut-off (percentage probability is larger than 50%). BMI: body mass index; BSA: body surface area; EOA: effective orifice area; iEOA: indexed effective orifice area; PPM: prosthesis-patient mismatch; SD: standard deviation.

PROVIDING INFORMATION FOR AN OPTIMAL SURGICAL HEART VALVE CHOICE

To facilitate SHV choice, the Task Force identified the following essential information regarding SHV characteristics that should be made easily available by valve manufacturers, for all SHV models and sizes: (i) SHV 'physical dimensions', presented in a complete and standardized way; (ii) 'tissue annulus ranges' in which SHVs can be implanted, characterized by the diameters of the valve-related tubular sizers; (iii) a standardized 'pictogram indicating the intended position of the SHV' after implantation, related to the patient tissue annulus; (iv) 'high-quality reference EOA values'; and (v) for aortic SHVs, a 'standardized chart to display the probability of severe PPM', based on high-quality in vivo reference EOAs, using standardized, BMI-adjusted PPM cut-offs, for realistic patient BSA ranges.

Although final SHV choice is typically made in the operating theatre, surgeons should be provided with all necessary information required for optimal SHV choice well before the operation. Currently, medical literature, marketing materials provided by valve manufacturers, package labels and instructions for use booklets are the primary sources of information regarding SHV characteristics [4]. The main purpose of package labels is to allow easy identification of the product for the end-user, and throughout the whole supply chain. Furthermore, labels must contain essential information regarding sterility, manufacturing and the intended use of the product. However, it is not possible to provide all information regarding SHV characteristics required for valve selection on package labels. On the other hand, instructions for use booklets are typically only accessible after opening the packaging of the SHV and, from a practical standpoint, it is not possible to study these booklets in detail in the time-pressured environment of an operating theatre, during intraoperative SHV implantation.

Therefore, instead of changing existing package labels, the Task Force suggests the introduction and the use of a standardized Valve Chart, to provide comprehensive information regarding SHV characteristics. Standardized Valve Charts should be provided by manufacturers and should contain the following information: (i) manufacturer name and type of the SHV; (ii) standardized table and pictogram to present SHV physical dimensions; (iii) sizer dimensions to indicate the tissue annulus ranges where the SHVs can be fitted; (iv) standardized pictogram indicating the intended implant position of the SHV; and (v) standardized PPM chart to predict the probability of PPM, for SHVs used in the aortic position (vi) issue date and version number. Valve Charts should have a standardized, uniform layout. Furthermore, to ensure easy access, Valve Charts should be made available online on a designated website endorsed by EACTS, STS and AATS, and in a smartphone application. Valve Charts should be regularly revised and updated

if new evidence becomes available. An example of standardized Valve Chart is provided in Fig. 10 for aortic valves and in Fig. 11 for mitral SHVs.

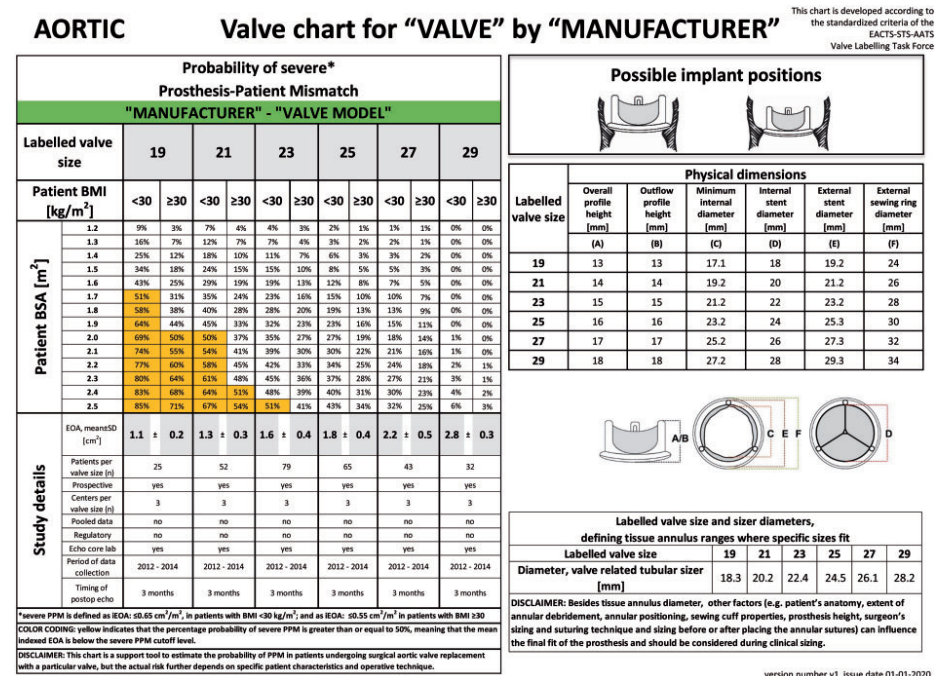


Figure 10: Standardized Valve Chart: aortic valves. Standardized Valve Charts provide essential information on surgical heart valve (SHV) characteristics in a uniform manner and allow for comparability between different SHV models without demanding radical changes in current SHV designs or labelling. Furthermore, Valve Charts highlight the necessity of considering multiple factors when selecting an SHV for implantation. BMI: body mass index; BSA: body surface area; EOA: effective orifice area; IEAO: indexed effective orifice area; PPM: prosthesis–patient mismatch; SD: standard deviation.

SELECTION AND COMPARISON OF SURGICAL HEART VALVES USING THE VALVE CHART

Valve Charts can be used preoperatively, intraoperatively or postoperatively, when comparing different SHVs, when selecting SHVs for implantation or when assessing SHV function. Possible uses of the Valve Charts in various clinical scenarios are summarized in Fig. 12.

MITRAL

Valve chart for "VALVE" by "MANUFACTURER"

This chart is developed according to the standardized criteria of the EACTS-SIS-AATS Valve Labelling Task Force

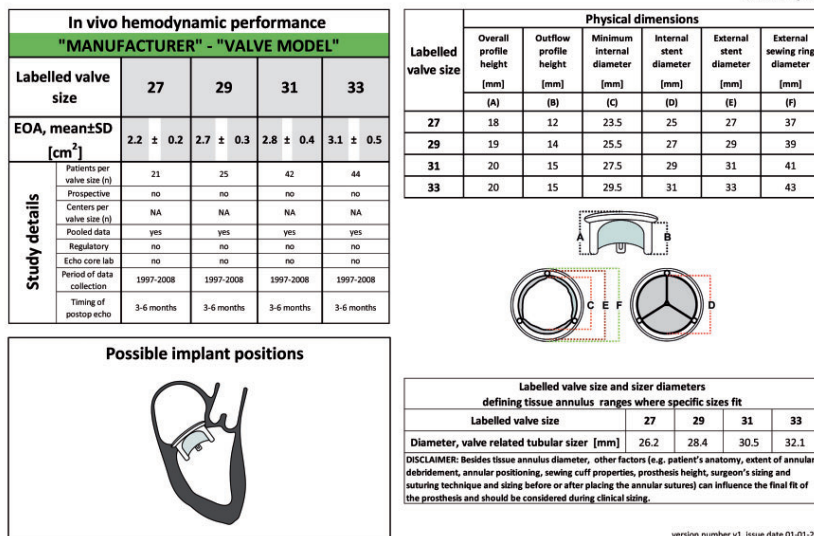


Figure 11: Standardized Valve Chart: mitral valves. Information on in vivo hemodynamic performance, physical dimensions, intended implant position and size dimensions should be made available for surgical heart valves in the mitral position. EOA: effective orifice area; SD: standard deviation.

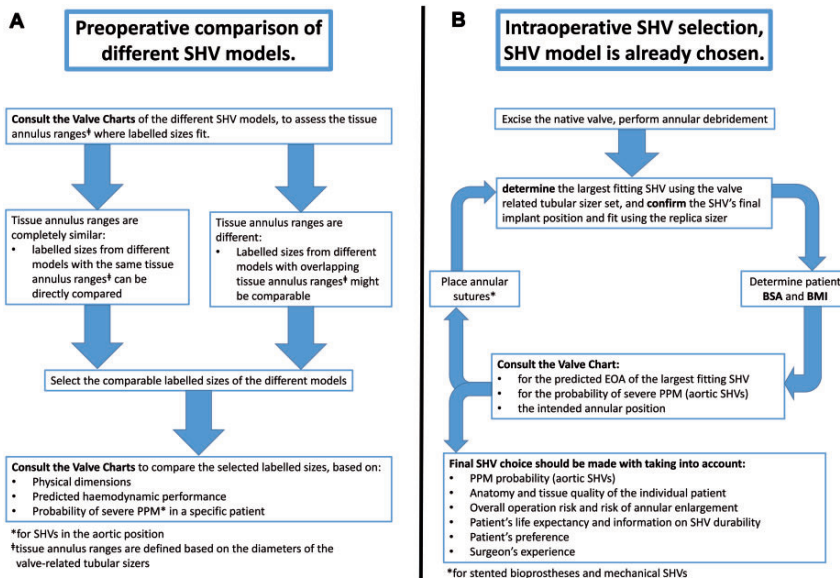


Figure 12: Comparison and selection of SHVs using the Valve Chart. Valve Charts can be used in various settings: when comparing SHVs from different manufacturers preoperatively (A) or when selecting SHVs for implantation (B). BMI: body mass index; BSA: body surface area; EOA: effective orifice area; PPM: prosthesis–patient mismatch; SHV: surgical heart valve.

DISCUSSION

Easy access to comprehensive information regarding SHV characteristics is required for an optimal SHV choice: in addition to determining which SHV would fit into the patient and knowing the intended annular position of the prosthesis, knowledge of the predicted haemodynamic performance of the SHV and the probability of PPM after implantation are matters of the uttermost importance.

On the standardized Valve Charts, this information could be provided for all SHV models in a uniform manner, without demanding radical changes in current SHV designs or labelling. As most of the required information is readily available, it should be possible to create these Charts relatively quickly and easily. Standardized Valve Charts highlight the necessity of considering multiple factors when selecting an SHV for implantation. The ability to consult such charts during the preoperative, intraoperative and postoperative periods makes objective comparison of different SHVs and optimal SHV selection possible, and it helps in the proper assessment of SHV function during patient follow-up.

Besides the information provided on the Valve Chart, individual patient characteristics, comorbidities, life expectancy and preference, local resources and expertise and predicted in vivo prosthesis durability and thrombogenicity should be considered when selecting an SHV for implantation. Due to the suboptimal quality and quantity of the currently available data on in vivo SHV durability and thrombogenicity and considering the significant heterogeneity of the definitions used to describe these important clinical end points [28–30], data regarding SHV durability and thrombogenicity are not provided on the Valve Charts.

Problems around SHV sizing and labelling can only be solved by the cooperation and joint effort of all stakeholders. The EACTS–STS–AATS Valve Labelling Project was set up with this intention. This Consensus Document can serve as a guide for regulatory bodies, when developing future standards or when refining the framework of surgical heart valve labelling. In the future, continuous dialogue and close collaboration of clinicians (represented by professional societies), engineers, regulatory bodies, the ISO Cardiac Valves Working Group and valve manufacturers are mandated to ensure that clinicians are provided with the necessary information regarding SHV characteristics all times.

CONCLUSIONS

This joint EACTS–STS–AATS Valve Labelling Task Force suggests the use of standardized Valve Charts to present essential information on SHV characteristics. Valve Charts should present information on the physical dimensions, implant position and haemodynamic

performance of an SHV in a uniform, standardized manner. For valves used in the aortic position, Valve Charts should include a standardized PPM chart to assess the probability of PPM after implantation.

Continuous dialogue and collaboration of clinicians, engineers, regulatory bodies, the ISO Cardiac Valves Working Group and valve manufacturers are essential to ensure that clinicians are provided with the necessary information regarding SHV characteristics.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the fundamental work of Stuart J. Head in the development of the concept of the standardized PPM charts and the help of Rianne Kalkman in coordinating the Task Force activities.

Funding

This work was supported by the European Association for Cardio-Thoracic Surgery (EACTS).

Conflict of interest

Vinayak Bapat is a consultant for Medtronic, Boston Scientific and Edwards Lifesciences; Edward P. Chen is a speaker and consultant for Medtronic; Gry Dahle is a proctor for Tendyne; John A. Eleftheriades is a member of the Data and Safety Monitoring Boards of Jarvik Heart and Terumo, a founder and principal of CoolSpine and a consultant for DuraBiotec; Alan Speir is on the Medtronic North America Cardiac Surgery Advisory Board; Giordano Tasca received lecture fees from Abbott Medical Italia SpA. All other authors reported no conflict of interest regarding the content of this manuscript.

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APPENDIX: TASK FORCE MEMBERS

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4

The PPM chart: A new tool to assess prosthesis-patient mismatch probability before aortic valve replacement.

Durko AP, Pibarot P, De Paulis R; EACTS-STs-AATS Valve Labeling Task Force.

J Thorac Cardiovasc Surg. 2021 May;161(5):e373-e375.

REPLY TO THE EDITOR:

We thank Vriesendorp and colleagues¹ for their letter discussing prosthesis-patient mismatch (PPM) after aortic valve replacement and the new PPM Chart proposed by the European Association for Cardio-Thoracic Surgery-Society of Thoracic Surgeons-American Association for Thoracic Surgery Valve Labelling Task Force.¹ They raise important issues that require attention.

First, it is important to outline the fundamental differences between traditional indexed effective orifice area (EOAi) charts and the new PPM Chart. Traditional EOAI charts calculate the mean expected EOAI to classify expected PPM as severe (typically red fields), moderate (yellow fields), or absent/mild (green fields), based on this value falling under or above a predefined cutoff. This seemingly attractive simplicity comes with a serious and established tradeoff in terms of reliability.^{2,3} In contrast to traditional EOAI charts, the new PPM Chart proposed by the Valve Labelling Task Force provides the calculated percent probability of expected severe PPM based on the distribution of normal reference effective orifice area (EOA) values. By providing a percent probability, the new PPM Chart is meant to correct, at least in part, the inaccuracy of traditional EOAI charts, which classify expected PPM merely as a binary outcome (present vs absent). However, we agree with Vriesendorp and colleagues¹ that because PPM charts are based on in vivo reference EOAs, characteristics of the population in which these EOA values were determined could influence their accuracy.

Second, Vriesendorp and colleagues¹ question the validity of current definitions for PPM, which are based on EOAI cutoffs.^{4,5} Although these cutoffs might be challenged,⁶ it is logical that the assessment of PPM after aortic valve replacement employs EOAI cutoffs determined by echocardiography^{4,5,7} because the severity of native aortic stenosis is also assessed using similar, echocardiography-derived criteria.^{8,9} The mandate of the Valve Labelling Task Force was not to challenge or revise existing PPM definitions, but rather help surgeons to estimate the risk of severe PPM at the time of a procedure, while highlighting the limitations of PPM prediction using reference EOAs.

Finally, Vriesendorp and colleagues¹ discuss the potential danger of unnecessary aortic annulus enlargement procedures due to expected PPM based on the new PPM Chart suggested by the Task Force. Indeed, traditional EOAI charts (Figure 1, A) could potentially push surgeons to perform preventive procedures during AVR if the patient falls into the red areas (ie, severe PPM), although these procedures may not always be necessary nor justified. The new PPM Chart proposed by the Valve Labelling Task Force provides percent probability of severe PPM. These charts are thus more granular and far less categorical and dictatorial than traditional EOAI charts (Figure 1, B). We believe that these new charts can help surgeons to make more balanced and better informed decisions when selecting prosthetic valves or choosing a treatment strategy for their patients.

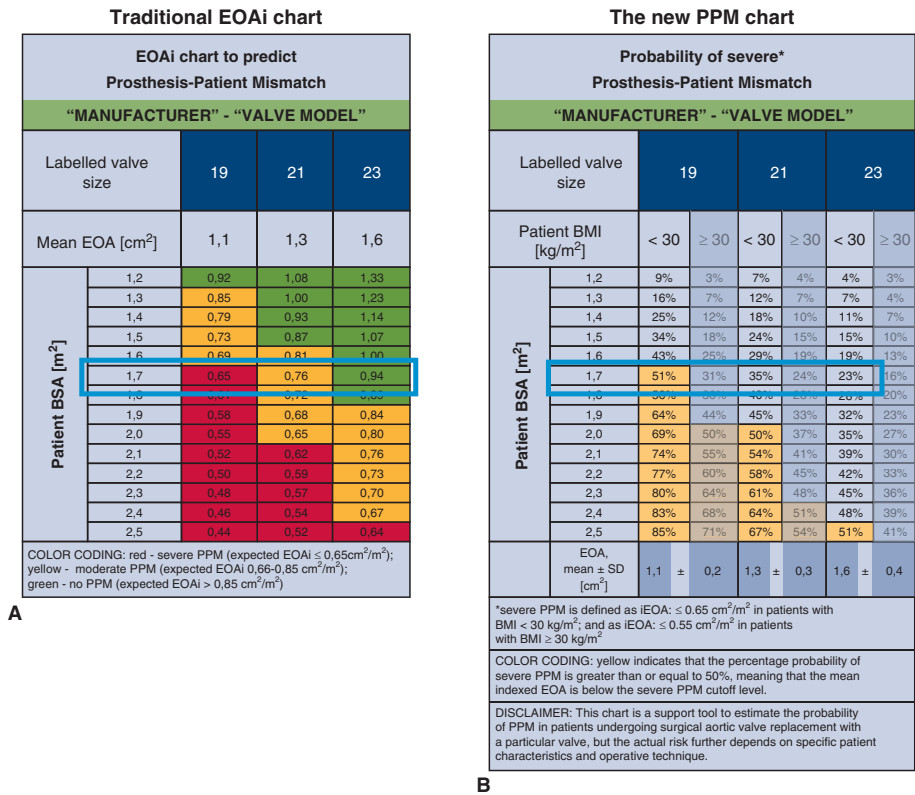


FIGURE 1. Assessing expected prosthesis-patient mismatch (PPM) using traditional indexed effective orifice area (EOAI) charts and with the new PPM Chart. Example charts for the same valve model. A, Traditional EOAI charts are trichotomous (red = severe PPM, yellow = moderate PPM, and green = no PPM) and categorize expected PPM as a binary outcome (present or absent). B, The new PPM chart provides the percent probability of expected severe PPM. Note the differences in how expected PPM is expressed with the traditional EOAI chart and with the new PPM chart, for a patient with a body surface area (BSA) of 1.7 m² (light blue boxes). Using percent probability to describe expected PPM highlights the limitations of using reference effective orifice areas in PPM prediction and could lead to better-informed decisions when considering annular enlargement procedures. BMI, Body mass index.

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5

Outcomes of surgical aortic valve replacement over three decades.

Çelik M, Durko AP, Bekkers JA, Oei FBS, Mahtab EAF, Bogers AJJC.

J Thorac Cardiovasc Surg. 2021 Apr 28:S0022-5223(21)00748-0.

ABSTRACT

Objective

The study objective was to analyze temporal changes in baseline and procedural characteristics and long-term survival of patients undergoing surgical aortic valve replacement over a 30-year period.

Methods

A retrospective analysis of patients undergoing surgical aortic valve replacement between 1987 and 2016 in the Erasmus Medical Center (Rotterdam, The Netherlands) was conducted. Patient baseline and procedural characteristics were analyzed in periods according to the date of surgical aortic valve replacement (period A: 1987-1996; B: 1997-2006; C: 2007-2016). Survival status was determined using the Dutch National Death Registry. Relative survival was obtained by comparing the survival after surgical aortic valve replacement with the survival of the age-, sex-, and year-matched general population.

Results

Between 1987 and 2016, 4404 patients underwent SAVR. From period A to C, the mean age increased from 63.9 ± 11.2 years to 66.2 ± 12.3 years ($P < .001$), and the prevalence of diabetes mellitus, hypertension, hypercholesterolemia, previous myocardial infarction, and previous stroke at baseline increased (P values for trend for all $< .001$). The prevalence of concomitant procedures increased from 42.4% in period A to 48.3% in period C ($P = .004$). Bioprosthesis use increased significantly (18.8% in period A vs 67.1% in period C, $P < .001$). Mean survival after surgical aortic valve replacement was 13.8 years. Relative survival at 20 years in the overall cohort was 60.4% (95% confidence interval, 55.9-65.2) and 73.8% (95% confidence interval, 67.1-81.1) in patients undergoing isolated primary surgical aortic valve replacement.

Conclusions

Patient complexity has been continuously increasing over the last 30 years, yet long-term survival after surgical aortic valve replacement remains high compared with the age-, sex-, and year-matched general population.

Key Words: aortic valve disease, aortic valve replacement, aortic valve stenosis, intervention

Invasive treatment of aortic valve disease has been continuously evolving since the first surgical aortic valve replacement (SAVR) was performed in the 1960s.¹ Technical and procedural refinements, continuous prosthesis development, and periprocedural care improvement resulted in a substantial improvement of SAVR outcomes over the last decades.² Concurrently, patient characteristics have changed considerably, and the comorbidity burden is increasing.^{2,3}

The latest revolution in treating aortic valve replacement was the introduction of transcatheter aortic valve replacement (TAVR) in the early 2000s.⁴ Attractive for its less invasiveness, TAVR quickly became an established treatment modality for patients with aortic stenosis (AS) having high or intermediate surgical risk.^{5,6} More recently, clinical trial results have even challenged the role of SAVR in low-risk patients with AS.^{7,8} These results forecast a new era in treating aortic valvular pathology, when optimal treatment allocation will become increasingly important.

Detailed analysis of patient and procedural characteristics, especially long-term survival after SAVR, is inevitable for informed treatment decisions. This study aimed to assess the trends in patient and procedural characteristics and the long-term survival in SAVR in a high-volume tertiary center over the last 3 decades.

MATERIALS AND METHODS

Study design and data collection

Adult patients undergoing SAVR between 1987 and 2016 at the Erasmus Medical Center, Rotterdam, The Netherlands, were analyzed. Patients receiving bioprosthetic or mechanical aortic valve prosthesis with or without concomitant cardiac procedures were included. Patients aged less than 18 years and patients receiving valved conduits were excluded. Baseline and procedural characteristics were collected retrospectively from electronic medical records. Survival status was obtained through the Dutch National Death Registry.

This study was conducted according to the privacy policy of the Erasmus Medical Center and regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the Declaration of Helsinki (Institutional MEC Number: MEC-2019-0721), and patient informed consent was waived. All the authors vouch for the validity of the data and adherence to the protocol.

End points and definitions

The primary end point was the differences in baseline and procedural characteristics in the overall and primary isolated SAVR cohort, in three 10-year time periods according to the date of SAVR (period A: 1987-1996; B: 1997-2006; C: 2007-2016). The survival in the

overall and primary isolated SAVR cohort was analyzed and compared with the survival of the matched general population (relative survival). SAVR within 24 hours of establishing the indication was classified as urgent. SAVR after 24 hours was classified as (semi-) elective. Left ventricular function was classified as normal if the left ventricular ejection fraction (LVEF) was greater than 50%, as reduced if the LVEF was 30% to 50%, and as severely reduced if the LVEF was less than 30%, as measured or estimated by a trained echocardiographer. Low-, intermediate-, and high-risk patients are defined as logistic European System for Cardiac Operative Risk Evaluation of 10 or less, 10 to 20, and 20 or greater, respectively.

Statistical analysis

Categorical variables are presented as numbers, percentages, or proportions and compared with the chi-square test or the Fisher exact test, where appropriate. Continuous variables are presented as means \pm standard deviation or median with the interquartile range and compared with the 2-sample *t* test or Wilcoxon rank-sum test where appropriate. Patients were classified into 10-year time periods based on surgery date (period A: 1987-1996; period B: 1997-2006; period C: 2007-2016). Trend analysis was performed with the chi-square test for trend.

The relative survival can be used as an estimate of cause-specific mortality. It is defined as the ratio between the observed survival and the expected survival in the general population.⁹ The Human Mortality Database was used to obtain the age-, sex-, and year-matched expected survival data of the general population of The Netherlands.¹⁰ The Human Mortality Database is continuously updated and includes mortality data from the Netherlands up until 2016. Relative survival is estimated through the Ederer II method.^{11,12} Data management and statistical analyses were performed using SPSS 25.0 (SPSS Inc, Chicago, Ill) and R software, version 3.5 (R Foundation, Vienna, Austria).

RESULTS

Baseline characteristics

Between 1987 and 2016, a total of 4404 patients underwent SAVR with a biological (*n* = 2301) or mechanical (*n* = 2103) valve prosthesis. No patients were lost to follow-up for survival, with a mean follow-up of 13.8 years. Mean age was 65.5 ± 12.1 years, and 38.2% (*n* = 1683) were female. A total of 46.3% (*n* = 2041) required concomitant procedures, and 5.6% (*n* = 247) had redo SAVR. The indication for operation was AS or combined AS and aortic regurgitation in most cases (83.9%). The most common comorbidities included hypertension (35.1%, *n* = 1545), atrial fibrillation (17.6%, *n* = 775), and diabetes mellitus (14.9%, *n* = 656). The median logistic European System for Cardiac Operative

Risk Evaluation (available since 2003; $n = 2605$) was 5.0%, with 18.8% ($n = 480$) of the patients having a logistic European System for Cardiac Operative Risk Evaluation of 10% or greater and 6.0% ($n = 153$) having a logistic European System for Cardiac Operative Risk Evaluation of 20% or greater. Further baseline characteristics are shown in Table 1 for the overall cohort and in Tables E1 and E2 for the isolated SAVR and the SAVR with concomitant CABG cohort.

TABLE 1. Baseline characteristics over three decades in the overall cohort

	All patients ($n = 4404$)	Period A 1987-1996 ($n = 911$)	Period B 1997-2006 ($n = 1627$)	Period C 2007-2016 ($n = 1866$)	Chi-square <i>P</i> value
Age at operation, y (mean \pm SD)	65.5 \pm 12.1	63.9 \pm 11.2	65.5 \pm 12.3	66.2 \pm 12.3	<.001
<40	180 (4.1)	33 (3.6)	67 (4.1)	80 (4.3)	.427
40-49	302 (6.8)	74 (8.1)	121 (7.4)	107 (5.6)	.006
50-59	649 (14.7)	157 (17.2)	239 (14.7)	253 (13.6)	.013
60-69	1330 (30.2)	326 (35.8)	448 (27.5)	556 (29.8)	.012
70-79	1641 (37.3)	297 (32.6)	641 (39.4)	703 (37.7)	.041
≥ 80	303 (6.9)	24 (2.6)	111 (6.8)	168 (9.0)	<.001
Female	1683 (38.2)	338 (37.1)	679 (41.7)	666 (35.7)	.134
Indication ($n = 4370$)					
AS	2894 (66.2)	499 (55.4)	1086 (66.9)	1309 (70.9)	<.001
AR	771 (17.6)	163 (18.1)	277 (17.1)	331 (17.9)	.966
Combined AS + AR	705 (16.1)	239 (26.5)	260 (16.0)	206 (11.2)	<.001
Bicuspid aortic valve	697 (15.8)	234 (25.7)	255 (15.7)	208 (11.2)	<.001
Endocarditis	292 (6.6)	67 (7.4)	95 (5.8)	130 (7.0)	.983
Logistic euroSCORE ($n = 2073$)(median, IQR)	5.0 (2.9-8.4)	N/A	5.0 (2.7-8.1)	5.1 (2.9-8.4)	.188
≥ 10	480 (18.8)		127 (18.4)	353 (18.9)	.772
≥ 20	153 (6.0)		36 (5.2)	117 (6.3)	.320
Previous cardiac operation	553 (12.6)	146 (16.0)	200 (12.3)	207 (11.1)	<.001
SAVR	247 (5.6)	74 (8.1)	72 (4.4)	101 (5.4)	.023
Creatinine ≥ 2 mg/dL	132 (3.0)	25 (2.7)	36 (2.2)	71 (3.8)	.020
Previous hemodialysis	32 (0.7)	5 (0.5)	10 (0.6)	17 (0.9)	.240
Atrial fibrillation	775 (17.6)	160 (17.6)	258 (15.9)	357 (19.1)	.134
Diabetes mellitus	656 (14.9)	69 (7.6)	205 (12.6)	382 (20.5)	<.001
Cardiac decompensation	728 (16.5)	210 (23.1)	259 (15.9)	259 (13.9)	<.001
Hypertension	1545 (35.1)	186 (20.4)	456 (28.0)	903 (48.4)	<.001
Hypercholesterolemia	720 (16.3)	47 (5.2)	207 (12.7)	466 (25.0)	<.001
Previous myocardial infarction	507 (11.5)	92 (10.1)	178 (10.9)	237 (12.7)	.030

TABLE 1. Baseline characteristics over three decades in the overall cohort (*continued*)

	All patients (n = 4404)	Period A 1987-1996 (n = 911)	Period B 1997-2006 (n = 1627)	Period C 2007-2016 (n = 1866)	Chi-square P value
Previous PCI	306 (6.9)	27 (3.0)	82 (5.0)	197 (10.6)	<.001
COPD	455 (10.3)	72 (7.9)	157 (9.6)	226 (12.1)	<.001
History of cancer	314 (7.1)	27 (3.0)	111 (6.8)	176 (9.4)	<.001
History of stroke	398 (9.0)	45 (4.9)	132 (8.1)	221 (11.8)	<.001
Arterial disease	195 (4.4)	21 (2.3)	59 (3.6)	115 (6.2)	<.001
Peripheral	170 (3.9)	20 (2.2)	51 (3.1)	99 (5.3)	<.001
Carotid	32 (0.7)	1 (0.1)	12 (0.7)	19 (1.0)	.010
LVEF (n = 4026)					
Good	3147 (78.2)	577 (77.4)	1185 (79.3)	1385 (77.5)	.771
Reduced	729 (18.1)	120 (16.1)	264 (17.7)	345 (19.3)	.046
Severely reduced	150 (3.3)	48 (6.4)	46 (3.1)	56 (3.1)	.001

Values are presented as n (%) or as mean \pm SD or median (interquartile range) if otherwise stated. *SD*, Standard deviation; *AS*, aortic stenosis; *AR*, aortic regurgitation; *euro-SCORE*, European System for Cardiac Operative Risk Evaluation; *IQR*, interquartile range; *N/A*, not available; *SAVR*, surgical aortic valve replacement; *PCI*, percutaneous coronary intervention; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricular ejection function.

Changes in patient profile over three decades

During the 30-year observation period, the annual number of patients undergoing SAVR per period increased, from an annual average of 91 in period A to 187 in period C (Figure 1). The mean age increased from 63.9 ± 11.2 years in period A to 66.2 ± 12.3 years in period C ($P < .001$). The proportion of patients aged 70 years or more increased from 35.2% in period A to 46.7% in period C ($P < .001$). Between periods A and C, the prevalence of diabetes mellitus in the study population increased from 7.6% to 20.5% ($P < .001$), hypercholesterolemia from 5.2% to 25.0% ($P < .001$), and chronic obstructive pulmonary disease from 7.9% to 12.1% ($P < .001$). The percentage of patients with previous cardiac operations ($P < .001$) and redo SAVR decreased ($P = .023$). Further changes in baseline characteristics are shown in Table 1 for the overall cohort and in Tables E1 and E2 for the primary isolated SAVR and the primary SAVR with concomitant CABG cohort.

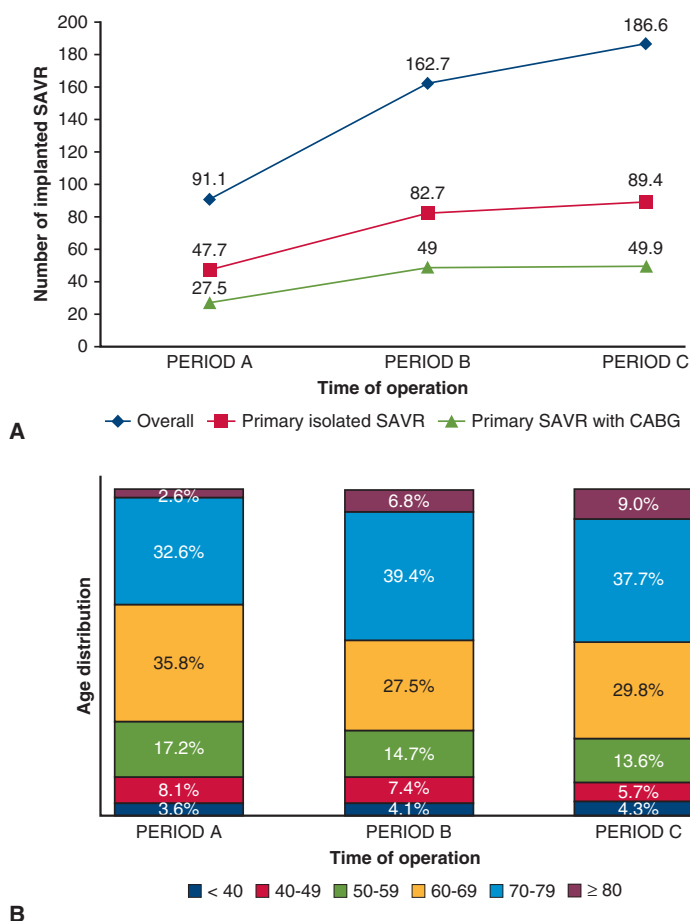


FIGURE 1. Age at operation and annual number of patients undergoing SAVR over 30 years. Over 30 years, the percentage of elderly patients and the annual number of patients undergoing SAVR increased considerably. Results are reported according to the time of SAVR (period A: 1987-1996; B: 1997-2006; C: 2007-2016). A, Annual average of patients undergoing SAVR, according to the type of surgery. Y-axis represents the absolute number of patients. B, Age distribution of patients at the time of SAVR. SAVR, Surgical aortic valve replacement; CABG, coronary artery bypass grafting.

Trends in procedural characteristics and prosthesis use

During the study period, 46.3% (n = 2041) of the SAVR patients underwent concomitant procedures (Table 2), with a significant increase from 42.4% in period A to 48.3% in period C ($P = .004$). Most commonly, concomitant CABG was performed (n = 1433, 32.5%). Among patients undergoing concomitant CABG, 41.2% (n = 590) had single-vessel disease and 58.8% (n = 843) had multiple-vessel disease. The proportion of patients requiring concomitant CABG for single-vessel disease remained constant during the 30-year observation period ($P = .412$). Patients with concomitant CABG were older com-

pared with patients not requiring revascularization (70.1 ± 8.3 vs 65.0 ± 12.0 ; $P < .001$). From period A to period C, the incidence of concomitant tricuspid and aortic procedures increased. The proportion of patients receiving bioprosthetic valves increased significantly, from 18.8% in period A to 67.1% in period C ($P < .001$, Figure 2). Detailed trends regarding changes in procedural characteristics and concomitant procedures are provided in Table 2.

TABLE 2. Procedural characteristics over three decades in the overall cohort

	All patients (n = 4404)	Period A 1987-1996 (n = 911)	Period B 1997-2006 (n = 1627)	Period C 2007-2016 (n = 1866)	Chi-square P value
Urgency (n = 3763)					.640
(Semi-)elective (>24 h)	98.0	97.6	98.0	98.0	
Urgent (<24 h)	2.0	2.4	2.0	2.0	
Concomitant cardiac procedure	46.3	42.4	46.3	48.3	.004
CABG	32.5	32.8	34.0	31.1	.226
1VD	41.2	45.2	39.1	41.1	.412
2VD	29.2	30.4	30.0	27.7	.362
3VD	29.7	24.4	30.9	31.2	.060
MV procedure	10.5	10.0	10.4	10.9	.465
TV procedure	2.6	1.0	2.1	3.8	<.001
MV and TV procedure	1.8	0.9	1.5	2.6	.001
Ascending aorta/arch replacement	3.0	0.3	2.6	4.5	<.001
Prosthesis type					<.001
Mechanical	47.8	81.2	46.1	32.9	
Biological	52.2	18.8	53.9	67.1	
Prosthesis size	23.6 ± 2.4	23.9 ± 2.2	23.7 ± 2.5	23.3 ± 2.3	<.001
19	3.9	1.6	3.0	5.8	<.001
21	22.6	19.3	21.8	24.9	.001
23	32.7	34.3	31.6	32.9	.630
25	24.9	28.1	24.2	23.9	.029
27	12.1	12.6	13.2	10.9	.106
29	3.5	3.6	5.8	1.4	<.001

Values are presented as percentages. CABG, Coronary artery bypass grafting; VD, vessel disease; MV, mitral valve; TV, tricuspid valve.

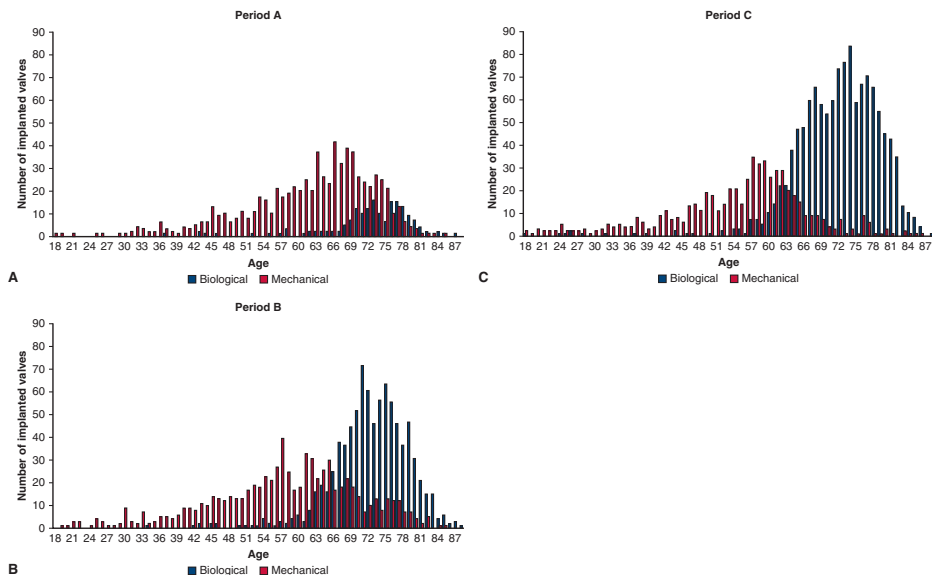


FIGURE 2. Mechanical and bioprosthetic valve use across 3 decades. Absolute number of bioprosthetic and mechanical valves implanted according to patient age and time of SAVR (period A: 1987-1996; B: 1997-2006; C: 2007-2016). Note the considerable increase in patients receiving bioprosthetic valves from period A to C and the decrease in mechanical valve use above the age of 65 years. The X-axis represents the age at SAVR.

Trends in 30-day mortality and long-term survival

The 30-day mortality in the overall cohort decreased from 2.7% in period A to 1.8% in period C ($P = .003$). The 30-day mortality across 3 decades decreased, nonsignificantly, from 1.9% to 0.9% ($P = .190$) for primary isolated SAVR, and from 4.1% to 3.0% ($P = .384$) for primary SAVR with CABG (Table E3). The 10-year survival was 59.8% in the overall cohort, 65.5% in the isolated SAVR cohort, and 51.1% in the SAVR with concomitant CABG group (Table 3).

From period A to C, 10-year survival did not change in the overall cohort and patients receiving isolated SAVR from 62.8% to 60.3% ($P = .051$) and 66.9% to 67.2%, respectively (Table 3). Further trends in 10-year survival in various subgroups are displayed in Table 3 and Figures E1 to E3. Further trends in survival are shown in Tables E4 and E5.

TABLE 3. Ten-year survival after primary surgical aortic valve replacement over three decades

	10-y survival				P value
	All patients	Period A 1987-1996	Period B 1997-2006	Period C 2007-2016	
Overall cohort	59.9	61.8	58.7	60.5	.243
Isolated SAVR	65.5	66.9	63.7	67.2	.312
SAVR + CABG	51.1	54.9	49.3	50.3	.352
SAVR + MV procedure	64.4	65.1	59.3	70.2	.253
Isolated SAVR					
≥70 y	48.8	49.7	47.5	50.2	.772
60-69 y	70.6	70.6	67.7	76.3	.323
50-59 y	81.3	76.4	80.9	85.6	.294
Mechanical	74.6	69.3	75.2	83.6	.001
Biological	55.7	56.6	53.6	58.7	.450
Female	66.7	66.7	65.7	66.8	.676
Male	64.6	67.0	62.0	67.8	.287
High-risk patients (LES ≥20)	40.0	N/A	45.5	30.6	.727
Intermediate-risk patients (LES 10-20)	47.3	N/A	42.2	54.2	.418
Low-risk patients (LES <10)	70.4	N/A	71.5	69.5	.671
SAVR with CABG					
≥70 y	41.0	40.2	39.2	44.5	.447
60-69 y	61.3	63.7	59.9	59.8	.909
50-59 y	75.5	80.6	77.8	62.6	.293
Mechanical	57.9	55.4	62.3	54.4	.381
Biological	46.8	53.3	43.2	49.5	.124
Female	48.0	51.4	45.6	49.3	.700
Male	52.6	56.6	51.0	50.7	.484
High-risk patients (LES ≥20)	23.6	N/A	20.0	24.6	.814
Intermediate-risk patients (LES 10-20)	46.1	N/A	37.6	52.4	.322
Low-risk patients (LES <10)	55.2	N/A	58.2	52.2	.412

Values are presented as percentages. SAVR, Surgical aortic valve replacement; CABG, coronary artery bypass grafting; MV, mitral valve; LES, logistic European System for Cardiac Operative Risk Evaluation; N/A, not available.

Relative survival

In the overall cohort, relative survival at 1, 5, 10, and 20 years was 95.7% (confidence interval [CI], 95.0-96.5), 95.4% (CI, 94.1-96.8), 85.8% (CI, 83.5-88.1), and 60.4% (CI, 55.9-65.2), respectively (Figure 3). In the cohort undergoing primary isolated SAVR, the relative survival was 98.1% (CI, 97.3-99.0), 99.9% (CI, 98.3-101.6), 92.4% (CI, 89.4-95.6), and 73.8% (CI, 67.1-81.1) at 1, 5, 10, and 20 years, respectively (Figure 4). In patients undergoing primary SAVR with CABG, the relative survival was 94.8% (CI, 93.2-96.4),

94.3% (95% CI, 91.6-97.3), 83.4% (95% CI, 78.5-88.4), and 41.6% (95% CI, 33.4- 52.0), at 1, 5, 10, and 20 years, respectively (Figure 5). Long-term actual and relative survivals in the overall cohort are shown in Figure 6.

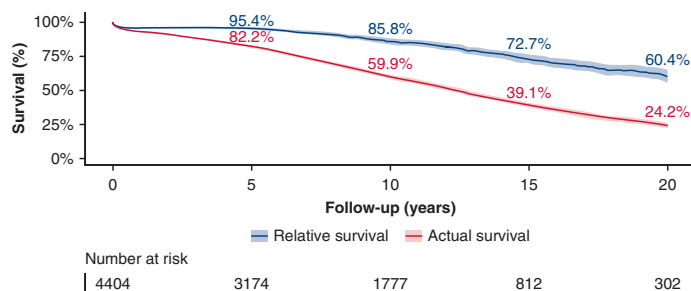


FIGURE 3. Long-term survival after SAVR. Actual survival of patients in the overall SAVR cohort (red line) and relative survival compared with the age-, gender-, and year-matched Dutch population (blue line). The relative survival after SAVR is approximately 85% at 10 and 60% at 20 years when compared with that of the matched general population.

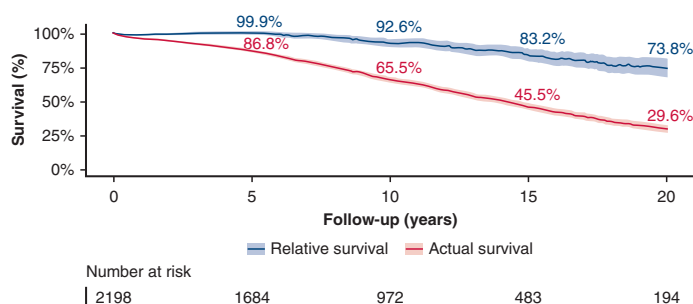


FIGURE 4. Long-term survival after primary isolated SAVR. Actual survival (red line) and relative survival compared with the age-, gender-, and year-matched population (blue line). Note the relative survival of 73.8% after primary isolated SAVR at 20 years.

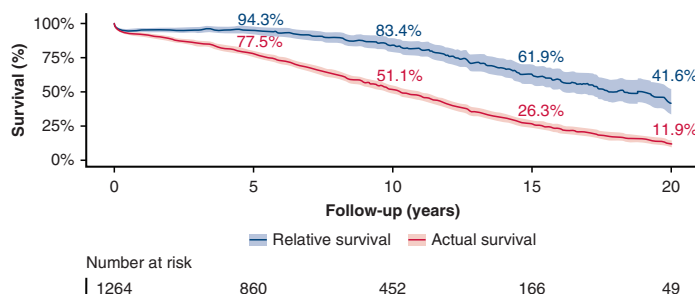


FIGURE 5. Long-term actual and relative survival after primary SAVR with concomitant CABG. Actual survival (red line) and relative survival compared with the age-, gender-, and year-matched population (blue line). Note the relative survival of 41.6% after SAVR with concomitant CABG at 20 years.

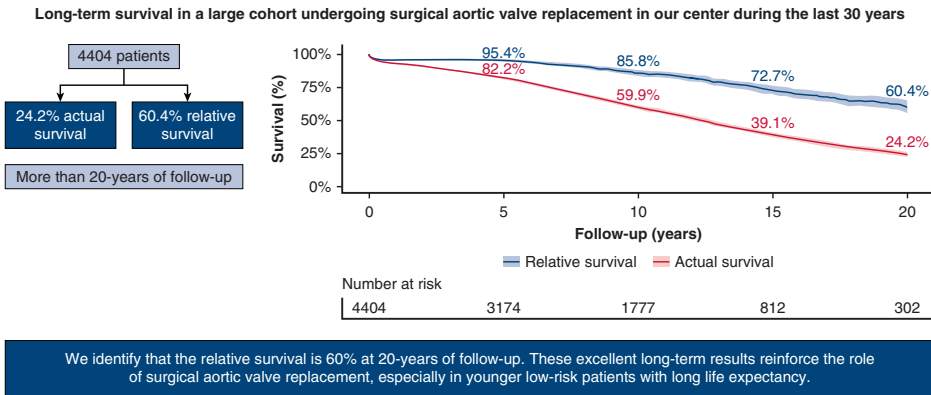


FIGURE 6. Long-term actual and relative survivals in the overall cohort. Long-term survival after SAVR. Actual survival of patients in the overall SAVR cohort (*red line*) and relative survival compared with the age-, gender-, and year-matched Dutch population (*blue line*). Note the relative survival of 85.8% at 10 and 60.4% at 20 years, respectively.

DISCUSSION

In this study, although the age, frequency of comorbid conditions, and complexity of patients undergoing SAVR increased over a 30-year period, the trends in 10-year survival remained stable or improved. Relative survival after SAVR was 85.8% (CI, 83.5-88.1) at 10 years. In patients undergoing primary isolated SAVR, the relative survival was 92.4% (CI, 89.4-95.6) and 73.8% (CI, 67.1-81.1) at 10 and 20 years, respectively. These excellent long-term results reinforce the role of SAVR in the treatment of aortic valve disease, especially in the younger low-risk patient population with long life expectancy and lower operative risk.

In our cohort, we saw a continuous increase in the number of patients undergoing SAVR. This increase is parallel to the growing number of SAVRs performed annually in Europe and the United States over the last decades,¹³ and is most likely a result of a combination of factors. The ageing of the population led to an increase in the prevalence of AS in the Western countries,^{14,15} and improvements in imaging might have led to an increase of patients being referred for SAVR.¹⁶ Simultaneously, expanding indications for SAVR and practice-related changes had a positive effect on the number of SAVRs performed.^{5,17} Of note, this trend might be halted by the growing use of TAVR in elderly patients, which can eventually lead to a decrease in the annual number of SAVRs, a recent trend already observed in some countries.^{18,19}

The increasing frequency of comorbidities in our patient population is in accordance with the previously described changes in the profile of patients undergoing cardiac surgery.²⁰ The prevalence of diabetes mellitus, hypercholesterolemia, and hypertension

has at least doubled during the 30-year observation period. Diabetes is associated with worse outcomes in patients undergoing cardiac surgery.²¹ Further, 31.1% of the patients in this study underwent concomitant CABG. Hypercholesterolemia and hypertension are well known to be associated with coronary artery disease. Coronary artery disease is present in up to 40% of the patients with AS undergoing SAVR and in up to 50% in SAVR patients aged 70 years or more.^{22,23} Patients with concomitant CABG reflect a population with more advanced heart disease and diminished life expectancy due to higher short- and long-term mortality compared with those undergoing isolated SAVR.²⁴ Likewise, patients requiring complex or multivalvular surgery represent a group with higher risk.²⁴⁻²⁶ These patients should be carefully selected and directed to high-volume centers.²⁵

Prosthesis choice is an important element of treatment decisions in aortic valve disease. Both mechanical and bioprosthetic valves are associated with inherent risks.²⁷ Mechanical valves require lifelong anticoagulation associated with bleeding events, and bioprosthetic valves are prone to degeneration, necessitating a second intervention in the long term.²⁸ In our study, a 4-fold increase in bioprosthetic valve use was observed over the last 3 decades, mimicking a worldwide trend.²⁸ The shift from mechanical to bioprosthetic valves was most prominent in patients aged 60 to 70 years.²⁹ Additionally, the age profile of SAVR patients changed considerably, with an increasing number of elderly patients undergoing SAVR. These patients form the bulk of the contemporary SAVR population and received almost exclusively a bioprosthetic valve. Although the first randomized controlled trial comparing bioprosthetic and mechanical valves showed better survival in patients receiving mechanical valves,³⁰ recent literature supports the benefit of bioprosthetic valves compared with mechanical valves in patients aged 60 years and older.^{28,31} Although younger patients might benefit from bioprosthetic valves, caution is warranted.³² Valve-in-valve TAVR in prospect might be an option when considering bioprosthetic valves in younger patients.^{33,34}

Despite the increasing patient age and complexity, the 30-day mortality decreased or remained stable over the 30-year observation period in the different cohorts. This may reflect advances in surgical technique and perioperative care over the last decades.³⁵ Although long-term actual survival after SAVR is influenced by the competing risk of mortality due to other factors, relative survival provides a good estimate of the disease- and intervention-related risks, because it compares the survival of the investigated population with the survival of the matched general population.³⁶ Glaser and colleagues³⁷ reported a relative survival of 97% and 88% at 5 and 10 years after SAVR, respectively, and Kvidal and colleagues²³ described a 74.9% relative survival at 15 years in a large SAVR cohort. In our study, the relative survival after isolated SAVR was similar to that of the age-, sex-, and year-matched Dutch population at 5 years, greater than 90% at 10 years, indicating an excellent long-term result. However, the decrease after-

ward in relative survival is not negligible and emphasizes the impact of disease- and intervention-related hazards in the extended long term.³⁷

The growing use of TAVR challenges the traditional role of SAVR in the treatment of aortic valve stenosis. In the light of recent trial results, the elderly SAVR population might have overlapping indications for both TAVR and SAVR in the future.^{7,8} In the current 5-year data regarding intermediate-risk patients with severe symptomatic aortic stenosis, there was no difference between the incidence of the composite end point of mortality and disabling stroke in patients receiving TAVR and SAVR, 47.9% and 43.4%, respectively.³⁸ The added value even translated to the low-risk population. Patients classified as low risk had noninferior outcomes regarding the composite end point of mortality and disabling stroke at 2 years of follow-up, 5.3% and 6.7% in TAVR and SAVR, respectively.⁸ Further research regarding the long-term durability of TAVR and the use of TAVR in specific patient groups, such as patients with high anatomic risk, including bicuspid morphology, dilated aortic root, heavy annular calcification, and expected future coronary access, remain warranted. Regular formal heart team discussions are recommended by the clinical guidelines.^{5,6} These meetings allow for informed decisions in a multidisciplinary setting, where the preferred intervention can be discussed on the basis of the individual patient profile, local resources and expertise, and the evidence available on procedure-related risks and long-term results.³⁹

Study limitations

The results presented are based on data from a single center in The Netherlands. As with all retrospective studies, inherent shortcomings related to data capture are present. In addition, our study evaluated only survival as a long-term clinical outcome, because other important clinical outcomes (eg, quality of life, structural valve dysfunction or valve-related thromboembolic, and bleeding events) were not captured in our database. The amount of patients with newer-generation valves such as sutureless valves is low, which might yield different outcomes. Other potential limitations include selective outcome reporting.

CONCLUSIONS

The present study demonstrates the patient-related changes over time in patients receiving SAVR and the excellent SAVR-related outcomes over the last 3 decades. Isolated SAVR has proven itself with excellent long-term relative survival (73.8% at 20 years in our study). The existing SAVR cohort overlaps with the expected future TAVR cohort; therefore, our findings may serve as a benchmark for future TAVR population studies.

Conflict of interest statement

The authors reported no conflicts of interest. The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

CENTRAL MESSAGE

In a large SAVR cohort, relative survival is close to 90% at 10 years. This excellent long-term result reinforces the role of SAVR, especially in younger low-risk patients with long life expectancy.

PERSPECTIVE

These excellent long-term results, especially in the younger low-risk patient population with long life expectancy and lower operative risk, reinforce the role of SAVR in the treatment of aortic valve disease and serve as a benchmark for future dedicated long-term TAVR studies.

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SUPPLEMENT

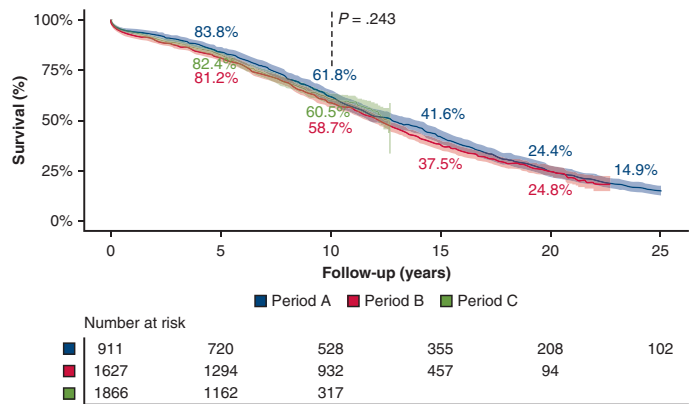


FIGURE E1. Long-term survival after SAVR in the overall cohort according to period operated. Actual survival of patients in the overall SAVR cohort. Patients operated between 1987 and 1996 (period A) are shown with the red line; patients operated between 1997 and 2006 (period B) are shown with the blue line; and patients operated between 2007 and 2017 (period C) are shown with the orange line. Comparison within periods is done for 10 years of follow-up and shown as P value.

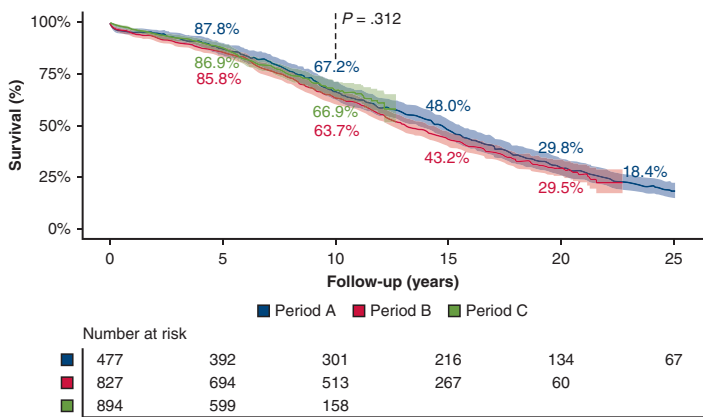


FIGURE E2. Long-term survival after primary isolated SAVR according to period operated. Actual survival of patients with primary isolated SAVR. Patients operated between 1987 and 1996 (period A) are shown with the red line; patients operated between 1997 and 2006 (period B) are shown with the blue line; and patients operated between 2007 and 2017 (period C) are shown with the orange line. Comparison within periods is done for 10 years of follow-up and shown as P value.

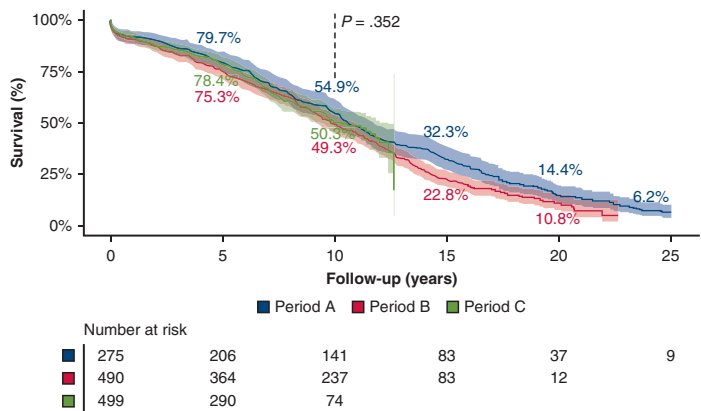


FIGURE E3. Long-term actual after primary SAVR with concomitant CABG according to period operated. Actual survival of patients with primary SAVR and concomitant CABG. Patients operated between 1987 and 1996 (period A) are shown with the *red line*; patients operated between 1997 and 2006 (period B) are shown with the *blue line*; and patients operated between 2007 and 2017 (period C) are shown with the *orange line*. Comparison within periods is done for 10 years of follow-up and shown as *P* value.

TABLE E1. Baseline and procedural characteristics over 3 decades in patients undergoing primary isolated surgical aortic valve replacement

	All patients (n = 2198)	Period A 1987-1996 (n = 477)	Period B 1997-2006 (n = 827)	Period C 2007-2016 (n = 894)	Chi-square P value
Age at operation, y (mean \pm SD)	65.0 \pm 12.0	63.7 \pm 10.7	65.1 \pm 12.4	65.5 \pm 12.3	.029
<40	3.6	2.9	3.9	3.8	.474
40-49	7.6	8.4	8.1	6.6	.188
50-59	15.8	16.8	15.5	15.7	.646
60-69	31.4	39.0	28.4	30.1	.004
70-79	35.0	31.0	36.9	35.3	.197
≥ 80	6.6	1.9	7.3	8.5	<.001
Female	41.1	38.8	45.6	38.1	.387
Indication (n = 2198)					
AS	68.2	56.8	67.2	75.3	<.001
AR	13.5	13.2	14.6	12.6	.606
Combined	18.1	29.8	18.1	11.7	<.001
Bicuspid aortic valve	20.9	35.2	20.4	13.8	<.001
Endocarditis	5.4	4.8	4.5	6.5	.120
Logistic euroSCORE (n = 1239) (median, IQR)	4.2 (2.4-7.0)	N/A	4.2 (2.2-7.2)	4.2 (2.4-6.9)	.965
Logistic euroSCORE ≥ 10 n (%)	12.7		16.2	11.3	.019
Logistic euroSCORE ≥ 20 n (%)	3.0		3.2	2.9	.795
Previous cardiac operation	6.3	6.5	7.0	5.6	.400
Creatinine ≥ 2 mg/dL	2.3	2.1	1.9	2.7	.400
Previous hemodialysis	0.7	0.4	0.6	0.9	.287
Atrial fibrillation	12.9	13.8	13.3	12.1	.325
Diabetes mellitus	12.3	7.8	8.9	17.9	<.001
Cardiac decompensation	14.2	23.1	12.7	10.9	<.001
Hypertension	34.4	22.4	28.4	46.4	<.001
Hypercholesterolemia	15.2	5.0	12.3	23.3	<.001
Previous myocardial infarction	5.6	5.5	4.4	6.7	.187
Previous PCI	5.7	1.9	4.2	9.2	<.001
COPD	11.2	9.0	11.1	12.5	.051
History of cancer	6.7	2.1	7.3	8.7	<.001
Stroke	8.4	4.0	8.0	11.1	<.001
Arterial disease	3.0	1.0	2.5	4.5	<.001
Peripheral	2.6	1.0	2.3	3.8	.002
Carotid	0.5	0	0.4	0.8	.035

TABLE E1. Baseline and procedural characteristics over 3 decades in patients undergoing primary isolated surgical aortic valve replacement (*continued*)

	All patients (n = 2198)	Period A 1987-1996 (n = 477)	Period B 1997-2006 (n = 827)	Period C 2007-2016 (n = 894)	Chi-square P value
LVEF (n = 2006)					
Good	81.8	78.4	82.8	82.4	.161
Reduced	14.9	15.1	14.7	14.8	.933
Severely reduced	3.3	6.5	2.5	2.8	.005
Urgency (n = 1942)					.910
(Semi-) Elective (>24 h)	98.7	98.6	1.3	1.3	
Urgent (<24 h)	1.3	1.4	98.7	98.7	
Prosthesis type					<.001
Mechanical	48.8	82.0	46.9	32.9	
Bioprosthetic	51.2	18.0	53.1	67.1	
Prosthesis size	23.6 ± 2.4	24.0 ± 2.3	24.0 ± 2.5	23.1 ± 2.3	<.001
19	3.9	1.5	2.3	6.7	<.001
21	22.5	17.9	20.7	26.7	<.001
23	32.0	32.8	30.7	32.7	.884
25	24.9	30.5	24.8	22.1	.001
27	11.9	12.2	13.9	10.0	.106
29	4.4	5.0	7.0	1.6	<.001

Values are presented as n (%) or as mean ± SD or median (interquartile range) if otherwise stated. *SD*, Standard deviation; *AS*, aortic stenosis; *AR*, aortic regurgitation; *euro-SCORE*, European System for Cardiac Operative Risk Evaluation; *IQR*, interquartile range; *N/A*, not available; *PCI*, percutaneous coronary intervention; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricular ejection function.

TABLE E2. Baseline and procedural characteristics over three decades in patients undergoing isolated surgical aortic valve replacement + coronary artery bypass grafting

	All patients (n = 1264)	Period A 1987-1996 (n = 275)	Period B 1997-2006 (n = 490)	Period C 2007-2016 (n = 499)	Chi-square P value
Age at operation, y (mean ± SD)	70.1 ± 8.3	68.5 ± 8.0	70.0 ± 8.5	71.0 ± 8.2	<.001
40-49	2.5	1.8	3.3	2.2	.938
50-59	9.2	13.1	9.4	6.8	.004
60-69	29.9	35.3	26.1	30.7	.376
70-79	48.1	44.4	52.7	45.7	.897
≥80	10.3	5.5	8.6	14.6	<.001
Female	30.1	33.5	32.0	26.3	.023
Indication (n = 1264)					
AS	80.2	70.2	80.8	85.2	<.001
AR	8.8	9.1	9.2	8.2	.632
Combined	10.9	20.4	10.0	6.6	<.001
Bicuspid aortic valve	10.5	19.3	9.0	7.2	<.001
Endocarditis	1.5	2.2	1.6	1.0	.186
Logistic euroSCORE (n = 697) (median, IQR)	5.3 (3.3-8.7)	N/A	5.5 (3.7-8.4)	5.3 (3.2-8.9)	.977
Logistic euroSCORE ≥10 n (%)	19.1		17.7	19.6	.552
Logistic euroSCORE ≥20 n (%)	5.6		5.1	5.8	.694
Previous cardiac operation	5.5	8.7	6.3	2.8	<.001
Creatinine ≥2 mg/dL	2.8	2.5	2.7	3.0	.686
Previous hemodialysis	0.9	1.1	0.6	1.0	.984
Atrial fibrillation	12.5	13.1	12.0	12.6	.911
Diabetes mellitus	21.2	8.0	20.0	29.7	<0.001
Cardiac decompensation	15.6	18.5	16.3	13.2	.043
Hypertension	41.2	22.5	31.4	61.1	<.001
Hypercholesterolemia	21.8	6.9	17.8	34.1	<.001
Previous myocardial infarction	24.4	20.0	24.7	26.7	.046
Previous PCI	10.2	5.8	7.3	15.4	<.001
COPD	9.9	7.3	8.6	12.6	.010
History of cancer	7.5	3.3	6.1	11.2	<.001
Stroke	9.3	4.7	8.2	12.8	<.001
Arterial disease	8.4	5.8	6.5	11.6	.002
Peripheral	7.2	5.5	5.7	9.6	.016
Carotid	1.5	0.4	1.4	2.2	.044
LVEF (n = 1185)					

TABLE E2. Baseline and procedural characteristics over three decades in patients undergoing isolated surgical aortic valve replacement + coronary artery bypass grafting (*continued*)

	All patients (n = 1264)	Period A 1987-1996 (n = 275)	Period B 1997-2006 (n = 490)	Period C 2007-2016 (n = 499)	Chi-square P value
Good	75.7	75.8	76.8	74.5	.589
Reduced	20.5	17.8	19.7	22.6	.114
Severely reduced	3.8	6.4	3.5	2.9	.033
Urgency (n = 1104)					.536
(Semi-) Elective (>24 h)	98.6	99.4	98.5	98.5	
Urgent (<24 h)	1.4	0.6	1.5	1.5	
Prosthesis type					<.001
Mechanical	36.1	74.9	32.2	18.4	
Biological	63.9	25.1	67.8	81.6	
Prosthesis size	23.5 ± 2.2	23.6 ± 2.1	23.7 ± 2.3	23.2 ± 2.1	.003
19	3.8	2.2	2.4	6.0	.003
21	21.6	20.0	21.8	22.2	.495
23	35.5	38.9	34.5	34.7	.296
25	26.3	24.7	24.9	28.7	.181
27	10.9	12.7	13.5	7.4	.008
29	1.5	1.5	2.2	0.8	.307

SD, Standard deviation; AS, aortic stenosis; AR, aortic regurgitation; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; N/A, not available; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection function.

TABLE E3. Thirty-day mortality after primary surgical aortic valve replacement over 3 decades

	30-d mortality				P value
	All patients	Period A 1987-1996	Period B 1997-2006	Period C 2007-2016	
Overall cohort	2.7 (4157)	2.7 (837)	3.7 (1555)	1.8 (1765)	.003
Isolated SAVR	1.5 (2198)	1.9 (477)	1.8 (827)	0.9 (894)	.190
SAVR + CABG	3.9 (1264)	4.1 (275)	4.7 (490)	3.0 (499)	.384
SAVR + MV procedure	4.8 (235)	3.8 (57)	7.7 (92)	2.3 (86)	.220
Isolated SAVR					
≥70 y	2.5 (914)	3.8 (157)	3.0 (365)	1.5 (392)	.224
60-69 y	0.1 (690)	0.5 (186)	0 (235)	0 (269)	.258
50-59 y	1.7 (348)	2.5 (80)	1.6 (128)	1.4 (140)	.811
Mechanical	1.7 (1073)	2.1 (391)	2.1 (388)	0.7 (294)	.293
Biological	1.3 (1125)	1.2 (86)	1.6 (439)	1.0 (600)	.700
Female	1.3 (903)	2.2 (185)	1.9 (377)	0.3 (341)	.104
Male	1.5 (1295)	1.7 (292)	1.8 (450)	1.3 (553)	.776
High-risk patients (LES ≥20)	8.3 (37)	N/A	9.1 (11)	7.9 (26)	.936
Intermediate-risk patients (LES 10-20)	2.5 (120)	N/A	2.2 (45)	2.7 (75)	.873
Low-risk patients (LES<10)	0.7 (1082)	N/A	1.1 (289)	0.5 (793)	.302
SAVR with CABG					
≥70 y	4.8 (738)	5.2 (137)	5.3 (300)	4.0 (301)	.719
60-69 y	2.7 (378)	3.2 (97)	3.9 (128)	1.3 (153)	.380
50-59 y	0.9 (116)	0 (36)	2.2 (46)	0 (34)	.467
Mechanical	4.6 (456)	4.9 (206)	4.5 (158)	4.3 (92)	.975
Biological	3.5 (808)	1.4 (69)	4.8 (332)	2.7 (407)	.184
Female	4.8 (380)	4.4 (92)	5.1 (157)	4.6 (131)	.957
Male	3.5 (884)	3.9 (183)	4.5 (333)	2.5 (368)	.325
High-risk patients (LES ≥20)	12.8 (39)	N/A	10.0 (10)	13.8 (29)	.742
Intermediate-risk patients (LES 10-20)	5.4 (94)	N/A	4.0 (25)	5.9 (69)	.725
Low-risk patients (LES<10)	2.1 (564)	N/A	3.1 (163)	1.8 (401)	.323

Values are given in percentages with (number of patients). SAVR, Surgical aortic valve replacement; CABG, coronary artery bypass grafting; MV, mitral valve; LES, logistic European System for Cardiac Operative Risk Evaluation; N/A, not available.

TABLE E4. 1-y survival after primary surgical aortic valve replacement over 3 decades

	1-y survival				P value
	All patients	Period A 1987-1996	Period B 1997-2006	Period C 2007-2016	
Overall cohort	93.5	94.4	92.0	94.4	.012
Isolated SAVR	95.7	95.7	94.7	96.6	.154
SAVR + CABG	91.5	91.7	90.8	92.1	.727
SAVR + MV procedure	89.9	94.3	83.2	94.1	.026
Isolated SAVR					
≥70 y	93.5	92.3	92.0	95.4	.133
60-69 y	98.2	98.9	97.4	98.5	.484
50-59 y	95.9	94.8	96.1	96.4	.831
Mechanical	95.9	95.3	95.6	97.3	.376
Biological	95.5	97.6	94.0	96.3	.131
Female	95.9	94.5	94.6	98.2	.027
Male	95.6	96.5	94.8	95.7	.574
High-risk patients (LES ≥20)	89.0	N/A	90.9	88.1	.797
Intermediate-risk patients (LES 10-20)	94.2	N/A	93.3	94.7	.780
Low-risk patients (LES<10)	97.3	N/A	97.9	97.1	.491
SAVR with CABG					
≥70 y	89.4	89.3	88.3	90.6	.639
60-69 y	94.1	93.6	93.7	94.7	.913
50-59 y	96.6	97.2	97.8	94.1	.647
Mechanical	91.3	90.5	93.0	90.2	.659
Biological	91.6	95.6	89.7	92.6	.185
Female	91.7	92.1	93.6	89.2	.432
Male	91.5	91.6	89.5	93.2	.215
High-risk patients (LES ≥20)	76.9	N/A	90.0	72.4	.282
Intermediate-risk patients (LES 10-20)	89.2	N/A	91.8	88.3	.628
Low-risk patients (LES<10)	94.1	N/A	93.8	94.2	.841

SAVR, Surgical aortic valve replacement; CABG, coronary artery bypass grafting; MV, mitral valve; LES, logistic European System for Cardiac Operative Risk Evaluation; N/A, not available.

TABLE E5. Five-year survival after primary surgical aortic valve replacement over 3 decades

	5-y survival				P value
	All patients	Period A 1987-1996	Period B 1997-2006	Period C 2007-2016	
Overall cohort	82.4	84.5	80.9	82.9	.059
Isolated SAVR	86.8	86.9	85.8	87.8	.454
SAVR + CABG	77.5	79.7	75.3	78.4	.301
SAVR + MV procedure	79.3	82.8	73.0	84.6	.143
Isolated SAVR					
≥70 y	81.2	79.9	80.3	82.6	.624
60-69 y	89.6	91.4	87.8	89.8	.471
50-59 y	91.4	86.9	91.3	94.0	.210
Mechanical	89.7	87.2	89.2	93.9	.019
Biological	84.0	85.6	82.9	84.7	.618
Female	88.8	86.0	87.3	92.1	.049
Male	85.5	87.4	84.6	85.1	.546
High-risk patients (LES ≥20)	75.6	N/A	81.8	71.5	.559
Intermediate-risk patients (LES 10-20)	78.7	N/A	80.0	78.0	.766
Low-risk patients (LES<10)	89.1	N/A	89.0	89.2	.928
SAVR with CABG					
≥70 y	71.9	72.4	69.2	74.4	.343
60-69 y	84.1	84.1	84.1	84.1	>.999
50-59 y	90.3	94.4	88.9	87.4	.596
Mechanical	81.2	80.2	83.2	79.7	.716
Biological	75.3	78.3	71.5	78.1	.097
Female	80.0	81.3	80.7	78.2	.813
Male	76.4	79.0	72.7	78.5	.120
High-risk patients (LES ≥20)	50.4	N/A	40.0	54.7	.694
Intermediate-risk patients (LES 10-20)	73.1	N/A	66.8	75.3	.431
Low-risk patients (LES<10)	81.0	N/A	81.3	80.8	.947

SAVR, Surgical aortic valve replacement; CABG, coronary artery bypass grafting; MV, mitral valve; LES, logistic European System for Cardiac Operative Risk Evaluation; N/A, not available.

6

Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections.

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Eur Heart J. 2018 Jul 21;39(28):2635-2642.

ABSTRACT

Aims

The number of transcatheter aortic valve implantation (TAVI) procedures is rapidly increasing. This has a major impact on health care resource planning. However, the annual numbers of TAVI candidates per country are unknown. The aim of this study was to estimate current and future number of annual TAVI candidates in 27 European countries, the USA and Canada.

Methods and results

Systematic literature searches and meta-analyses were performed on aortic stenosis (AS) epidemiology and decision-making in severe symptomatic AS. The incidence rate of severe AS was determined. Findings were combined with population statistics and integrated into a model employing Monte Carlo simulations to predict the annual number of TAVI candidates. Various future scenarios and sensitivity analyses were explored. Data from 37 studies ($n = 26\,402$) informed the model. The calculated incidence rate of severe AS was 4.4‰/year [95% confidence interval (95% CI) 3.0–6.1‰] in patients ≥ 65 years. AS-related symptoms were present in 68.3% (95% CI 60.8–75.9%) of patients with severe AS. Despite having severe symptomatic AS, 41.6% (95% CI 36.9–46.3%) did not undergo surgical aortic valve replacement. Of the non-operated patients, 61.7% (95% CI 42.0–81.7%) received TAVI. The model predicted 114 757 (95% CI 69 380–172 799) European and 58 556 (95% CI 35 631–87 738) Northern-American TAVI candidates annually.

Conclusion

Currently, approximately 180 000 patients can be considered potential TAVI candidates in the European Union and in Northern-America annually. This number might increase up to 270 000 if indications for TAVI expand to low-risk patients. These findings have major implications for health care resource planning in the 29 individual countries.

Keywords: Aortic valve stenosis • Epidemiology • Incidence • Transcatheter aortic valve implantation

INTRODUCTION

The growing elderly population and the concomitant age-related high prevalence of degenerative aortic stenosis (AS) have a major impact on society.^{1,2} Historically, a considerable proportion of patients with severe AS were denied surgical treatment due to advanced age and elevated operative risk. More recently, transcatheter aortic valve implantation (TAVI) has emerged as the preferred management strategy for inoperable and high-risk patients, and consequently procedural volume has grown exponentially in recent years.³ This has important implications for health care resource planning. Our group previously estimated the number of potential high- and excessiverisk TAVI candidates based on practice patterns at that time.⁴ Since then, transfemoral TAVI has been shown to be non-inferior to surgical aortic valve replacement (SAVR) among intermediate-risk patients.⁵⁻¹²

Considering the results of the recent trials suggesting the extension of TAVI to patients at intermediate operative risk, our objectives were; (i) assess the prevalence of AS in patients above 65 years old; (ii) to systematically estimate the annual number of potential TAVI candidates under current practice, assuming unrestricted TAVI availability; and (iii) to predict the annual number of potential TAVI candidates if this technology further extends into low operative risk patients with severe AS.

METHODS

Literature search

Separate systematic literature searches on the prevalence, symptom status, and clinical decision-making in severe AS were performed using Medline, Embase®, and Cochrane databases in January 2017. Prespecified literature search strategies, without time restriction, were constructed using the following search terms: 'valvular heart disease', 'heart valve disease', 'aortic stenosis', 'aortic valve stenosis', 'prevalence', 'symptoms', 'symptomatic', 'asymptomatic', 'decision making', 'treatment decision' and 'heart team'. The literature search was carried out independently by two investigators (A.P.D. and M.M.) and targeted full-length articles published in peer-reviewed journals and congress abstracts. Relevant articles identified by cross-referencing were added manually. After duplicate removal in EndNote, all references were first screened for title and abstract, applying the following eligibility criteria: (i) prevalence: population above 65 years, AS severity assessed by echocardiography; (ii) symptoms: reporting of AS-related symptoms in those with severe AS; (iii) decision-making: studies reporting the current TAVI era decision-making process in severe AS. After screening, full-length manuscripts were carefully assessed for eligibility. The echocardiographic definition of AS was extracted from all studies, along

with other essential information related to study design, including country, population characteristics, and risk categorization. The diagnosis of severe AS had to be aligned with contemporary guidelines: maximum jet velocity (V_{\max}) $\geq 4.0\text{m/s}$; aortic valve area (AVA) $\leq 1.0\text{ cm}^2$; mean gradient $\geq 40\text{mmHg}$.^{12,13} The search on clinical decision-making in AS was directed to identify studies focusing on (i) the proportion of patients declined SAVR in the pre-TAVI era, and (ii) the proportion of patients treated with TAVI or medical therapy if declined SAVR. Data detailing the risk distribution among SAVR patients and contemporary TAVI utilization were also collected.

Analysis

Meta-analyses were performed to create a pooled estimate for each specific question regarding AS epidemiology and clinical decision-making. Fixed- and random-effects models were used, applying the inverse variance method and the DerSimonian and Laird methods for the fixed- and random-effect analyses, respectively. Heterogeneity was tested by Cochran Q test and I^2 statistics. The exact method was used to calculate the 95% binomial confidence intervals for proportions derived from the included studies. Results were presented as Forest plots. All statistical analyses were performed using Stata software (version 12.0, StataCorp, College Station, TX, USA).

To estimate the number of annual TAVI candidates, first the annual number of newly diagnosed cases of severe symptomatic AS was determined. As prevalence is less useful in this regard, we determined the yearly incidence rate using the following equation: (Incidence rate) = (Prevalence)/(Average untreated disease duration). Prevalence was based on epidemiological reports on AS in the general population.^{1,2,14–16} Average disease duration to death was determined using reports on the survival of untreated cases of severe symptomatic AS.¹⁷

A decision-making flowchart was built in TreeAge Pro (version 2016, TreeAge Software, Williamstown, MA, USA). Sequential steps of the flowchart were informed with distributions derived from the metaanalyses. Latest available census data on the population aged 65 years or older were collected for the USA, Canada, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the UK.^{18–20} Beta distributions were utilized at each step of the model and per-country estimates were determined using 10 000 Monte Carlo simulations. Results are presented as numbers of annual TAVI candidates per country along with their 95% confidence intervals (95% CI). When estimating the number of potential annual candidates in individual countries, local reimbursement policies were not considered, and unlimited TAVI availability was assumed.

Scenario and sensitivity analyses

To make future estimates, two scenario analyses were performed. Scenario 1: TAVI will be the treatment of choice in intermediate-risk patients, while SAVR–TAVI distribution in the low-risk group remains unchanged. Scenario 2: TAVI will become the treatment of choice in intermediate-risk patients and elderly (>75 years) low-risk SAVR candidates (representing approximately 50% of the low-risk population) will become TAVI candidates as well. The impact of prevalence and average disease duration on the annual numbers of the European and Northern- American candidates were assessed in separate sensitivity analyses.

RESULTS

Epidemiology of symptomatic severe aortic stenosis

The search on AS prevalence generated 5355 articles (Figure 1). After duplicate removal, 4996 records were screened for title/abstract, and 145 were assessed for eligibility. Forty-one were included in the qualitative synthesis and finally five in the meta-analysis.

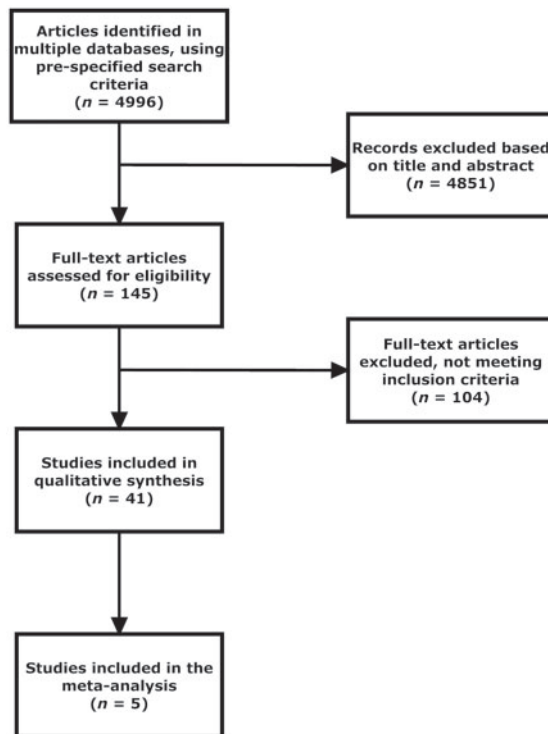


Figure 1 Flowchart of study selection.

The included studies reported on 16 514 patients from three continents. Studies were heterogeneous, especially with respect to age and echocardiographic definitions of AS. Study details are summarized in Supplementary material online, Table S1.

Heterogeneity was considerable after performing the metaanalysis [$I^2=89.0\%$, $Q=36.3$, $P<0.001$ (Supplementary material online, Figure S1)]. The largest study specifically reporting AS prevalence in subjects ≥ 65 years was used in the decision-making model.² In a population of 13 349 patients, Nkomo reported a 0.8% (95% CI 0.7–1.0%) prevalence of severe AS (Nkomo, personal communication). This value was used for incidence rate calculations, and when divided by an average disease duration of 1.8 years,¹⁷ corresponded to an incidence rate of 4.4%/year (95% CI 3.0–6.1‰).

Annual candidates for transcatheter aortic valve implantation

The number of potential annual TAVI candidates was estimated using the model presented in Figure 2. This model was informed by the results of separate meta-analyses (Figures 3 and 4).

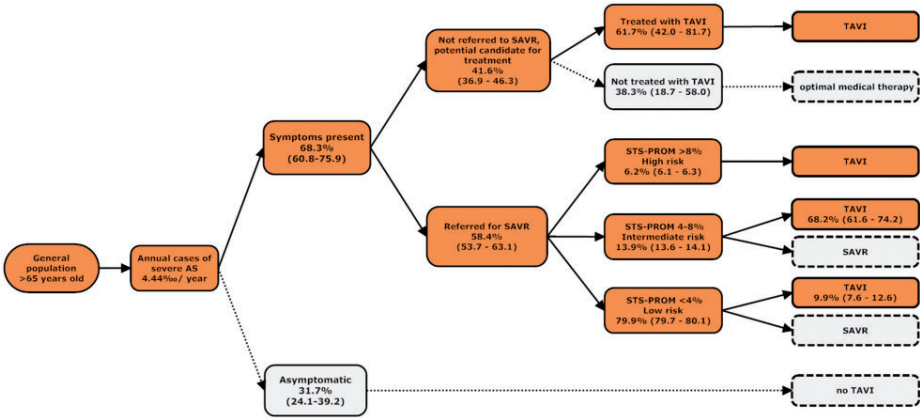


Figure 2 Model for the estimation of annual transcatheter aortic valve implantation candidates. AS, aortic stenosis; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

Based on the analysis of 14 studies, we estimate that 68.3% (95% CI 60.8–75.9%) of patients with severe AS were symptomatic (Figure 3A, Supplementary material online, Table S2). Analysis of 20 studies (Supplementary material online, Table S3) revealed that in the pre-TAVI era, 41.6% (95% CI 36.9–46.3%) of all severe symptomatic AS patients did not receive SAVR (Figure 3B). These patients were deemed to be possible TAVI candidates, though importantly an analysis of nine studies (Supplementary material online, Table S4) reporting on contemporary decision-making in this population demonstrated that 38.3% (95% CI 18.7–58.0%) of these patients were not offered TAVI and were assigned

to medical therapy only. There was substantial variability among different countries in offering TAVI to inoperable patients (Figure 4).

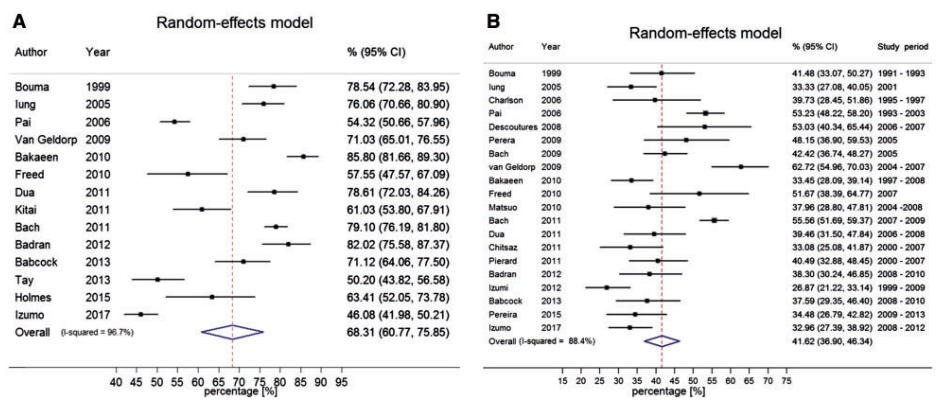


Figure 3 Forest plots of the different steps in the model. (A) Prevalence of symptoms in patients with severe aortic stenosis. (B) Percentage of patients not receiving surgical aortic valve replacement despite having severe symptomatic aortic stenosis. AS, aortic stenosis; CI, confidence interval; SAVR, surgical aortic valve replacement.

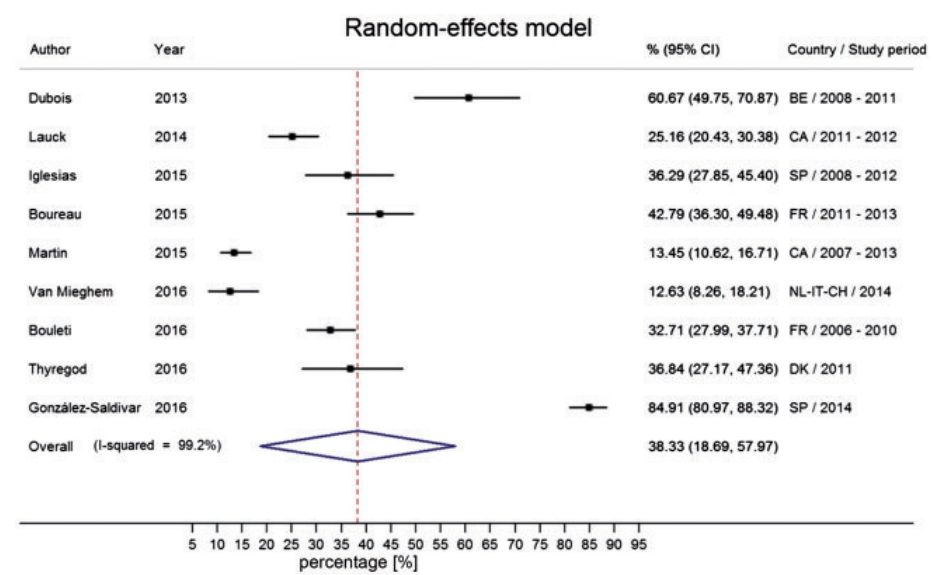


Figure 4 Percentage of patients not considered for surgical aortic valve replacement, who are also not treated with transcatheter aortic valve implantation. BE, Belgium; CA, Canada; CH, Switzerland; CI, confidence interval; DK, Denmark; FR, France; IT, Italy; NL, Netherlands; SAVR, surgical aortic valve replacement; SP, Spain; TAVI, transcatheter aortic valve implantation.

Large studies from both Europe and Northern-America confirmed that most patients undergoing SAVR are at low risk.^{21,22} In the Society of Thoracic Surgeons (STS) data set comprising 141 905 patients undergoing SAVR, 6.2% (95% CI 6.1–6.3%), 13.9% (95% CI 13.8– 14.1%), and 79.9% (95% CI 79.7–80.1%) of all patients were at high (STS-PROM> 8%), intermediate (4–8%), and low (<4%) operative risk.

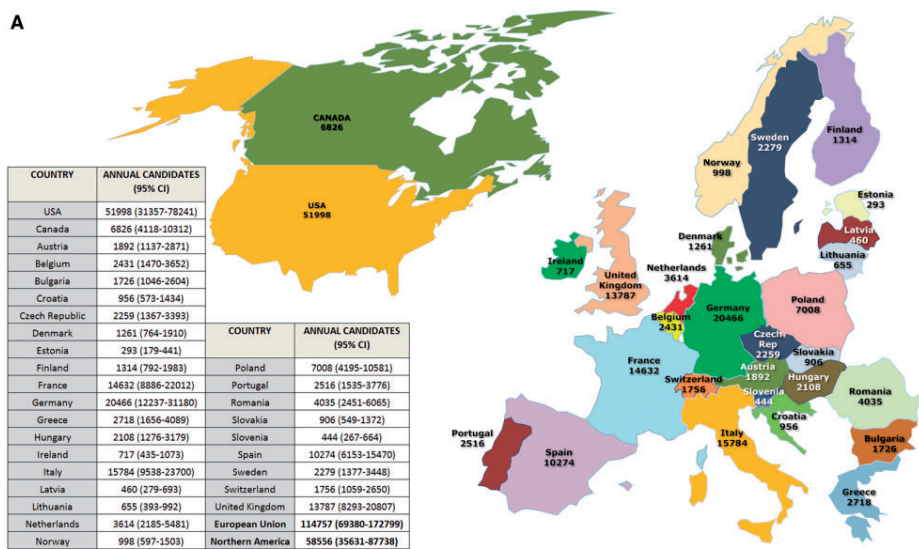
A recent study from Denmark reported that among the severe symptomatic AS population traditionally treated with SAVR, 100% of high-risk, 68.2% (95% CI 61.6–74.2%) of intermediate-risk, and 9.9% (95% CI 7.8–12.6%) of low-risk patients undergo TAVI.²³

Ultimately, our model estimated the number of potential TAVI candidates to be 114 757 (95% CI 69 380–172 799) in Europe and 58 556 (95% CI 35 631–87 738) in Northern-America per annum (Take home figure, A).

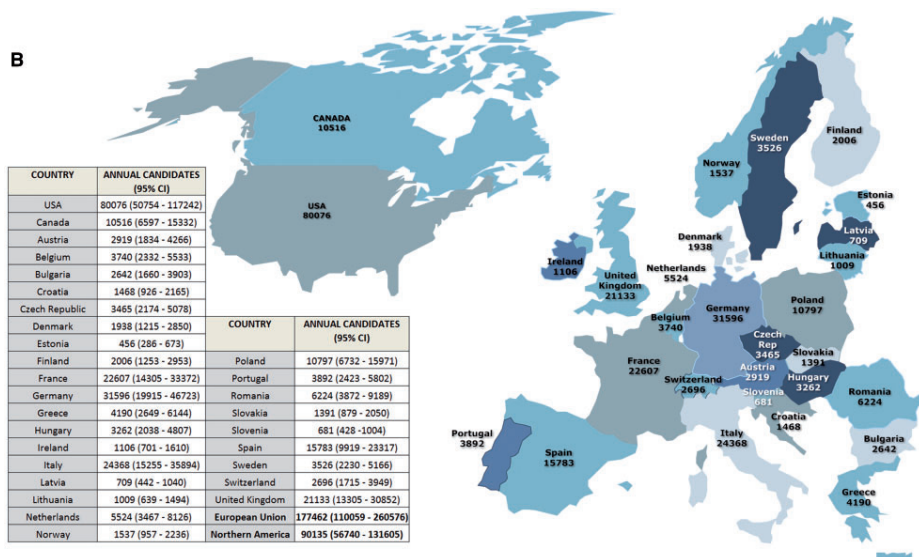
Scenario and sensitivity analyses

In Scenario 1, where all intermediate-risk patients receive TAVI while SAVR remains the preferred treatment for low-risk patients, the annual number of potential TAVI candidates would increase only by 7%, meaning 122 402 (95% CI 74 208–185 127) annual candidates in Europe and 62 467 (95% CI 38 170–93 322) in Northern-America (Supplementary material online, Figure S2). In Scenario 2, if TAVI becomes the choice of treatment for all intermediate-, and for elderly low-risk patients, the model predicted a 50% further increase in annual candidates compared to the base case analysis [177 462 (95% CI 110 059–260 576) and 90 135 (95% CI 56 740–131 605) for Europe and Northern-America, respectively]. The per-country estimates for Scenario 2 are demonstrated in Take home figure, B. Sensitivity analyses on the impact of average disease duration and prevalence are displayed in Supplementary material online, Figure S3.

A



B



Take home figure Estimated annual numbers of transcatheter aortic valve implantation candidates in different countries. (A) Under current indications; (B) if transcatheter aortic valve implantation indications expand into the low-risk category.

DISCUSSION

In this meta-analysis and modelling study, we estimate a yearly incidence rate of severe AS of 4.4%/year in the general population ≥ 65 years of age. Approximately 40% of symptomatic severe AS patients do not undergo SAVR. Although the policy of offering

TAVI is highly variable among different countries, approximately 60% of these inoperable patients can be considered potential TAVI candidates. Among patients traditionally treated with SAVR, a substantial number are now considered potential TAVI candidates, predominantly in the high- and intermediate-risk category. Based on epidemiological data and decision-making studies, there are approximately 115 000 and 58 000 annual candidates for TAVI in the EU and in Northern-America, respectively.

These findings have a major impact on health care resource planning. Knowing the number of potential candidates aid health care systems preparing for the future needs. Human resource and hospital volume requirements can be forecasted, along with the expected budgetary requirements.²⁴ Moreover, these numbers help the industry tailor their production capacity to the future demands.

Epidemiology of severe symptomatic aortic stenosis

The prevalence of severe AS is largely age-dependent, with a marked increase ≥ 75 years of age.^{1,2} Logically, the same correlation is true for incidence rate. The 0.8% prevalence of severe AS might seem relatively low compared to other reports.^{14–16} This reflects the fact that prevalence was determined in a larger population (≥ 65 years) containing fewer elderly (≥ 75 years) subjects. Additionally, epidemiological studies often only report the combined prevalence of moderate-severe AS, while we used a more strict AS definition.² To eliminate the effect of heterogeneity observed in the studies reporting AS prevalence (Supplementary material online, Figure S1), we decided to use only the largest and most reliable study for the model. This decision conferred the further advantage of determining the prevalence and average disease duration of AS in the same, US population. In addition, it is reassuring that the calculated incidence rate of 4.4‰/year used in this study is in harmony with the only previous report on severe AS incidence from the Tromsø study (4.9 ± 0.81 ‰/ year).¹

Under-treatment and under-diagnosis of aortic stenosis

A sizeable number of patients with the diagnosis of severe symptomatic AS are not treated invasively. Recent data from the OxVALVE Population Cohort Study (Oxfordshire, UK) suggest that AS is underdiagnosed in some cases.²⁵ In this population-based study, involving 2500 individuals aged ≥ 65 years, participants were screened for undiagnosed valvular heart disease with transthoracic echocardiography. Although subjects with pre-existing valvular heart disease were excluded, a considerable number of AS patients were identified, predominantly in the lower socioeconomic classes. Based on these findings, the ‘therapeutic gap’ in AS might be even larger than previously anticipated.

Current and future trends in the numbers of candidates for invasive treatment

The annual number of TAVI procedures has been growing since its introduction, while at the same time the number of annual SAVR procedures remained more or less unchanged, or even increased.^{26–28} However, now TAVI has been demonstrated to be non-inferior to SAVR in intermediate-risk patients this trend is changing and in some countries, annual TAVI numbers are exceeding the number of isolated SAVRs.^{8–12,29,30} Ongoing randomized-controlled trials are investigating TAVI in the low-risk group (PARTNER 3, NOTION-2, Medtronic Transcatheter Aortic Valve Replacement in Low Risk Patients; clinicaltrials.gov identifiers: NCT02675114, NCT02825134, and NCT02701283, respectively). The vast majority (80%) of AS patients currently treated with SAVR belong to this low-risk category.²² If results of these trials favour TAVI over SAVR, this will fundamentally change the number of annual TAVI candidates, as represented in our scenario analyses. Currently, aortic valve replacement is only indicated in asymptomatic AS if strict criteria are met.^{11–13} Recently, a multi-centre, randomized-controlled trial (EARLY TAVR, clinicaltrials.gov identifier: NCT03042104) was launched to compare TAVI and watchful waiting in patients with asymptomatic severe AS. Evidence favouring early TAVI in this group would result in a substantial increase in annual TAVI numbers. Beside this, current trends of increased bioprosthetic surgical heart valve utilization in younger patients will likely lead to growing numbers of valve-in-valve procedures in the future.

Factors limiting the expansion of transcatheter aortic valve implantation

There are several factors that might constrain expansion of TAVI. First of all, data on the long-term durability of transcatheter prostheses are still in accumulation.^{31–36} Unfavourable long-term results may prevent the expansion of TAVI indications towards the younger or lower-risk groups of patients. Additionally, in certain patient groups, mechanical prosthesis will remain the preferred option for aortic valve replacement.³⁷

Secondly, TAVI may be futile in some patients because of severe comorbidities precluding quality-of-life improvement or survival benefits.³⁸ It is important to assess the expected benefit for the individual patient in the Heart Team.³⁹

Moreover, health economic considerations and reimbursement decisions play a role in TAVI expansion.^{40–43} The cost-effectiveness profile of TAVI vs. SAVR in low-risk patients is unknown. The added benefits of TAVI in terms of quality-of-life and survival need to justify the higher costs. Both the effectiveness and costs in low-risk patients need to be studied carefully. Importantly, the large number of current and potential TAVI candidates presented in this study has a large budget impact on health care systems. Both cost-effectiveness and health care budget impact studies at national levels need to be considered in reimbursement policy decisions.

Study limitations

The use of a model based on currently available literature, containing multiple steps to estimate numbers has its inherent limitations. The determination of AS-related symptoms and SAVR- or TAVI-eligibility were based on the decision of individual physicians in each included study. The assessment of heterogeneity in the meta-analyses, and the confidence intervals—determined at each step in the model and presented along the final estimations—are aimed to represent this uncertainty.

According to the 2017 European Society of Cardiology: Cardiovascular Disease Statistics report, substantial differences exist in health care systems among individual countries in Europe.⁴⁴ While predicting the number of potential TAVI candidates, this study did not consider the effect of local reimbursement or health insurance policies, regional differences in social background or life expectancy. It provides an insight into how many patients can potentially be candidates, combining all latest available epidemiological and clinical data, assuming unlimited TAVI availability.

As the yearly incidence rate of severe AS was calculated, both prevalence and average disease duration used for the calculation influence our estimations. The impact of these uncertainties was explored in sensitivity analyses.

Additionally, our estimations have a certain timeframe of validity. However, we are confident that our current and future predictions are valid unless robust data would show limited long-term TAVI durability in the future.

CONCLUSIONS

This study estimates the current and future potential number of TAVI candidates. An estimated 115 000 and 58 000 potential annual candidates are eligible for TAVI in Europe and Northern-America, respectively. These numbers will increase dramatically, up to 177 000 and 90 000 if ongoing clinical trials establish the evidence for TAVI in low-risk patients.

Acknowledgements

We acknowledge the financial support from the Netherlands Cardio Vascular Research Initiative: the Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development, and the Royal Netherlands Academy of Sciences.

Conflict of interest: A.P.K.: principal investigator of the SURTAVI trial and also employee of Medtronic Inc.; N.V.M.: study chair of the SURTAVI trial sponsored by Medtronic Inc., and reports grants from Medtronic, Abbott, Boston Scientific and Claret Medical, outside the submitted work. All other authors declare that they have no conflicts of interest.

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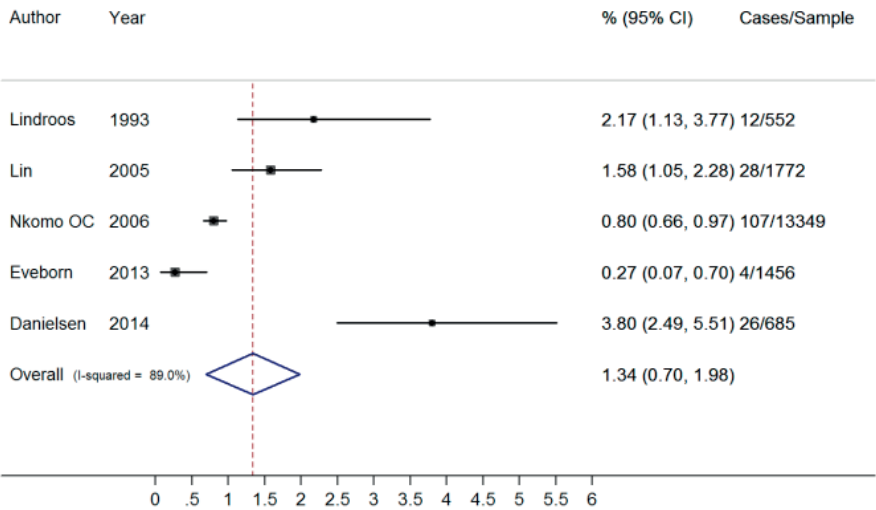
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SUPPLEMENTARY DATA

Severe AS in the population aged >65 years old
Random-effects model



Online Figure 1: Metaanalysis on the prevalence of severe aortic stenosis above 65 years

Online Table 1: Prevalence of severe aortic stenosis above 65 years

Author	Year of publication	Study	Country	Study design	Study period	Number of population	Age of population	Number of severe AS	Definition of severe AS by transthoracic echocardiography
Lindroos (1)	1993	Helsinki Ageing Study	Finland	prospective, cross sectional sub-study of a larger population-based study	1990 - 1991	552	>55 y	12	Critical AS: VR ≤ 0.35 and AVA ≤ 0.8 cm ²
Lin (2)	2005		Taiwan	prospective cross-sectional study	NR	1772	>60 y	28	Severe AS: gradient >50 mmHg
Nkomo (personal communication)	2006	Olmsted County cohort	USA	cross-sectional sub-study of a larger community based study	1990-2000	13349	>65 y	107	severe AS: Vmax >4 m/s and AVA <1.0 cm ²
Eveborn (4)	2013	Tromsø study	Norway	population based study, data used from Tromsø study 6 (T6, 2008)	1974 -	1456	mean 70.3 y	4	severe AS: transvalvular mean gradient ≥ 50 mmHg
Danielsen (5)	2014	AGES-Reykjavik	Iceland	sub-study of a larger population based study	2006 -	685	mean 76 \pm 6 y (67 - 95)	26	severe AS: indexed AVA ≤ 0.6 cm ² /m ²

AS, aortic stenosis; AVA, aortic valve area; ; NR, not reported; Vmax, peak velocity

Online Table 2: Studies reporting symptomatic status among patients with severe aortic stenosis

Author	Year of publication	Study design	Definition of severe AS	Definition of symptomatic status	Number of population	Number of symptomatic
Bouma (6)	1999	cohort analysis based on a prospective registry	AVA < 1.0 cm ² or a maximum gradient of >50 mmHg	Asymptomatic: no angina or dyspnea (NYHA I)	205	161
lung (7)	2005	Euro Heart Survey: prospective multicenter survey in various European countries	indexed AVA ≤ 0.6 cm ² /m ² BSA or mean gradient ≥ 50 mmHg	dyspnea (NYHA class III – IV) and angina pectoris	284	216
Pai (8)	2006	retrospective database review	AVA ≤ 0.8 cm ²	exertional chest pain, shortness of breath, or syncope	740	402
Van Geldorp (9)	2009	retrospective cohort	at least one of the following: AVA < 1.0 cm ² , Vmax > 4.0 m/s, peak aortic gradient > 64 mmHg or mean aortic gradient > 40 mmHg or ratio between the velocity time integral over the aortic valve and the left ventricular outflow tract > 4.0	NR	252	179
Bakaeen (10)	2010	retrospective database review	AVA < 1.0 cm ²	NR	345	296
Freed (11)	2010	retrospective database review	AVA < 1.0 cm ² and a mean aortic valve gradient of ≥ 40 mmHg and/or an aortic jet velocity of ≥ 4 m/s	chest pain, dizziness, syncope, dyspnea and heart failure	106	61
Dua (12)	2011	retrospective cohort study	AVA < 1.0 cm ²	exertional angina or chest pain, syncope or presyncope, and either symptoms and/or diagnosis of heart failure	187	147
Kirai (13)	2011	retrospective cohort study	maximal jet velocity ≥ 4 m/s, mean pressure gradient ≥ 40 mmHg, or AVA < 1.0 cm ²	NR	195 (166 + 29)	119 (52 + 38 + 29)

Online Table 2: Studies reporting symptomatic status among patients with severe aortic stenosis (continued)

Author	Year of publication	Study design	Definition of severe AS	Definition of symptomatic status	Number of population	Number of symptomatic
Bach (14)	2011	retrospective multicenter survey	mean gradient ≥ 40 mm Hg, effective orifice area < 1.0 cm ² , or an overall interpretation of severe AS	chest pain or angina pectoris, dyspnea or other symptoms of heart failure, or presyncope or syncope.	842	666
Badran (15)	2012	retrospective database review	AVA < 1 cm ² , mean pressure gradient ≥ 40 mmHg, or visually severe on echocardiography	NR	178	146
Babcock (16)	2013	single center retrospective analysis of an echocardiography database	mean gradient > 40 mmHg, AVA < 1.0 cm ² , velocity > 4 m/s, in conjunction with dimensionless index ≤ 0.25	syncope, angina, or dyspnea (at least NYHA class II)	187	133
Tay (17)	2013	retrospective database review	Doppler-derived maximum jet velocity across the aortic valve of 4 m/s, a mean gradient > 40 mmHg or an estimated AVA of < 1 cm ²	dyspnea, chest pain, syncope, acute coronary syndrome	249	125
Holmes (18)	2015	retrospective database review	indexed AVA ≤ 0.6 cm ² /m ² BSA and LV ejection fractions (LVEFs) $\geq 50\%$	angina, syncope, dyspnea	82	52
Izumo (19)	2017	retrospective database review	AVA < 1.0 cm ²	chest pain, heart failure, syncope	586	270

AS, aortic stenosis; AVA, aortic valve area; BSA, body surface area; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association; Vmax, peak velocity

Online Table 3: Studies reporting the percentage of patients with symptomatic severe AS, traditionally not treated with surgical AVR (before TAVI become widely available)

Author	Year	study design	study period	definition of severe AS	AS related symptoms present?	TAVI available?	Age	number treated with SAVR	not treated with SAVR
Bouma (6)	1999	prospective registry	1991 - 1993	AVA ≤ 1.0 cm ² or gradient ≥ 50 mmHg	yes	no	median 78 y (70-93)	79	56
Iung (7)	2005	European Heart Survey: prospective registry	2001	AVA ≤ 0.6 cm ² /m ² of BSA and/or gradient ≥ 50 mmHg	yes	no	mean 81.7 \pm 4.8 y	144	72
Charlson (20)	2006	retrospective database	1995 - 1997	AVA ≤ 0.8 cm ² or gradient ≥ 50 mmHg	yes	no	mean 81.5 \pm 8.3 y	44	29
Pai (8)	2006	retrospective database	1993 - 2003	AVA ≤ 0.8 cm ²	yes	no	mean 71 \pm 15 y	188	214
Descoutures (21)	2008	prospective registry	2006 - 2007	AVA ≤ 0.7 cm ²	yes	no	>70 y (83 \pm 6 y)	31	35
Perera (22)	2009	retrospective	2005	NR	yes	no	76.9 \pm 13.9 y	42	39
Bach (23)	2009	retrospective database	2005	AVA ≤ 0.9 cm ² , gradient ≥ 40 mmHg, or "clinical impression consistent with severe AS	yes	no	72.8 \pm 13.1 all	171	126
van Geldorp (9)	2009	retrospective database	2004 - 2007	at least one of the following: AVA < 1.0 cm ² , maximum aortic jet velocity > 4.0 m/s, peak aortic gradient > 64 mmHg or mean aortic gradient > 40 mmHg	yes	yes (10 underwent)	mean 71 y	63	116-10
Bakaeen (10)	2010	retrospective database	1997 - 2008	AVA ≤ 1.0 cm ²	yes	no	mean 73 y	197	99
Freed (11)	2010	retrospective database	2007	AVA < 1.0 cm ² , mean aortic valve gradient ≥ 40 mmHg and/or Vmax ≥ 4 m/s	yes	no	mean 75 y	29	31
Matsuo (24)	2010	retrospective database	2004 - 2008	NR	yes	no	NR	67	41

Online Table 3: Studies reporting the percentage of patients with symptomatic severe AS, traditionally not treated with surgical AVR (before TAVI become widely available) (continued)

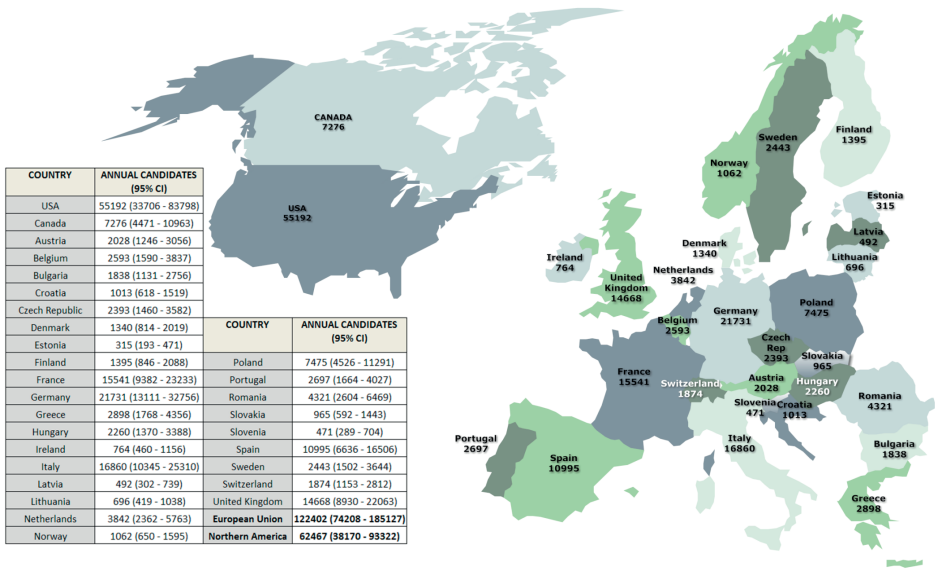
Author	Year	study design	study period	definition of severe AS	AS related symptoms present?	TAVI available?	Age	number treated with SAVR	not treated with SAVR
Bach (14)	2011	retrospective database	2007 - 2009	mean gradient ≥ 40 mm Hg, AVA < 1.0 cm ² , or an overall interpretation of severe AS	yes	yes (1 awaiting)	mean 80.3 \pm 10.5 y	296	370
Dua (12)	2011	retrospective database	2006 - 2008	AVA ≤ 1.0 cm ²	yes	no	mean 74 y	89	58
Chitsaz (25)	2011	retrospective database	2000 - 2007	AVA < 1.0 cm ² , mean gradient ≥ 40 mmHg	yes	no	mean 73 y	87	43
Pierard (26)	2011	prospective registry	2000 - 2007	AVA < 1.0 cm ² , mean gradient > 30 mmHg	yes	yes (excluded)	mean 84 \pm 3 y	97	66
Badran (15)	2012	retrospective database	2008 - 2010	AVA: < 1 cm ² , mean pressure gradient: ≥ 40 mmHg, or visually severe on echocardiography	yes	yes (5 underwent)	mean age 82 y	87	59-5
Izumi (27)	2012	retrospective database	1999 - 2009	AVA < 1.0 cm ²	yes	NR / no	median 75 y	166	61
Babcock (16)	2013	retrospective database	2008 - 2010	AVA < 1.0 cm ² , mean gradient > 40 mmHg, Vmax > 4 m/s, or dimensionless index ≤ 0.25	yes	NR	mean 73 y	83	50
Pereira (28)	2015	retrospective database	2009 - 2013	AVA ≤ 1.0 cm ²	yes	NR	mean 73.9 \pm 8.9 y	95	50
Izumo (19)	2017	retrospective registry	2008 - 2012	AVA < 1.0 cm ²	yes	NR	76 \pm 9 y	182	88

AS, aortic stenosis; AVA, aortic valve area; BSA, body surface area; NR, not reported; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; Vmax, peak velocity

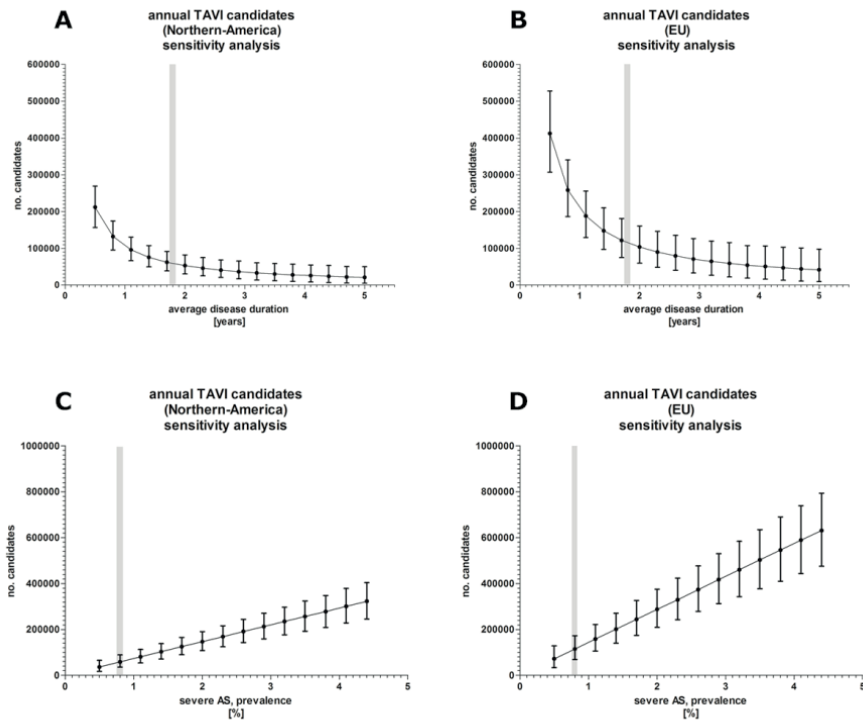
Online Table 4: Studies reporting the number of patients severe symptomatic AS patients, whom not received SAVR, and were not offered TAVI

Author	Year of publication	Study period	Study design	Age	% male	Risk profile	treated with SAVR	treated with TAVI	treated with medical therapy	medical therapy / (medical therapy + TAVI)
Dubois (29)	2013	2008-2011	prospective single-centre registry	reported only in separate groups	44%	HIGH	74	35	54	54 / (54+35) = 60,7%
Lauck (30)	2014	2011-2012	retrospective	NR	NR	HIGH	92	232	78	78 / (78+232) = 25,2%
Iglesias (31)	2015	2008-2012	prospective registry	mean 83.7 y	43%	HIGH (mean EuroScore 19.8±12.3)	13	79	45	45 / (45+79) = 36,3%
Boureau (32)	2015	2011-2013	retrospective observational	> 75 y, mean 83±4 y	49%	ALL	108	131	98	98 / (98+131) = 42,8%
Martin (33)	2015	2007-2013	retrospective observational	mean 79.2 ± 8.2 y for TAVI	49,8% for TAVI	HIGH	103	444	69	69 / (69+444) = 13,5%
Van Mieghem (34)	2016	2014	international prospective registry	> 50 y, mean 76,4±11.6 y	55%	ALL (STS PROM; 2.9% (IQR 1.6 - 6.9)	200	166	24	24 / (24+166) = 12,6%
Bouleti (35)	2016	2006-2010	prospective single-centre registry	reported only in separate groups	reported only in separate groups	HIGH (STS PROM >10%, EuroScore > 20%, or HT decision)	102	253	123	123 / (123+253) = 32,7%
Thyregod (36)	2016	2011	prospective registry	> 18 y, mean 75 y (IQR 44 - 96)	62%	ALL (only 3% with STS-PROM > 8%)	392	60	35	35 / (35+60) = 36,8%
González-Saldivar (37)	2016	2014	multicenter registry	mean 77.3 ± 10.6 y	48,20%	ALL	199	59	332	332 / (332+59) = 84,9%

AS, aortic stenosis; AVA, aortic valve area; BSA, body surface area; EuroScore, European System for Cardiac Operative Risk Evaluation; HT, heart team; IQR, interquartile range; NR, not reported; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; TAVI, transcatheter aortic valve implantation;



Online Figure 2: Scenario 1. – Estimated annual TAVI numbers, if TAVI will be the treatment of choice in the high- and intermediate-risk category.
TAVI, transcatheter aortic valve implantation;



Online Figure 3: Sensitivity analysis on the effect of the average disease duration and the prevalence of AS.

AS, aortic stenosis; EU, European Union; TAVI, transcatheter aortic valve implantation;

The grey bars are indicating the base case scenario

6A Estimated annual TAVI numbers in North-America, in relation to the average duration of AS.

6B Estimated annual TAVI numbers in the EU, in relation to the average duration of AS.

6C Estimated annual TAVI numbers in North-America, in relation to the prevalence of AS.

6D Estimated annual TAVI numbers in the EU, in relation to the prevalence of AS.

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7

Neurological Complications After Transcatheter Aortic Valve Implantation or Surgical Aortic Valve Replacement in Intermediate-Risk Patients.

Durko AP, Reardon M, Kleiman N, Popma JJ, Van Mieghem NM, Gleason T, Bajwa T, O'Hair D, Brown D, Ryan W, Chang Y, De Leon S, Kappetein AP.

J Am Coll Cardiol. 2018 Oct 30;72(18):2109-2119.

ABSTRACT

Background

Neurological events after aortic valve interventions are associated with increased mortality and morbidity. Transcatheter aortic valve replacement (TAVR) is increasingly offered for lower-risk patients with severe aortic stenosis, previously considered candidates for surgical aortic valve replacement (SAVR). Differences in post-procedural neurological events have important implications in treatment allocation.

Objectives

The authors sought to analyze the neurological events in the randomized SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trial.

Methods

Patients with severe, symptomatic aortic stenosis at intermediate surgical risk were randomized 1:1 to TAVR or SAVR. The rates of neurological events and quality of life were analyzed at 30 days, and 6 and 12 months post-procedure in a modified intention-to-treat population (mean age 79.8 ± 6.2 years; $N = 1,660$).

Results

The rates of early (30-day) stroke and post-procedural encephalopathy were higher after SAVR versus TAVR (5.4% vs. 3.3%; $p = 0.031$; and 7.8% vs. 1.6%; $p < 0.001$, respectively). At 12 months, the rate of stroke was not different between SAVR and TAVR (6.9% vs. 5.2%; $p = 0.136$). Early stroke and early encephalopathy resulted in an elevated mortality at 12 months in both treatment groups. Quality of life after an early stroke was significantly lower in SAVR versus TAVR patients at 30 days and was similar at 6 and 12 months.

Conclusions

The early stroke rate was lower after TAVR than SAVR. In patients with early strokes, QOL improved earlier after TAVR. At 12-month follow-up, stroke rates and QOL were not different between TAVR and SAVR patients. (Surgical Replacement and Transcatheter Aortic Valve Implantation [SURTAVI]; NCT01586910)

Key words aortic stenosis, neurological events, stroke, surgical aortic valve replacement, transcatheter aortic valve replacement

Neurological events carry significant burden of disease with potential long-term consequences and substantial health care–related costs. Neurological events after open heart surgery have long been a major concern because of their adverse effects on post-procedural quality of life (QOL) and survival, potentially jeopardizing the overall positive results of the procedure (1,2).

Recently, 2 large, randomized controlled trials demonstrated the comparative effectiveness of transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) in patients with severe symptomatic aortic stenosis (AS) at intermediate-risk for surgery at 2-year follow-up (3,4). In-depth analysis of major post-procedural complications is crucial when attempting to compare 2 treatment modalities (5).

The objective of this analysis was to assess and compare the incidence, characteristics, predictors, and consequences of neurological events after TAVR and SAVR in patients enrolled in the randomized SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trial (4).

METHODS

Study design

The design and details of the SURTAVI trial have been previously reported (4). In brief, patients with symptomatic severe AS at intermediate surgical risk were recruited at 87 centers in Europe, the United States, and Canada, and randomized 1:1 to TAVR with a self-expanding transcatheter bioprosthesis or conventional surgery. Severe AS was defined as an aortic valve area (AVA) ≤ 1.0 cm², or an indexed AVA ≤ 0.6 cm²/m² and a mean transvalvular gradient >40 mm Hg or a maximum aortic velocity >4 m/s or a Doppler velocity index <0.25 . Medtronic funded the trial and developed the study protocol in collaboration with the executive committee. The trial was conducted in compliance with the International Conference on Harmonization and the Declaration of Helsinki and was approved by local institutional review boards or medical ethics committees at each center. All participating patients provided written informed consent.

Patient population

The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, as well as other nontraditional risk factors such as comorbidities or frailty, were considered when determining patient risk. Patients with an estimated 30-day surgical mortality risk of 3% to 15% were considered eligible. During study screening, multislice computed tomography or magnetic resonance imaging was performed in all patients to assess the vascular system from the aortic valve to the iliofemoral arteries. Symptomatic carotid

or vertebral artery disease, successful treatment of carotid stenosis within 6 weeks of randomization, and true porcelain aorta were exclusion criteria. Performing a routine pre-operative ultrasound examination of the carotid arteries was left to the discretion of the local investigators. Detailed inclusion and exclusion criteria have been previously described (4).

Neurological assessment

Neurological assessment of the study participants was carried out by qualified study-trained neurologists or stroke specialists. All neurological events were adjudicated by an independent clinical events committee. Baseline neurological assessments comprised recording the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Score (mRS). All patients underwent routine post-procedural neurological examinations (Table 1). The suspicion of a new neurological event triggered examination by a certified neurologist or stroke specialist. For patients with a neurological event, additional NIHSS assessments were performed at 30 and 90 days post-event, and the mRS was completed at 7 days post-event or discharge (whichever occurred first), 30 and 90 days post-event. It was recommended to have imaging (multislice computed tomography or diffusion-weighted magnetic resonance imaging, preferably with intravenous contrast material) to support the diagnosis of stroke.

TABLE 1 Timing and Types of Neurological and QOL Testing

	Neurological Assessment		Quality-of-Life Assessment	
	NIHSS	mRS*	KCCQ-OS	SF-36
Baseline	•	•	•	•
Post-procedure†	•			
Discharge	•	•		
30 days	•		•	•
6 months	•		•	•
12 months	•	•	•	•

*Performed by a neurologist or stroke specialist. †Within 24 h of index procedure and any aortic valve or ascending aortic intervention.

KCCQ-OS ¼ Kansas City Cardiomyopathy Questionnaire Overall Summary Score; mRS ¼ modified Rankin Score; NIHSS ¼ National Institutes of Health Stroke Scale; QOL ¼ quality of life; SF-36 ¼ Short-Form 36.

Neurological endpoints

For this analysis, neurological events included disabling and nondisabling stroke, transient ischemic attack (TIA), and encephalopathy. Strokes were classified according to the Valve Academic Research Consortium (VARC)-2 criteria (6). Disabling stroke was defined as an mRS ≥2 at 90 days post-event with an increase of at least 1 mRS category from the pre-stroke baseline. Nondisabling stroke was defined as an mRS <2 at 90 days after the

event, or as a stroke that does not result in an increase of at least 1 mRS category from the pre-stroke baseline. TIA was defined as a new focal neurological deficit lasting <24 h without neuroimaging evidence of tissue injury. Encephalopathy was defined as an altered level of consciousness after exclusion of stroke or TIA during an examination by a neurologist. For the purposes of this study, neurological events were classified as occurring early (0 to 30 days) or late (31 to 365 days) post-procedure. In this study, the characteristics and consequences of early neurological complications were analyzed in depth.

QOL after neurological events

Generic health status after stroke was evaluated using the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire. The SF-36 assesses 8 dimensions of health status and provides a physical and mental component summary scale, which are scored such that the U.S. population mean is 50 ± 10 , with higher scores representing better health status (7). The minimum clinically important differences for the SF-36 physical and mental component scores are approximately 2 points (8). The schedule of QOL examinations is summarized in Table 1.

Statistics

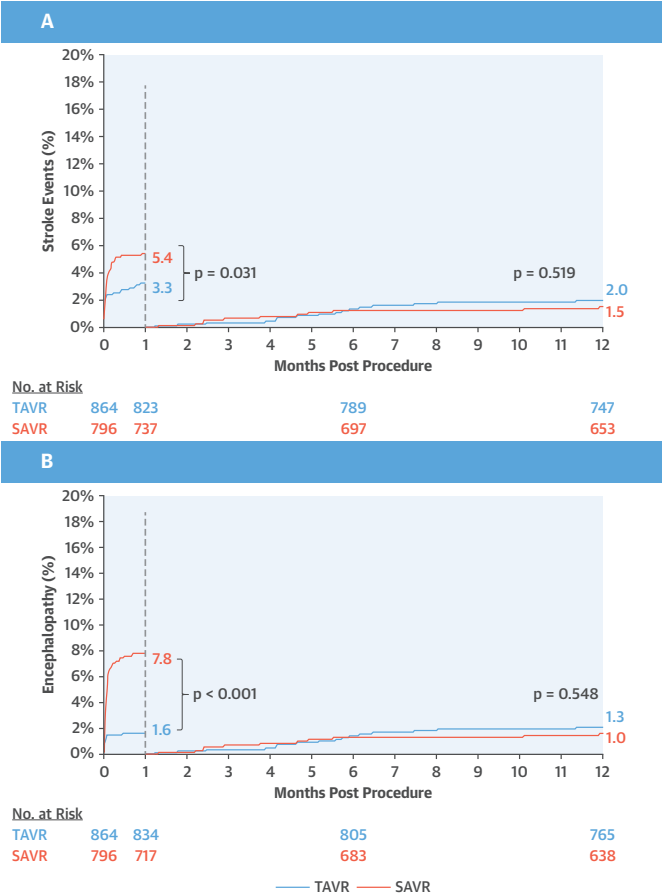
Analysis was performed in the modified intention-to-treat population where patients underwent randomization and an attempted procedure. Continuous variables were summarized as mean \pm SD and compared with the Student's *t*-test, or median (interquartile range) and compared with Wilcoxon rank sum test. Categorical data were summarized by frequencies and percentages, and were compared using the chi-square or Fisher exact test. Kaplan-Meier estimates were used for the time-to-event analysis and were compared using the log-rank test. Landmark analyses after 30 days postprocedure were performed. The instantaneous hazard of stroke was modeled using the Epanechnikov kernel-smoothing method with bandwidth set to 10 grid points. Univariable analyses with Cox proportional hazards model were used to identify potential predictors of stroke from a list of pre- and postprocedural variables believed to be clinically relevant. Stroke hazard after TAVR and SAVR was compared in different subgroups. Results are expressed as hazard ratios (95% confidence intervals), and all testing used a 2-sided alpha level of 0.05. All statistical analyses were performed using statistical software SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 1,746 patients underwent randomization between June 19, 2012, and June 30, 2016. The modified intention-to-treat population comprised 1,660 patients: 864 in the TAVR and 796 in the SAVR group. Patient flow is provided in Online Figure 1. Only 2 patients (SAVR) were lost to follow-up.

Incidence of neurological events

Fewer early strokes occurred after TAVR than after SAVR (3.3% vs. 5.4%; $p = 0.031$). Early encephalopathy was more frequent after SAVR than after TAVR (7.8% vs. 1.6%; $p < 0.001$).



Durko, A.P. et al. *J Am Coll Cardiol.* 2018;72(18):2109-19.

CENTRAL ILLUSTRATION Incidence of Neurological Events to 1 Year After TAVR and SAVR

The cumulative incidence of (A) all strokes; and (B) encephalopathy to 30 days and from 31 to 365 days. Log-rank p values are reported. Only the first event is included. SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

The incidences of post-procedural neurological events are displayed in the Central Illustration and in Table 2.

TABLE 2 The Incidence of Neurological Events

	Early Events (≤30 Days)			Late Events (31–365 Days)			All Events (0–365 Days)		
	TAVR	SAVR	p Value*	TAVR	SAVR	p Value*	TAVR	SAVR	p Value*
All stroke	3.3	5.4	0.031	2.0	1.5	0.519	5.2	6.9	0.136
Disabling stroke	1.2	2.4	0.058	1.0	0.9	0.969	2.1	3.3	0.129
Nondisabling stroke	2.1	3.0	0.230	1.0	0.6	0.333	3.1	3.6	0.548
TIA	1.4	1.0	0.474	1.7	0.8	0.114	3.1	1.8	0.104
Encephalopathy	1.6	7.8	<0.001	1.3	1.0	0.548	3.0	8.8	<0.001

Values are Kaplan-Meier rates as percentages. Kaplan-Meier estimates for late events were obtained via a landmark analysis. *Log-rank test.

SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

Baseline characteristics

The mean age was 79.8 ± 6.2 years, and all patients were at intermediate risk for surgery (STS-PROM $4.5 \pm 1.6\%$). There were no differences in baseline clinical and demographic characteristics between patients with and without an early stroke (Table 3).

Stroke event details

Of all strokes (disabling and nondisabling) through 12 months, 28 of 44 (63.6%) in the TAVR and 43 of 54 (79.6%) in the SAVR group occurred early ($p = 0.078$). The stroke hazard was highest in the immediate post-procedural period in both groups, rapidly decreasing by 30 days (Figure 1). Among patients experiencing an early stroke, none experienced a subsequent stroke during the first year of follow-up. Most early strokes were thromboembolic (93.1% in the TAVR group and 97.8% in the SAVR group), with only a minority being of hemorrhagic origin. Late strokes were primarily thromboembolic in 71.4%, hemorrhagic in 25.0%, and undetermined in 3.6%.

Intraprocedural factors

Procedural characteristics of patients with and without early strokes are shown in Table 4 for TAVR and in Table 5 for SAVR. In the TAVR group, there was a trend toward a longer total procedure time in patients who had an early stroke (67.5 ± 43.2 min vs. 51.8 ± 32.2 min; $p = 0.072$). In the SAVR group, there were no differences in the duration of cardiopulmonary bypass, aortic crossclamp time, or procedure time for patients with or without a stroke. The rate of early strokes was not increased if concomitant CABG was added.

TABLE 3 Baseline Characteristics of Patients With and Without Early Stroke

	TAVR (n = 864)		p Value	SAVR (n = 796)		p Value
	Early Stroke (n = 28)	Without Early Stroke (n = 836)		Early Stroke (n = 43)	Without Early Stroke (n = 753)	
Age, yrs	78.5 ± 8.2	80.0 ± 6.1	0.345	80.3 ± 6.9	79.7 ± 6.0	0.537
Male	14 (50.0)	484 (57.9)	0.406	25 (58.1)	413 (54.8)	0.673
BSA, m ²	1.9 ± 0.3	1.9 ± 0.2	0.496	1.9 ± 0.2	1.9 ± 0.2	0.251
STS-PROM, %	4.4 ± 1.7	4.4 ± 1.5	0.888	4.4 ± 1.6	4.5 ± 1.6	0.549
Logistic EuroSCORE, %	12.6 ± 10.7	11.9 ± 7.5	0.739	11.6 ± 7.6	11.6 ± 8.0	0.995
NYHA functional class			0.385			0.350
I	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
II	9 (32.1)	335 (40.1)		22 (51.2)	311 (41.3)	
III	17 (60.7)	455 (54.4)		17 (39.5)	394 (52.3)	
IV	2 (7.1)	46 (5.5)		4 (9.3)	48 (6.4)	
Medical history						
History of hypertension	29 (96.4)	774 (92.6)	0.715	34 (79.1)	685 (91.0)	0.010
Peripheral vascular disease	8 (28.6)	258 (30.9)	0.796	13 (30.2)	225 (29.9)	0.961
Cerebrovascular disease	7 (25.0)	144 (17.2)	0.287	6 (14.0)	124 (16.5)	0.665
Prior stroke	2 (7.1)	55 (6.6)	0.707	4 (9.3)	53 (7.0)	0.540
Prior TIA	4 (14.3)	54 (6.5)	0.112	4 (9.3)	42 (5.6)	0.304
Coronary artery disease	20 (71.4)	521 (62.3)	0.327	26 (60.5)	485 (64.4)	0.600
Atrial fibrillation or flutter	6 (21.4)	237 (28.3)	0.423	10 (23.3)	201 (26.7)	0.619
Diabetes mellitus	10 (35.7)	285 (34.1)	0.859	15 (34.9)	262 (34.8)	0.990
Chronic lung disease/COPD	7 (25.0)	298 (35.7)	0.243	16 (37.2)	251 (33.3)	0.601
Creatinine level >2 mg/dl	0 (0.0)	14 (1.7)	0.490	0 (0.0)	17 (2.3)	0.319
Pre-operative antiplatelet therapy or anticoagulation						
Single antiplatelet agent	17 (60.7)	418 (50.0)	0.265	21 (48.8)	444 (59.0)	0.190
Dual antiplatelet agent	4 (14.3)	213 (25.5)	0.266	5 (11.6)	83 (11.0)	0.902
Oral anticoagulants	7 (25.0)	179 (21.4)	0.650	10 (23.3)	166 (22.0)	0.852

Values are mean ± SD or n (%).

BSA = body surface area; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; other abbreviations as in Table 2.

Post-procedural characteristics

In both treatment groups, patients with early stroke experienced prolonged intensive care unit and in-hospital stays, and were less likely discharged home directly after the procedure (Table 6).

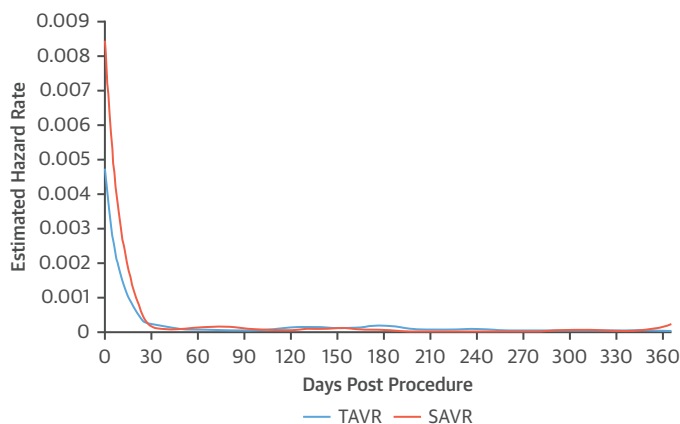


FIGURE 1 Estimated Hazard of Stroke Through 1 Year After TAVR and SAVR

The estimated hazard of stroke after TAVR and SAVR through 1 year. SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

TABLE 4 Procedural Characteristics of Patients With and Without Early Strokes After TAVR

	Early Stroke (n = 28)	Without Early Stroke (n = 836)	p Value
Total procedure time, min	67.5 ± 43.2	51.8 ± 32.2	0.072
Anesthesia			0.593
General anesthesia	20 (71.4)	634 (75.8)	
Conscious sedation	8 (28.6)	202 (24.2)	
Concomitant PCI performed*	2/4 (50.0)	50/124 (40.3)	0.699
Pre-TAVR balloon valvuloplasty	12 (42.9)	395 (47.2)	0.647
Post-TAVR balloon dilation	6 (21.4)	244 (29.2)	0.371
More than 1 valve implanted	4 (14.3)	54 (6.5)	0.112

Values are mean ± SD, n (%), or n/N (%). *Denominator is for all percutaneous coronary interventions (PCIs) performed. TAVR = transcatheter aortic valve replacement.

TABLE 5 Procedural Characteristics of Patients With and Without Early Strokes After SAVR

	Stroke (n = 43)	Without Stroke (n = 753)	p Value
CPB time, min	95.0 ± 34.9	98.0 ± 39.6	0.629
Cross-clamp time, min	72.1 ± 27.6	74.4 ± 30.6	0.630
Concomitant CABG	8 (18.6)	168 (22.3)	0.566
Total procedure time, min	200.6 ± 63.9	203.9 ± 69.4	0.765

Values are mean ± SD or n (%).

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; SAVR = surgical aortic valve replacement.

TABLE 6 Post-Procedural Characteristics of Patients With Early Strokes

	TAVR		p Value	SAVR		p Value
	Early Stroke (n = 28)	Without Early Stroke (n = 836)		Early Stroke (n = 43)	Without Early Stroke (n = 753)	
ICU stay, h	66.8 (31.4–118.5)	40.5 (23.1–55.0)	0.067	72.9 (26.2–117.7)	46.0 (24.2–74.6)	0.113
Hospital stay, days	7.0 (6.0–11.0)	4.0 (3.0–7.0)	<0.001	11.0 (8.0–14.0)	7.0 (6.0–10.0)	<0.001
Discharge location			<0.001			0.002
Home	10 (35.7)	725 (86.7)		12 (27.9)	420 (55.8)	
Another hospital	1 (3.6)	10 (1.2)		2 (4.7)	27 (3.6)	
Rehabilitation clinic	9 (32.1)	49 (5.9)		18 (41.9)	159 (21.1)	
Skilled nursing facility	4 (14.3)	30 (3.6)		5 (11.6)	101 (13.4)	
Other	1 (3.6)	12 (1.4)		5 (11.6)	36 (4.8)	
Patient died in hospital	3 (10.7)	10 (1.2)		1 (2.3)	10 (1.3)	

Values median (interquartile range) or n (%). Only patients who had an index procedure are included.

ICU = intensive care unit; other abbreviations as in Table 2.

Predictors of early stroke and subgroup analyses

Univariable analysis failed to identify any factors predicting early stroke in TAVR patients. In SAVR patients, the hazard of stroke was higher in the subgroup of patients without the history of hypertension (Online Tables 1 and 2). The hazard of early stroke was not statistically different between TAVR and SAVR patients in subgroups of sex, body mass index, diabetes, peripheral vascular disease, coronary artery disease, severe aortic calcification, left ventricular function, history of a neurological event, prior coronary artery bypass grafting, or preexisting atrial fibrillation (Figure 2).

Mortality after early neurological events

Neurological events in the early postoperative period considerably increased 1-year mortality rates in both treatment groups (Table 7). After an early stroke, the 1-year mortality rate was 17.9% in TAVR, and 14.0% in SAVR patients ($p = 0.589$). Early post-procedural encephalopathy resulted in a 1-year mortality rate of 21.4% and 17.9% ($p = 0.716$) in TAVR and SAVR patients, respectively.

QOL after early stroke

Baseline health status was significantly impaired in both treatment groups. The baseline SF-36 physical component score was 36.6 ± 9.8 and 36.8 ± 9.7 ($p = 0.664$) in TAVR and SAVR patients, respectively. Early stroke resulted in a significant decrease in the SF-36 physical component score, but not the mental component score in SAVR patients at 30 days. Despite an early stroke, SF-36 physical component scores continuously increased

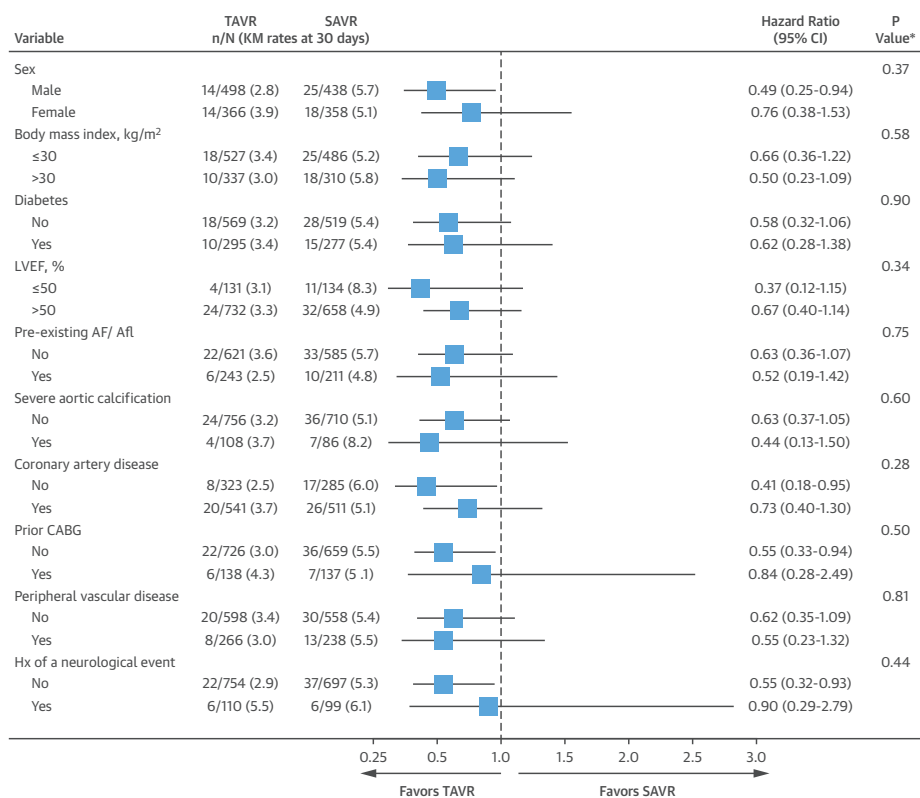


FIGURE 2 Subgroups in Early Stroke

The incidence of early stroke was consistent in the TAVR and SAVR patients across several subgroups. AF = atrial fibrillation; Afl = atrial flutter; CABG = coronary artery bypass grafting; CI = confidence interval; Hx = history; KM = Kaplan-Meier; LVEF = left ventricular ejection fraction; n = number of events; N = number of patients; other abbreviations as in Figure 1.

TABLE 7 1-Year Mortality Rates for Patients With Early (0 to 30 Days) Neurological Events

	TAVR	SAVR	p Value
No early neurological events*	36/801 (4.5)	26/673 (3.9)	0.586
Early stroke (all)†	5/28 (17.9)	6/43 (14.0)	0.589
Early disabling stroke†	4/10 (40.0)	5/19 (26.3)	0.327
Early nondisabling stroke†	1/18 (5.6)	1/24 (4.2)	0.822
Early TIA†	2/12 (16.7)	0/8 (0.0)	0.254
Early encephalopathy†	3/14 (21.4)	11/62 (17.9)	0.716

Values are n patients with an event/n patients included in the analysis (Kaplan-Meier rate as percentage). *Number of patients alive at day 31 without an early neurological event were included in the analysis. Kaplan-Meier analysis starts at day 31. †Patients with early neurological events were included in the analysis, and Kaplan-Meier analysis starts on day of procedure.

Abbreviations as in Table 2.

in patients after TAVR. During 1-year follow-up, QOL improved in all groups when compared with the baseline values. However, in both treatment groups, SF-36 physical and mental component scores were numerically lower after an early post-procedural stroke than in patients not experiencing early strokes (Online Tables 3 and 4). Time-related changes in SF-36 physical and mental component scores are displayed in Figure 3 and in Online Tables 5 and 6, for patients with and without early post-procedural stroke.

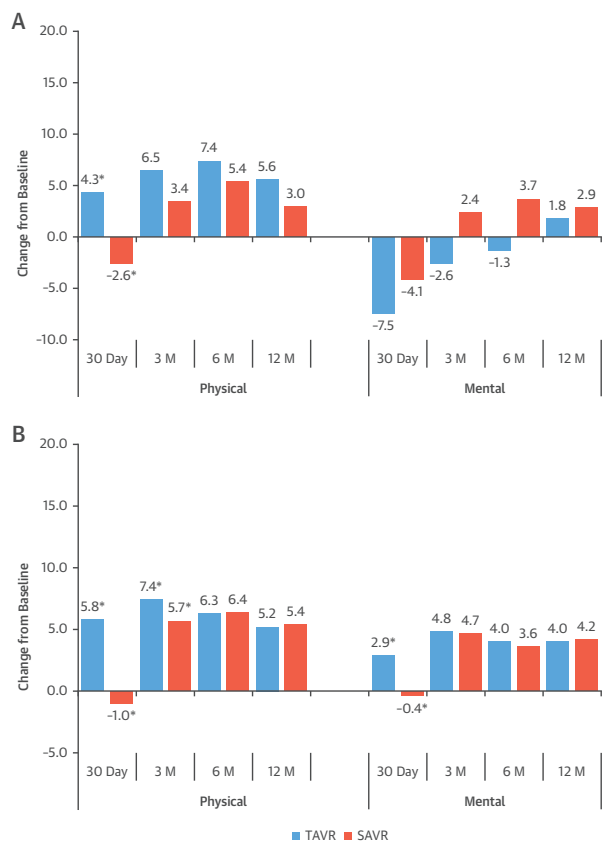


FIGURE 3 Changes in SF-36 Component Scores From Baseline to Follow-Up for Patients in the TAVR and SAVR Groups

The differences in SF-36 physical and mental component scores from baseline during follow-up for (A) patients who experienced an early stroke and (B) patients who did not experience an early stroke. *p < 0.05 for comparisons between TAVR and SAVR patients. M = month(s); SF-36 = Short-Form 36; other abbreviations as in Figure 1.

DISCUSSION

In the SURTAVI trial, comparing the outcomes of TAVR and SAVR in a population of 1,660 elderly patients (mean age 79.8 ± 6.2 years) with severe AS and intermediate risk for

surgery (STS PROM $4.5 \pm 1.6\%$), most neurological events occurred in the early postprocedural period. Early stroke and encephalopathy was less frequent after TAVR than after SAVR (3.3% vs. 5.4%; $p = 0.031$; and 1.6% vs. 7.8%; $p < 0.001$). Neurological events were associated with increased mortality at 1-year follow-up. After an early stroke, the SF-36 physical component scores were significantly higher at 30 days in the TAVR group compared with SAVR. However, this difference was no longer observed at 6- and 12-month follow-up but remained lower than in patients without a stroke.

Given their negative impact on post-procedural outcomes, every attempt should be made to reduce the risk of post-procedural neurological complications after aortic valve interventions. Recently, findings related to subclinical leaflet thrombosis subjected current post-procedural anticoagulation protocols after TAVR and SAVR to scrutiny (9). Embolic protection devices during aortic valve interventions have also been investigated with promising results (10–12). Of note, their use was not permitted in the SURTAVI trial.

Stroke rates

Most importantly, the rate of early strokes was significantly lower after TAVR than after SAVR in the SURTAVI trial. This contrasts with previous randomized clinical trial results, where early stroke rates after TAVR and SAVR were not different statistically (3,13,14).

Clearly, the actual event rate is highly influenced by the method of detection. According to a recent systematic review and meta-analysis, adjudication of neurological events after TAVR was undertaken only in 27% of the included studies, of which only 5% used an independent neurologist (15). This provides an explanation for the lower reported early stroke rates in large TAVR and SAVR registries (16,17). In this light, the relatively low event rate observed in our study is even more remarkable, because the SURTAVI trial applied a strict protocol for follow-up neurological examinations.

Prosthesis design can also influence the rate of peri-procedural neurological complications after TAVR. In the SURTAVI trial, exclusively self-expandable prostheses were used. A recent meta-analysis including over 30,000 TAVR patients did not find any difference in the 30-day stroke rate between self-expandable and balloon-expandable valve designs (18). Nevertheless, it is apparent that parallel to design development, the rate of complications after TAVR—including periprocedural stroke—is decreasing (19–21).

After SAVR, stroke rates were reported to be proportional to surgical risk category in a large U.S. registry (17). Interestingly, these findings were not confirmed in randomized-controlled trials comparing TAVR and SAVR: early stroke rates following SAVR were steady between 5% to 6% in the CoreValve U.S. Pivotal High-Risk, PARTNER II (Placement of Aortic Transcatheter Valves II), and SURTAVI trials, irrespective of surgical risk category (3,4,13).

Early post-procedural encephalopathy

Post-operative cognitive dysfunction has long been known to accompany major surgical procedures (22). One of the most remarkable findings of the SURTAVI trial was that post-procedural encephalopathy was far more common after SAVR than after TAVR. Postoperative cognitive dysfunction after SAVR and TAVR was investigated previously in smaller cohorts (23–25). Importantly, these studies used diverse definitions for encephalopathy, rendering unbiased comparison problematic. Therefore, the widespread use of universal definitions in future clinical trials investigating neurological endpoints is highly desirable (26).

Late neurological events

Late neurological events have a particular importance due to their connection with post-procedural anticoagulation (27). The anticoagulation protocol in the SURTAVI trial has been reported previously (4). Importantly, the rate of late neurological events remained low during 1-year follow-up, and no statistically significant differences in the rate of late events after TAVR and SAVR were detected.

Mortality after neurological events

The higher mortality rate in patients suffering postprocedural neurological events was confirmed in the SURTAVI trial, irrespective of the type of the initial procedure. These findings are similar to previous reports (28–30). However, the effect of post-procedural encephalopathy on 1-year mortality-rates deserves special attention, as it resulted in more than 3 times higher mortality in both treatment groups, than in TAVR and SAVR patients without early encephalopathy.

Possible predictors of early stroke

Interestingly, this analysis failed to identify any independent predictors of post-procedural stroke. This includes previously described predictors of stroke after TAVR, SAVR, or cardiac surgery such as post-procedural atrial fibrillation (15,28,30–33) and likely to be attributable to the low stroke rates in the SURTAVI trial. However, this does not weaken the importance of the previously described predictors: it only emphasizes the highly multifactorial nature of post-procedural stroke in AS patients.

Subgroup analysis

In this study, the hazard of early stroke was not different statistically between TAVR and SAVR in various subgroups. Of note, the hazard of early stroke was consistently lower in all subgroups after TAVR than after SAVR. This suggests a homogenous treatment effect and strengthens the main findings of this study.

Early post-procedural stroke and QOL

Besides mortality, post-procedural QOL is the most important measure of procedural success from the patient's perspective. After TAVR or SAVR, QOL is influenced by several factors: 1) the initial patient condition; 2) the relief of AS; 3) the procedure-related burden; and 4) the long-term effects of postprocedural complications (34–38). Although QOL improved earlier in TAVR patients after early strokes, this is most likely only a consequence of the greater invasiveness of SAVR compared with TAVR (8). Importantly, at 1-year follow-up, QOL was not different between SAVR and TAVR patients with early strokes.

Study limitations

The rate of neurological events in the SURTAVI trial was relatively low. However, due to the Kaplan-Meier method, neurological event rates might be slightly overestimated, because competing risk events were not considered in the calculation. Of note, although the analysis of neurological events was pre-specified in the SURTAVI trial, it was not powered to detect certain differences. The effect of the low event rate might be even more pronounced when analyzing small subgroups: these results can only be considered as hypothesis-generating for further investigations.

CONCLUSIONS

In the SURTAVI trial, investigating outcomes after TAVR and SAVR in 1,660 patients with intermediate risk for surgery, most neurological events occurred in the early post-procedural period. The rates of early stroke and early post-procedural encephalopathy were lower after TAVR than after SAVR.

Acknowledgment

Jane Moore, MS, ELS, an employee of the sponsor, provided copyediting assistance, created all figures, and formatted the manuscript for style.

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PERSPECTIVES

Competencies in patient care and procedural skills

Among patients with symptomatic severe aortic stenosis at intermediate surgical risk, 30-day rates of stroke and encephalopathy were higher after surgical than transcatheter valve replacement. These events were associated with higher mortality by 12 months after either type of procedure.

Translational outlook

Further research is needed to identify patient and procedural factors that predispose to neurological complications after aortic valve replacement and to evaluate the roles of embolism protection and antithrombotic medication in stroke prevention.

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SUPPLEMENT

Supplemental Table 1. Subgroups in early stroke for TAVR (univariable predictors)

Variable	n/N (KM Rates at 30 Days)	Hazard Ratio (95% CI)	P Value*
Age, years			
< 80	12/352 (3.4)	0.92 (0.43 to 1.94)	0.83
≥ 80	16/512 (3.1)		
Sex			
Male	14/498 (2.8)	1.37 (0.65 to 2.88)	0.40
Female	14/366 (3.9)		
Body mass index, kg/m ²			
≤ 30	18/527 (3.4)	0.86 (0.40 to 1.85)	0.69
> 30	10/337 (3.0)		
Society of Thoracic Surgeons Predictor of Mortality, %			
< 3	4/131 (3.1)	1.08 (0.37 to 3.11)	0.89
≥ 3	24/733 (3.3)		
< 4	10/345 (2.9)	1.20 (0.56 to 2.61)	0.64
≥ 4	18/519 (3.5)		
Logistic EuroSCORE, %			
< 10	14/429 (3.3)	0.98 (0.47 to 2.06)	0.96
≥ 10	14/435 (3.2)		
New York Heart Association class			
II	9/344 (2.6)	1.40 (0.63 to 3.10)	0.40
III/IV	19/520 (3.7)		
Left ventricular ejection fraction, %			
≤ 50	4/131 (3.1)	1.08 (0.38 to 3.12)	0.88
> 50	24/732 (3.3)		
Hypertension			
No	1/63 (1.6)	2.11 (0.29 to 15.50)	0.46
Yes	27/801 (3.4)		
Previous coronary artery bypass grafting			
No	22/726 (3.0)	1.42 (0.58 to 3.51)	0.44
Yes	6/138 (4.3)		
Peripheral vascular disease			
No	20/598 (3.4)	0.90 (0.40 to 2.05)	0.81
Yes	8/266 (3.0)		
Prior percutaneous coronary intervention			
No	19/680 (2.8)	1.75 (0.79 to 3.88)	0.16
Yes	9/184 (5.0)		
5-Meter gait speed, sec			

Supplemental Table 1. Subgroups in early stroke for TAVR (univariable predictors) (continued)

Variable	n/N (KM Rates at 30 Days)	Hazard Ratio (95% CI)	P Value*
≤ 6	12/399 (3.0)	1.09 (0.50 to 2.36)	0.82
> 6	14/428 (3.3)		
Diabetes			
No	18/569 (3.2)	1.06 (0.49 to 2.31)	0.87
Yes	10/295 (3.4)		
Need for revascularization			
No	22/695 (3.2)	1.12 (0.46 to 2.77)	0.80
Yes	6/169 (3.6)		
Severe aortic calcification			
No	24/756 (3.2)	1.15 (0.40 to 3.31)	0.80
Yes	4/108 (3.7)		
Pre-TAVR balloon valvuloplasty performed			
No	16/457 (3.5)	0.84 (0.40 to 1.78)	0.65
Yes	12/407 (3.0)		
Post-TAVR balloon valvuloplasty performed			
No	22/613 (3.6)	0.66 (0.27 to 1.64)	0.37
Yes	6/250 (2.4)		
Mini-Mental State Examination score			
< 25	3/107 (2.8)	1.06 (0.31 to 3.54)	0.93
≥ 25	21/703 (3.0)		
Maximum activated clotting time, sec			
≤300	15/465 (3.2)	1.10 (0.53 to 2.32)	0.79
> 300	13/365 (3.6)		
Coronary artery disease			
No	8/323 (2.5)	1.50 (0.66 to 3.40)	0.33
Yes	20/541 (3.7)		
History of a neurological event†			
No	22/754 (2.9)	1.89 (0.77 to 4.65)	0.17
Yes	6/110 (5.5)		
Pre-existing atrial fibrillation/atrial flutter			
No	22/621 (3.6)	0.69 (0.28 to 1.70)	0.42
Yes	6/243 (2.5)		
Chronic lung disease/chronic obstructive pulmonary disease			
No	21/557 (3.8)	0.61 (0.26 to 1.43)	0.25
Yes	7/305 (2.3)		
Serum creatinine >2 mg/dl			

Supplemental Table 1. Subgroups in early stroke for TAVR (univariable predictors) (*continued*)

Variable	n/N (KM Rates at 30 Days)	Hazard Ratio (95% CI)	P Value*
No	28/850 (3.3)	NA	0.99
Yes	0/14 (0.0)		
Postoperative atrial fibrillation / flutter			
No	23/771 (3.0)	1.81 (0.69 to 4.76)	0.23
Yes	5/93 (5.4)		
General anesthesia			
No	8/210 (3.8)	0.80 (0.35 to 1.82)	0.60
Yes	20/654 (3.1)		
Femoral/iliac access			
No	2/55 (3.6)	0.88 (0.21 to 3.70)	0.86
Yes	26/809 (3.2)		
More than one valve implanted			
No	22/776 (2.8)	2.47 (1.00 to 6.10)	0.05
Yes	6/88 (6.9)		

*Cox proportional hazard model was used with the data up to 1 month. †Stroke or transient ischemic attack. TAVR = transcatheter aortic valve replacement; KM = Kaplan-Meier; CI = confidence interval.

Supplemental Table 2. Subgroups in early stroke for SAVR (univariable predictors)

Variable	n/N (KM Rates at 30 Days)	Hazard Ratio (95% CI)	P Value*
Age, years			
< 80	19/330 (5.8)	0.89 (0.49 to 1.63)	0.71
≥ 80	24/466 (5.2)		
Sex			
Male	25/438 (5.7)	0.89 (0.48 to 1.63)	0.70
Female	18/358 (5.1)		
Body mass index, kg/m ²			
≤ 30	25/486 (5.2)	1.12 (0.61 to 2.06)	0.71
> 30	18/310 (5.8)		
Society of Thoracic Surgeons Predictor of Mortality, %			
< 3	9/123 (7.3)	0.69 (0.33 to 1.44)	0.33
≥ 3	34/673 (5.1)		
< 4	15/299 (5.0)	1.14 (0.61 to 2.13)	0.69
≥ 4	28/497 (5.7)		
Logistic EuroSCORE, %			
< 10	22/432 (5.1)	1.15 (0.63 to 2.09)	0.65
≥ 10	21/363 (5.8)		
New York Heart Association class			
II	22/333 (6.6)	0.68 (0.38 to 1.24)	0.21
III/IV	21/463 (4.5)		
Left ventricular ejection fraction, %			
≤ 50	11/134 (8.3)	0.59 (0.30 to 1.17)	0.13
> 50	32/658 (4.9)		
Hypertension			
No	9/77 (11.7)	0.40 (0.19 to 0.83)	0.01
Yes	34/719 (4.7)		
Previous coronary artery bypass grafting			
No	36/659 (5.5)	0.94 (0.42 to 2.11)	0.88
Yes	7/137 (5.1)		
Peripheral vascular disease			
No	30/558 (5.4)	1.03 (0.54 to 1.97)	0.93
Yes	13/238 (5.5)		
Prior percutaneous coronary intervention			
No	32/627 (5.1)	1.28 (0.65 to 2.55)	0.47
Yes	11/169 (6.5)		
5-Meter gait speed, sec			
≤ 6	20/359 (5.6)	1.03 (0.57 to 1.88)	0.92
> 6	23/403 (5.7)		
Diabetes			
No	28/519 (5.4)	1.00 (0.53 to 1.87)	1.00
Yes	15/277 (5.4)		

Supplemental Table 2. Subgroups in early stroke for SAVR (univariable predictors) (continued)

Variable	n/N (KM Rates at 30 Days)	Hazard Ratio (95% CI)	P Value*
Need for revascularization			
No	36/633 (5.7)	0.75 (0.34 to 1.70)	0.50
Yes	7/163 (4.3)		
Severe aortic calcification			
No	36/710 (5.1)	1.63 (0.73 to 3.67)	0.24
Yes	7/86 (8.2)		
Mini-Mental State Examination score			
< 25	7/104 (6.7)	0.78 (0.35 to 1.77)	0.56
≥ 25	33/611 (5.4)		
Maximum activated clotting time, sec			
≤ 300	2/29 (6.9)	0.78 (0.19 to 3.21)	0.73
> 300	40/736 (5.5)		
Coronary artery disease			
No	17/285 (6.0)	0.85 (0.46 to 1.57)	0.60
Yes	26/511 (5.1)		
History of a neurological event†			
No	37/697 (5.3)	1.15 (0.49 to 2.73)	0.75
Yes	6/99 (6.1)		
Pre-existing atrial fibrillation/atrial flutter			
No	33/585 (5.7)	0.83 (0.41 to 1.69)	0.61
Yes	10/211 (4.8)		
Chronic lung disease/chronic obstructive pulmonary disease			
No	27/529 (5.1)	1.18 (0.63 to 2.19)	0.60
Yes	16/267 (6.0)		
Serum creatinine >2 mg/dl			
No	43/779 (5.5)	NA	0.98
Yes	0/17 (0.0)		
Postoperative atrial fibrillation / flutter			
No	21/472 (4.5)	1.54 (0.85 to 2.80)	0.16
Yes	22/324 (6.8)		
Aortic root enlargement performed			
No	41/782 (5.3)	3.17 (0.77 to 13.09)	0.11
Yes	2/13 (16.7)		
Total aortic cross-clamp time, min		1.00 (0.99 to 1.01)	0.62

*Cox proportional hazard model was used with the data up to 1 month. †Stroke or transient ischemic attack. SAVR = surgical aortic valve replacement; KM = Kaplan-Meier; CI = confidence interval.

Supplemental Table 3. SF-36 Physical Summary Scores in TAVR and SAVR patients, with or without early stroke.

SF-36 Physical Component Summary	Early Stroke			Without Early Stroke		
	TAVR N=28	SAVR N=43	P Value	TAVR N=836	SAVR N=753	P Value
Baseline	36.4 ± 9.2 (27)	37.0 ± 9.7 (43)	0.793	36.6 ± 9.8 (816)	36.8 ± 9.7 (723)	0.697
30 Days	39.7 ± 11.3 (21)	33.2 ± 8.5 (36)	0.016	42.5 ± 9.9 (784)	36.2 ± 9.1 (658)	<0.001
3 Months	40.6 ± 12.1 (21)	38.8 ± 12.1 (31)	0.603	44.0 ± 9.7 (748)	42.6 ± 9.7 (652)	0.007
6 Months	42.4 ± 11.4 (20)	41.6 ± 12.0 (32)	0.816	43.0 ± 9.9 (755)	43.6 ± 10.1 (638)	0.268
12 Months	40.8 ± 10.6 (20)	39.0 ± 10.7 (35)	0.544	42.2 ± 10.3 (708)	42.6 ± 10.3 (586)	0.434

Data presented as mean ± standard deviation (number of patients with data). TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement; SF-36 = Short-Form 36

Supplemental Table 4. SF-36 Mental Summary Scores in TAVR and SAVR patients, with or without early stroke.

SF-36 Mental Component Summary	Early Stroke			Without Early Stroke		
	TAVR N=28	SAVR N=43	P Value	TAVR N=836	SAVR N=753	P Value
Baseline	51.8 ± 14.3 (27)	48.0 ± 12.0 (43)	0.234	49.9 ± 11.4 (816)	49.2 ± 11.7 (723)	0.211
30 Days	44.0 ± 13.9 (21)	43.9 ± 16.0 (36)	0.990	53.0 ± 10.4 (784)	49.0 ± 12.3 (658)	< 0.001
3 Months	49.8 ± 12.1 (21)	50.6 ± 13.4 (31)	0.827	54.6 ± 9.6 (748)	54.0 ± 10.0 (652)	0.265
6 Months	51.0 ± 10.7 (20)	51.0 ± 12.0 (32)	>0.999	53.8 ± 9.6 (755)	53.0 ± 10.0 (638)	0.138
12 Months	52.4 ± 12.7 (20)	50.7 ± 14.5 (35)	0.664	53.9 ± 9.5 (708)	53.6 ± 9.4 (586)	0.610

Data presented as mean ± standard deviation (number of patients with data). TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement; SF-36 = Short-Form 36

Supplemental Table 5. SF-36 Physical and Mental Summary Score, differences from baseline values in patients with early stroke.

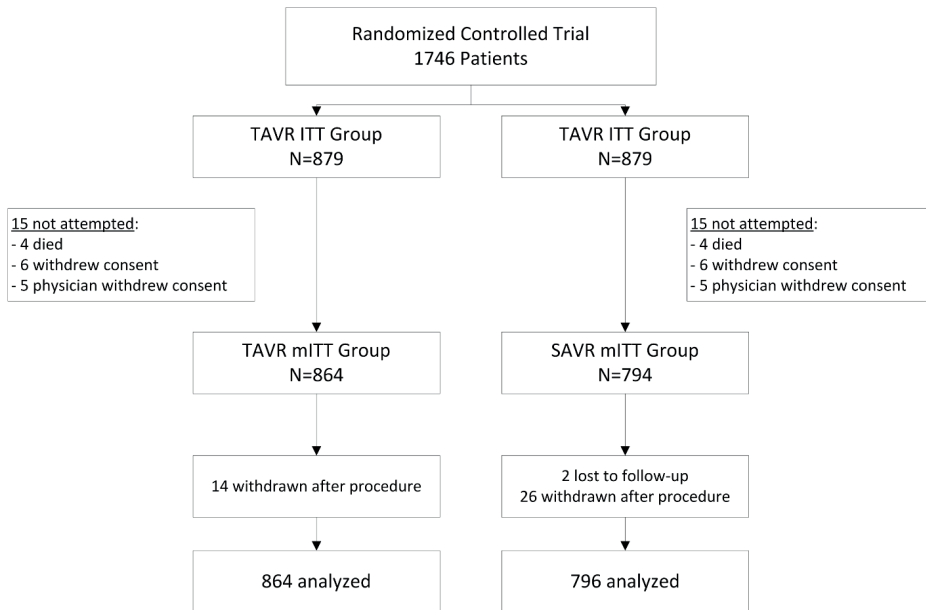
	TAVR N=28		SAVR N=43		
	n	Difference from baseline (95% CI)	n	Difference from baseline (95% CI)	P Value
SF-36 physical summary					
30 Days	21	4.3 (-0.5 - 9.1)	36	-2.6 (-5.8 - 0.6)	0.014
3 Months	20	6.5 (1.7 - 11.3)	31	3.4 (-0.6 - 7.4)	0.318
6 Months	19	7.4 (2.7 - 12.1)	32	5.4 (1.8 - 9.0)	0.485
12 Months	19	5.6 (1.3 - 9.9)	35	3.0 (-1.0 - 7.0)	0.402
SF-36 mental summary					
30 Days	21	-7.5 (-14.8 - -0.2)	36	-4.1 (-9.9 - 1.7)	0.469
3 Months	20	-2.6 (-10.8 - 5.6)	31	2.4 (-2.9 - 7.6)	0.269
6 Months	19	-1.3 (-8.5 - 6.0)	32	3.7 (-1.1 - 8.4)	0.226
12 Months	19	1.8 (-3.6 - 7.2)	35	2.9 (-1.5 - 7.3)	0.755

N= number of patients; n= number of patients with data; CI= confidence interval; TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement; SF-36 = Short-Form 36

Supplemental Table 6. SF-36 Physical and Mental Summary Score, differences from baseline values in patients with early stroke.

		TAVR N=836	SAVR N=753		
	n	Difference from baseline (95% CI)	N	Difference from baseline (95% CI)	P Value
SF-36 physical summary					
30 Days	770	5.8 (5.0 - 6.5)	637	-1.0 (-1.8 - -0.1)	< 0.001
3 Months	733	7.4 (6.7 - 8.2)	628	5.7 (4.8 - 6.5)	0.002
6 Months	737	6.3 (5.6 - 7.0)	616	6.4 (5.5 - 7.2)	0.927
12 Months	695	5.2 (4.4 - 5.9)	568	5.4 (4.5 - 6.2)	0.723
SF-36 mental summary					
30 Days	770	2.9 (2.1 - 3.8)	637	-0.4 (-1.4 - 0.7)	< 0.001
3 Months	733	4.8 (4.0 - 5.6)	628	4.7 (3.7 - 5.7)	0.883
6 Months	737	4.0 (3.2 - 4.9)	616	3.6 (2.7 - 4.6)	0.519
12 Months	695	4.0 (3.2 - 4.9)	568	4.2 (3.2 - 5.2)	0.778

N= number of patients; n= number of patients with data; CI= confidence interval; TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement; SF-36 = Short-Form 36



Supplemental Figure 1. Patient flow. The modified intention to treat (mITT) cohort includes patients who underwent an attempted implant.

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Coronary revascularization after surgical aortic valve replacement

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JTCVS Open doi: <https://doi.org/10.1016/j.xjon.2020.05.005>

ABSTRACT

Objective

It remains unclear how often coronary revascularization is necessary after aortic valve interventions, either by surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement. However, these data are relevant for treatment and prosthesis choice. The authors sought to analyze the incidence and characteristics of coronary revascularization after SAVR during follow-up.

Methods

Of 2256 patients undergoing isolated SAVR between 1987 and 2015, 420 patients (mean age 56.9 ± 15.5 years, 66.9% male) were followed at the Erasmus Medical Center. Incidence, predictors, and characteristics of coronary revascularization were analyzed. Cumulative incidence of revascularization was assessed using a competing risk approach.

Results

Mean follow-up after SAVR was 17.2 years (total of 4541 patient-years). A total of 24 patients underwent 28 procedures of revascularization. The cumulative incidence of revascularization after SAVR was 0.5%, 2.2%, 4.1%, and 6.9% at 1, 5, 10, and 20 years, respectively. The linearized rate of revascularization was 6.2 per 1000 patient-years. Percutaneous coronary intervention was the most common revascularization method (64%; $N = 18/28$). Revascularization before SAVR ($N = 36/420$; of whom 27 percutaneous coronary intervention) was an independent predictor of revascularization during follow-up (hazard ratio, 6.6; 95% confidence interval, 2.6-17.1; $P < .001$).

Conclusions

After SAVR, the rate of coronary revascularization was 6.9% ($N = 24/420$) at 20-year follow-up. Patients were at particular risk if they had undergone previous revascularization before SAVR. These data may furthermore be relevant to the transcatheter aortic valve replacement population

Key Words: aortic stenosis, aortic valve replacement, transcatheter, coronary artery bypass grafting, percutaneous coronary intervention

Transcatheter aortic valve replacement (TAVR) is now recommended for patients with severe aortic valve stenosis (AS) at intermediate and high surgical risk,^{1,2} adding more evidence to the already ongoing increase in the number of performed TAVR procedures in North America and Europe.^{3,4} Recent trials that included low-risk patients have reported noninferiority or even superiority of TAVR versus surgical aortic valve replacement (SAVR).^{5,6}

Reports have suggested that access to the coronary arteries may be difficult to establish after TAVR as a result of the positioning of the transcatheter valve.⁷ When indication expands toward low-risk patients, who often are younger, the need for coronary revascularization after TAVR may increase. However, due to the advanced age and presence of multiple comorbidities of patients in current TAVR trials and the relatively short-term follow-up available, the incidence of coronary revascularization has been difficult to determine. The probability of coronary revascularization after TAVR may increase in patients with longer life expectancies, with potential implications for procedure and prosthesis choices.

SAVR has been the standard of care for AS over the past 50 years. Therefore, long-term follow-up is available to determine the incidence of coronary revascularization after SAVR in low-risk patients. Since the historical SAVR patient population overlaps with current and future TAVR patient populations, data of revascularization after SAVR can provide insights into determining which surgical or transcatheter prostheses may be more appropriate in specific patients. The aim of this study was to assess the incidence and risk factors of coronary revascularization during long-term follow-up after SAVR.

METHODS

Study design

This observational, retrospective study consisted of adult (≥ 18 years) patients who underwent isolated SAVR with a mechanical or bioprosthetic valve between 1987 and 2015 at the Erasmus Medical Center (Erasmus MC), Rotterdam, The Netherlands. To ensure that all coronary revascularization procedures during follow-up were captured, only patients followed up at the outpatient clinic of the Erasmus MC were included in this study (Figure 1). Patients undergoing concomitant procedures or with active endocarditis were excluded. Coronary artery disease (CAD) was routinely assessed before SAVR by coronary angiography, and patients with CAD underwent concomitant coronary artery bypass grafting (CABG) according to the recommendations of clinical guidelines in use at the time of surgery and were excluded.

The study was approved by the local institutional review board, and patient-informed consent was waived. All the authors assured for the validity of the data and adherence to the protocol.

Data collection and follow-up

Baseline patient and procedural characteristics were collected from electronic medical records. Survival status was obtained through the National Death Registry.

After SAVR, patients returned to their referring cardiologist at Erasmus MC for routine, regular outpatient clinic visits at 3 and 6 months postoperatively and (bi-)annually thereafter. If CAD was diagnosed and revascularization was deemed necessary, patients underwent either percutaneous coronary intervention (PCI) or CABG at the Erasmus MC.

End points and definitions

The primary end point was coronary revascularization either by PCI or CABG. SAVR within 24 hours of establishing the indication was classified as urgent, between 24 hours and 3 days as semi-elective, and after 3 days as elective. Left ventricular function was classified as normal if the left ventricular ejection fraction (LVEF) was >50%, as mildly reduced if the LVEF was 40% to 50%, as moderately reduced if the LVEF was 30% to 40%, and as severely reduced if the LVEF was less than 30%, as measured or estimated by a trained echocardiographer.

Statistical analyses

Discrete variables are presented as numbers, percentages or proportions, and compared with either the χ^2 test or the Fisher exact test, where appropriate. Continuous variables are presented as means \pm standard deviation or median with the interquartile range if there was evidence of skewed data according to the Kolmogorov–Smirnov test, and compared with either the 2-sample *t* test or Wilcoxon rank-sum test, where appropriate.

Probabilities of the occurrence of revascularization and mortality were visualized using cumulative incidence curves with their according 95% confidence intervals. The cumulative incidence based on Kaplan–Meier estimates does not reflect the competing risk of death and the occurrence of revascularization and therefore overestimate the remaining lifetime risk of revascularization when the competing risk is high.⁸ To account for this overestimation, competing risk survival analysis was performed by means of nonparametric methods using the cumulative incidence competing risk method.^{9,10} Post-hoc subgroup analyses were performed according to whether revascularization had taken place before the SAVR procedure, age at time of SAVR (aged <65 or \geq 65 years), history of hypercholesterolemia, history of diabetes mellitus, indication of SAVR (AS, aortic valve regurgitation, or combined disease), and type of implanted valve (mechanical or bioprosthetic). Competing risk survival analyses in subgroups were compared

with the Fine and Gray test.¹¹ Furthermore, the linearized rate of revascularization was calculated per 1000 patient-years of follow-up.

Predictors of revascularization after SAVR were identified in a Cox proportional hazards model. Significant variables on univariable analyses were included in a multivariable Cox proportional hazards model. Data analyses were performed using SPSS 24.0 (IBM Corp, Armonk, NY) and R software, version 3.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline and procedural characteristics

From 4228 patients who underwent SAVR between 1987 and 2015, 420 patients underwent isolated SAVR and were followed up at the Erasmus MC and were included in this study (Figure 1). The mean age of the patients at the time of SAVR was 56.9 ± 15.5 years, and 66.9% (281/420) were male. The primary indication for SAVR was pure AS in 52.1% (219/420). A total of 8.6% (36/420) had previous revascularization. Mechanical valve prostheses were used in 66.7% (280/420). The rates of survival were 98.3%, 96.4%, 87.4%, 71.8%, 58.6%, and 47.4% at 30 days, and 1, 5, 10, 15, and 20 years of follow-up, respectively (Figure 2). Detailed baseline and procedural characteristics are provided in

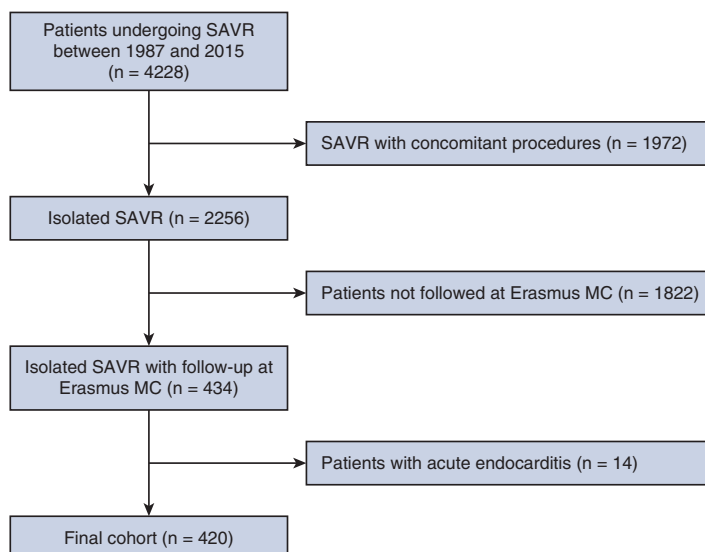


FIGURE 1. Flowchart of patient inclusion. A total of 4228 patients underwent SAVR at the Erasmus MC between 1987 and 2015, of whom a total of 420 patients were eligible for the study. SAVR, Surgical aortic valve replacement.

Table 1. Patients excluded from our study were older (66.1 ± 11.1 vs 56.9 ± 15.5 years, $P < .001$), had undergone more redo SAVR procedures (16.7% vs 4.3%, $P < .001$), more often underwent SAVR with an urgent indication (4.0% vs 0.4%, $P < .001$), and had less-frequent implantation of mechanical valve prosthesis (66.7% vs 48.0%, $P < .001$) compared with the included patients. Further detailed characteristics of patients excluded from our study are provided in Table 2.

TABLE 1. Baseline and procedural characteristics

	All patients (n = 420)	No revascularization (n = 396)	Revascularization (n = 24)	P value
Age, y	56.9 \pm 15.5 (420)	56.8 \pm 15.7 (396)	58.5 \pm 11.6 (24)	.592
Male sex	66.9 (281/420)	67.2 (266/396)	62.5 (15/24)	.637
Primary indication				.950
AS	52.1 (219/420)	52.3 (207/396)	50.0 (12/24)	
AR	25.5 (107/420)	25.5 (101/396)	25.0 (6/24)	
Combined AS + AR	22.4 (94/420)	22.2 (88/396)	25.0 (6/24)	
Bicuspid aortic valve	24.0 (101/420)	24.0 (95/396)	25.0 (6/24)	.910
Previous cardiac operation	28.6 (120/420)	28.8 (114/396)	25.0 (6/24)	.690
SAVR	16.7 (70/420)	16.7 (66/396)	16.7 (4/24)	>.999
CABG	2.6 (11/420)	2.3 (9/396)	8.3 (2/24)	.071
Other	9.3 (39/420)	9.3 (39/396)	0	.107
Hypertension	29.8 (125/420)	29.8 (118/396)	29.2 (7/24)	.948
Hypercholesterolemia	12.4 (52/420)	11.1 (44/396)	33.3 (8/24)	.001
Diabetes mellitus	9.3 (39/420)	8.8 (35/396)	16.7 (4/24)	.199
Arterial disease	3.6 (15/420)	3.3 (13/396)	8.3 (2/24)	.195
Peripheral	3.6 (15/420)	3.3 (13/396)	8.3 (2/24)	.195
Carotid	0.5 (2/420)	0.5 (2/396)	0	.727
Renal failure	2.6 (11/420)	2.5 (10/420)	4.2 (1/24)	.625
Previous myocardial infarction	4.3 (18/420)	4.0 (16/396)	8.3 (2/24)	.313
Previous revascularization	8.6 (36/420)	7.3 (29/396)	29.2 (7/24)	<.001
Previous PCI	6.4 (27/420)	5.6 (22/396)	20.8 (5/24)	.003
Previous CABG	2.6 (11/420)	2.3 (9/396)	8.3 (2/24)	.071
Previous decompensated heart failure	16.9 (71/420)	16.4 (65/396)	25.0 (6/24)	.276
Left ventricular function				.460
Preserved	77.6 (287/370)	77.6 (273/370)	77.8 (14/18)	
Mildly reduced	7.6 (28/370)	8.0 (28/370)	0	
Moderately reduced	9.2 (34/370)	8.8 (31/370)	16.7 (3/18)	
Severely reduced	5.7 (21/370)	5.7 (20/370)	5.6 (1/18)	
Atrial fibrillation	13.3 (56/420)	13.4 (53/396)	12.5 (3/24)	.902
Previous neurologic event	10.5 (44/420)	11.1 (44/396)	0	.084

TABLE 1. Baseline and procedural characteristics (*continued*)

	All patients (n = 420)	No revascularization (n = 396)	Revascularization (n = 24)	P value
CVA	4.8 (20/420)	5.1 (20/396)	0	.259
TIA	7.1 (30/420)	7.6 (30/396)	0	.162
COPD	8.3 (35/420)	8.3 (33/396)	8.3 (2/24)	>.999
Liver disease	1.4 (6/420)	1.5 (6/396)	0	.544
History of malignancy	8.1 (34/420)	8.1 (32/396)	8.3 (2/24)	.965
Urgency				.610
Elective	49.3 (173/351)	49.4 (165/334)	47.1 (8/17)	
Semi-elective	46.7 (164/351)	46.7 (156/334)	47.1 (8/17)	
Urgent	4.0 (14/351)	3.9 (13/334)	5.9 (1/17)	
Logistic EuroSCORE	5.7 ± 6.2 (204)	5.5 ± 6.1 (193)	8.8 ± 7.3 (11)	.085
Mechanical prosthesis	66.7 (280/420)	66.7 (264/396)	66.7 (16/24)	>.999
Year of operation				.383
1987-1994	24.5 (103/420)	23.7 (94/396)	37.5 (9/24)	
1995-2001	23.3 (98/420)	24.0 (95/396)	12.5 (3/24)	
2002-2008	26.7 (112/420)	26.8 (106/396)	25.0 (6/24)	
2009-2015	25.5 (107/420)	25.5 (101/396)	25.0 (6/24)	

Data are presented as % (n/N) and mean ± standard deviation or median (interquartile range). AS, Aortic valve stenosis; AR, aortic regurgitation, SAVR, surgical aortic valve replacement; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

TABLE 2. Baseline and procedural characteristics

	Patient followed-up in Erasmus MC	Patient not followed-up in Erasmus MC	P value
Age, y	56.9 ± 15.5 (420)	66.1 ± 11.1 (1782)	<.001
Male sex	66.9 (281/420)	57.4 (1023/1782)	<.001
Primary indication			
AS	52.1 (219/420)	69.8 (1243/1782)	<.001
AR	25.5 (107/420)	12.7 (226/1782)	<.001
Combined AS + AR	22.4 (94/420)	17.3 (308/1782)	.015
Bicuspid aortic valve	24.0 (101/420)	19.2 (343/1782)	.027
Previous cardiac operation	28.6 (120/420)	8.6 (154/1782)	<.001
SAVR	16.7 (70/420)	4.3 (76/1782)	<.001
CABG	2.6 (11/420)	3.7 (66/1782)	.276
Other	9.3 (39/420)	2.4 (43/1782)	<.001
Hypertension	29.8 (125/420)	34.3 (612/1782)	.073
Hypercholesterolemia	12.4 (52/420)	14.8 (264/1782)	.201
Diabetes mellitus	9.3 (39/420)	12.2 (218/1782)	.091

TABLE 2. Baseline and procedural characteristics (*continued*)

	Patient followed-up in Erasmus MC	Patient not followed-up in Erasmus MC	P value
Arterial disease	3.6 (15/420)	2.6 (47/1782)	298
Peripheral	3.6 (15/420)	2.4 (42/1782)	159
Carotid	0.5 (2/420)	0.3 (5/1782)	522
Renal failure	2.6 (11/420)	2.3 (33/1782)	312
Previous myocardial infarction	4.3 (18/420)	5.6 (99/1782)	297
Previous revascularization	8.6 (36/420)	7.8 (139/1782)	599
Previous PCI	6.4 (27/420)	5.1 (90/1782)	257
Previous CABG	2.6 (11/420)	3.7 (66/1782)	276
Previous decompensated heart failure	16.9 (71/420)	13.7 (245/1782)	097
Left ventricular function			
Preserved	77.6 (287/370)	82.5 (1348/1633)	026
Mildly reduced	7.6 (28/370)	6.3 (103/1633)	376
Moderately reduced	9.2 (34/370)	8.3 (136/1633)	592
Severely reduced	5.7 (21/370)	2.8 (46/1633)	006
Atrial fibrillation	13.3 (56/420)	13.5 (241/1782)	918
Previous neurologic event	10.5 (44/420)	8.0 (142/1782)	096
CVA	4.8 (20/420)	3.5 (62/1782)	212
TIA	7.1 (30/420)	5.1 (91/1782)	099
COPD	8.3 (35/420)	11.5 (205/1782)	061
Liver disease	1.4 (6/420)	0.2 (4/1782)	001
History of malignancy	8.1 (34/420)	6.1 (109/1782)	139
Urgency			
Elective	49.3 (173/351)	62.0 (975/1573)	<.001
Semi-elective	46.7 (164/351)	37.6 (591/1573)	001
Urgent	4.0 (14/351)	0.4 (7/1573)	<.001
Logistic EuroSCORE	5.7 ± 6.2 (204)	5.8 ± 5.8 (970)	740
Mechanical prosthesis	66.7 (280/420)	48.0 (855/1782)	<.001
Year of operation			
1987-1994	24.5 (103/420)	16.3 (290/1782)	<.001
1995-2001	23.3 (98/420)	25.4 (452/1782)	387
2002-2008	26.7 (112/420)	28.2 (502/1782)	536
2009-2015	25.5 (107/420)	30.2 (538/1782)	056

Data are presented as % (n/N) and mean ± standard deviation or median (interquartile range). AS, Aortic valve stenosis; AR, aortic regurgitation; SAVR, surgical aortic valve replacement; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

Revascularization after SAVR

The mean follow-up after SAVR was 17.2 years, with a total follow-up accumulating to 4541 patient-years. During follow-up, 24 patients underwent coronary revascularization, with 3 patients requiring a second and 1 patient requiring a third revascularization procedure. In the timeto- first event competing risk analysis with mortality, the rates of revascularization were 0.5%, 0.5%, 2.2%, 4.1%, 5.3%, and 6.9% at 30 days and 1, 5, 10, 15, and 20 years of follow-up, respectively (Figure 2). The mean time to the first revascularization was 8.9 ± 7.4 (range 0- 26.9 years). The linearized rate of revascularization was 6.2 per 1000 patient-years.

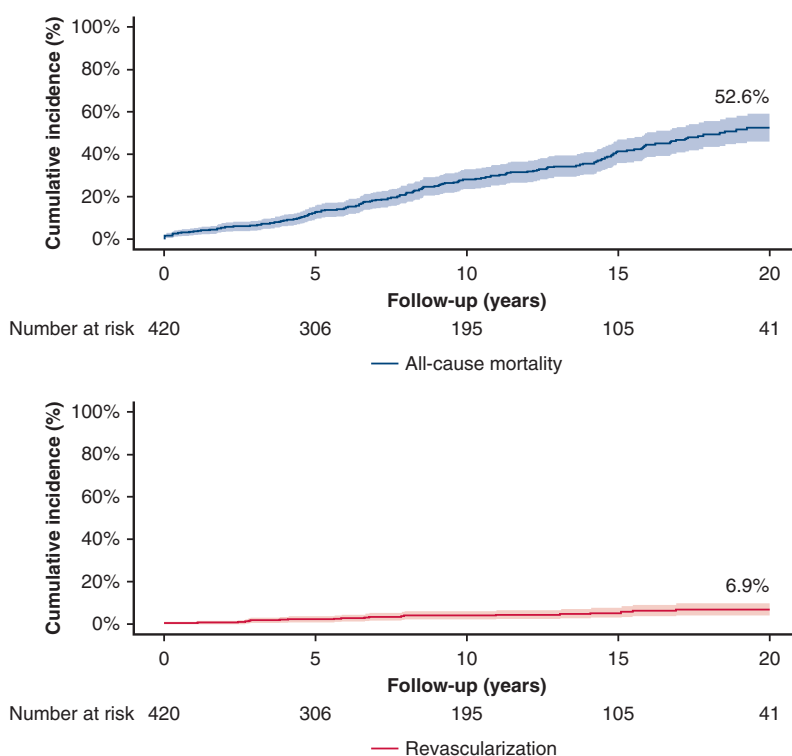


FIGURE 2. Mortality and coronary revascularization after SAVR. Competing risk cumulative incidences of mortality and coronary revascularization during 20-year follow-up according to (A) *blue line* presents the cumulative incidence of all-cause mortality competing with the risk of revascularization in our cohort and (B) *red line* presents the cumulative incidence of revascularization with either PCI or CABG competing with the risk of revascularization in our cohort. SAVR, Surgical aortic valve replacement; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Characteristics of revascularization

More patients underwent PCI than CABG, accounting for 64.2% of revascularization procedures ($n = 18/28$). Three patients (12.5%) needed urgent revascularization due to acute myocardial infarction (treated with PCI in all cases). Single-vessel disease was present in 16 patients (67%) and multivessel disease was present in 8 patients (33%). Four patients had lesions in both the left and right coronary artery. Characteristics of revascularization are displayed in Table 3.

Subgroup analysis and predictors of revascularization after SAVR

The incidence of revascularization at 15 years of followup was significantly greater in patients with previous revascularization than in patients without previous revascularization (22.1% vs 3.7%, $P < .001$), respectively. Further, the incidence of revascularization was greater in patients with hypercholesterolemia compared with patients without hypercholesterolemia (14.2% vs 4.1%, $P = .002$), respectively. There were no differences in revascularization rates during follow-up in subgroups according to age (4.9% for patients aged <65 vs 5.9% for patients aged ≥ 65 , $P = .42$), diabetes mellitus (8.8% for patients with a history of diabetes mellitus vs 5.0% for no diabetes mellitus, $P = .24$), primary indication for SAVR (5.6% for AS vs 7.9% for aortic valve regurgitation vs 2.2% for combined disease, $P = .36$), or type of valve used (6.8% for biological vs 4.4% for mechanical, $P = .16$) (Figures 3 and 4).

Factors associated with coronary revascularization during follow-up

Patients who underwent coronary revascularization during follow-up more often had hypercholesterolemia at baseline (8/24 vs 44/396, $P = .001$) and undergone revascularization before the index procedure (7/24 vs 29/396, $P < .001$) than patients that did not undergo revascularization during follow-up (Table 1). In multivariable analyses, the presence of revascularization, hypercholesterolemia, and diabetes mellitus before the index procedure were the only independent predictor of revascularization during follow-up (Table 4).

TABLE 3. Characteristics of revascularization after SAVR

Patient	Date of SAVR	Revascularization after SAVR			Previous revascularization before SAVR			Subsequent revascularization(s)	
		Date	Urgency	Lesion	Modality	Details	Date	Modality	
#1	June 25, 1987	June 1, 1995	Elective	OM, IM	PCI		September 11, 1995	PCI	
#2	August 12, 1987	December 20, 2007	Elective	OM, PD	CABG	SVG-OM-PD			
#3	May 18, 1988	June 24, 2003	Elective	LAD	CABG	SVG-LAD			
#4	June 3, 1988	November 21, 2003	Elective	RCA	PCI				
#5	September 1, 1988	August 4, 2015	Elective	LAD, LCx	PCI				
#6	March 21, 1989	November 4, 1994	Elective	RCA	PCI		January 29, 2001, and September 12, 2001	CABG and CABG	
#7	July 25, 1990	March 29, 1993	Elective	LAD	CABG	LIMA-LAD			
#8	October 7, 1993	September 27, 2004	Elective	LAD	PCI		August 27, 2012	PCI	
#9	November 9, 1993	March 10, 2015	Elective	LAD, RCA	PCI				
#10	July 1, 1998	August 3, 2012	Elective		CABG	SVG-RCA			
#11	August 7, 1998	June 30, 2015	Urgent	LAD, RCA	PCI				
#12	June 2, 2001	July 4, 2014	Elective	LAD	CABG	LIMA-LAD			
#13	November 28, 2002	September 3, 2009	Elective	LAD, IM, OM	CABG	LIMA-LAD SVG-IM-OM			
#14	January 31, 2003	December 6, 2005	Elective	RCA	PCI		October 30, 2002	PCI	

TABLE 3. Characteristics of revascularization after SAVR (continued)

Patient	Date of SAVR	Revascularization after SAVR			Lesion	Modality	Details	Previous revascularization before SAVR		Subsequent revascularization(s)	
		Date	Urgency					Date	Modality	Date	Modality
#15	December 20, 2004	October 26, 2010	Elective	OM	PCI						
#16	June 28, 2006	May 2, 2014	Urgent	SVG	PCI			May 2, 2000	CABG		
#17	October 31, 2008	December 7, 2012	Elective	RCA	PCI			January 19, 2004	PCI		
#18	November 4, 2008	August 27, 2012	Elective	RCA	PCI			September 27, 2004	PCI		
#19	May 13, 2009	December 31, 2015	Elective	LAD, LCx	PCI			May 20, 2003	PCI		
#20	December 2, 2011	January 9, 2013	Elective	OM	PCI			November 4, 2011	PCI		
#21	April 27, 2012	February 5, 2015	Urgent	LAD	PCI			July 17, 1997	CABG		
#22	October 5, 2012	March 11, 2015	Elective	LAD	CABG		LIMA-LAD				
#23	May 2, 2013	May 2, 2013	Elective	PD	CABG		SVG-PD				
#24	October 18, 2013	October 24, 2013	Elective	LCx	PCI						

SAVR, Surgical aortic valve replacement; OM, obtuse marginal artery; IM, intermediate artery; PCI, percutaneous coronary intervention; PD, posterior descending artery; SVG, saphenous vein graft; LAD, left anterior descending artery; RCA, right coronary artery; LCx, left circumflex artery; CABG, coronary artery bypass grafting; LIMA, left internal mammary artery.

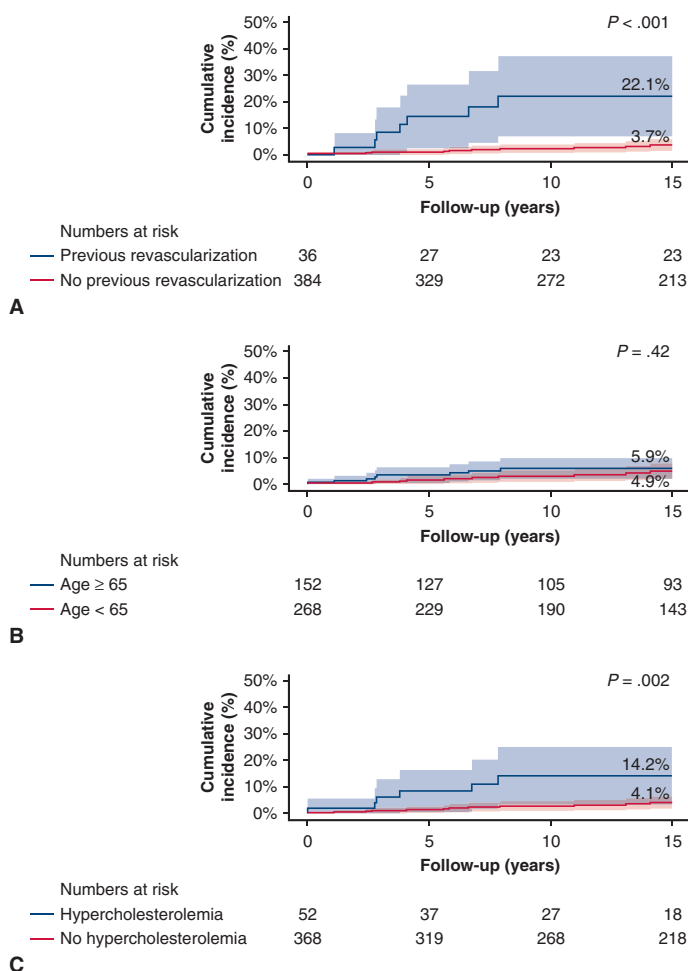


FIGURE 3. Revascularization after SAVR in various patient subgroups. Competing risk cumulative incidences of revascularization after SAVR in subgroups according to the following: (A) with and without previous revascularization. *Blue line* shows patients with no history of revascularization. *Red line* shows patients with a history of revascularization. (B) Age at SAVR younger or older than 65 years. *Blue line* shows patients aged 65 or older. *Red line* shows patients aged younger than 65 years. (C) With and without a history of hypercholesterolemia. *Blue line* shows patients with history of hypercholesterolemia. *Red line* shows patients without a history of hypercholesterolemia.

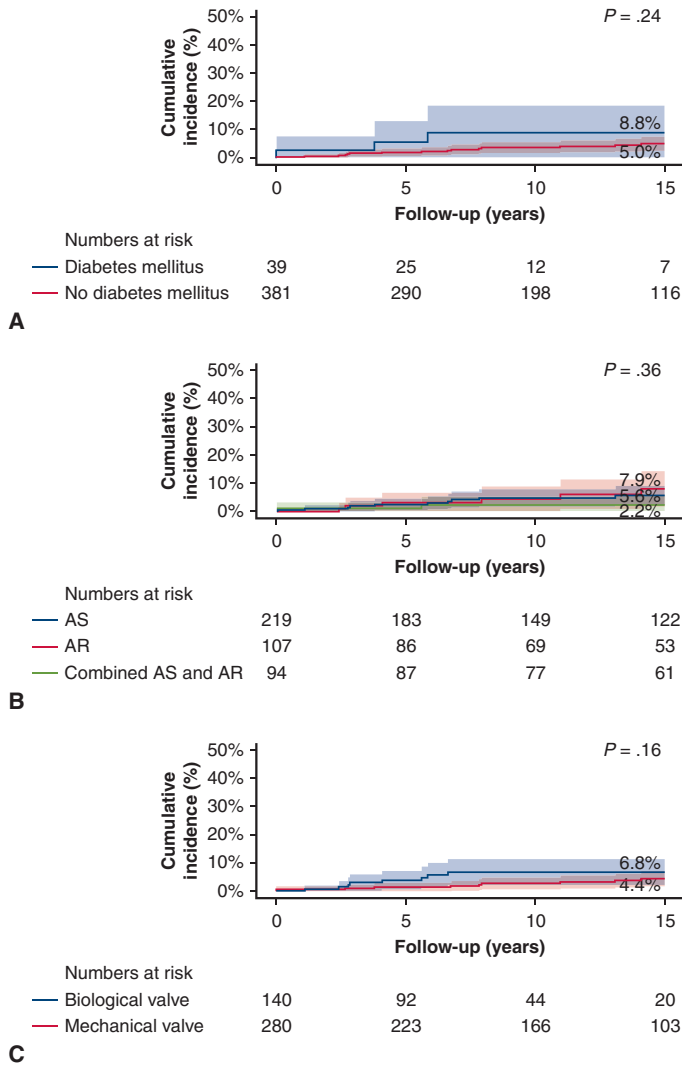


FIGURE 4. Revascularization after SAVR in various patient subgroups. Competing risk cumulative incidences of revascularization after SAVR in subgroups according to the following: (A) with and without a history of diabetes mellitus. Blue line shows patients with history of diabetes mellitus. Red line shows patients without a history of diabetes mellitus. (B) Primary indication for SAVR. Blue line shows patients undergoing SAVR for AS. Red line shows patients undergoing SAVR for AR. Green line shows patients undergoing SAVR for combined AS and AR. (C) Mechanical or biological prosthesis received. Blue line shows the use of a biological valve. Red line shows the use of a mechanical valve. AS, Aortic valve stenosis; AR, aortic regurgitation.

TABLE 4. Predictors of revascularization after SAVR

Characteristics	Univariable HR (95% CI); <i>P</i> value	Multivariable HR (95% CI); <i>P</i> value
Age	1.0 (1.0-1.1); <i>P</i> = .16	
Sex (female)	1.5 (0.6-3.4); <i>P</i> = .35	
Indication AS	1.1 (0.5-2.5); <i>P</i> = .79	
Indication AR	1.1 (0.4-2.7); <i>P</i> = .90	
Indication AS + AR	0.8 (0.3-2.1); <i>P</i> = .68	
Hypertension	1.2 (0.5-2.9); <i>P</i> = .68	
Hypercholesterolemia	5.0 (2.1-11.7); <i>P</i> < .001	3.4 (1.3-8.6); <i>P</i> = .010
Diabetes mellitus	3.2 (1.1-9.7); <i>P</i> = .037	2.1 (0.7-6.5); <i>P</i> = .214
Arterial disease	3.7 (0.9-15.9); <i>P</i> = .08	
Renal failure	3.9 (0.5-29.1); <i>P</i> = .19	
Previous MI	2.7 (0.6-11.7); <i>P</i> = .17	
Previous revascularization	8.2 (3.3-20.2); <i>P</i> < .001	6.6 (2.6-17.1); <i>P</i> < .001
Decompensated heart failure	1.8 (0.7-4.6); <i>P</i> = .20	
LVEF <50%	1.2 (0.4-3.6); <i>P</i> = .76	
Atrial fibrillation	1.0 (0.3-3.4); <i>P</i> = .97	
Previous stroke or TIA	0.0 (0.0-18.5); <i>P</i> = .31	
COPD	1.7 (0.4-7.3); <i>P</i> = .49	
Urgent SAVR vs non-urgent	1.6 (0.2-12.2); <i>P</i> = .64	
Log EuroSCORE	1.1 (1.0-1.1); <i>P</i> = .078	
Mechanical prosthesis	0.5 (0.2-1.3); <i>P</i> = .18	

HR, Hazard ratio; CI, confidence interval; AS, aortic valve stenosis; AR, aortic regurgitation; MI, myocardial infarction; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; SAVR, surgical aortic valve replacement; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

DISCUSSION

In this cohort of 420 patients who underwent isolated SAVR, 24 (5.7%) patients underwent a total of 28 revascularization procedures. The cumulative incidence of revascularization was 6.9% at 20-year follow-up, with a linearized rate of 6.2 per 1000 patient-years. In the current study, concomitant CABG was generally performed in patients with significant coronary stenosis. The risk of requiring coronary intervention during follow-up after SAVR in patients with no significant coronary stenosis at the time of intervention appears to be low as 6.9% at 20-year follow-up (Figure 5).

The incidence of revascularization was greater than that of the general population. Subgroup analyses showed that patients who had undergone previous revascularization before SAVR and patients with a history of hypercholesterolemia had significantly greater rates of revascularization during follow-up. Clearly patients with already established CAD, but nonsignificant at the time of SAVR, carry a risk of progression of CAD to a

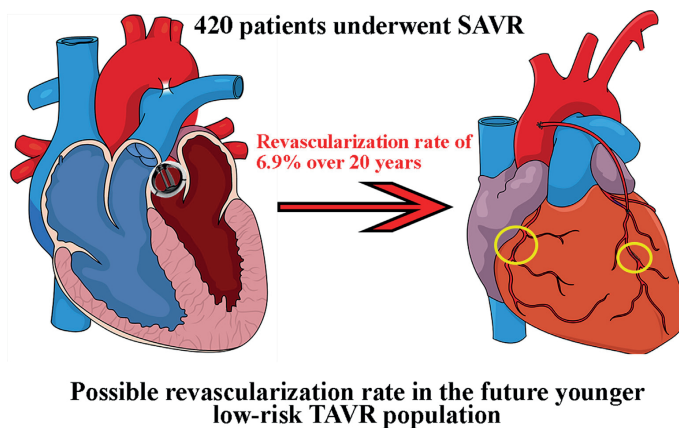


FIGURE 5. Cumulative competing risk incidence of revascularization presented as a graphical abstract. Competing risk cumulative incidence of coronary revascularization during 20-year after surgical aortic valve replacement. Coronary revascularization either done with coronary artery bypass grafting or percutaneous coronary intervention. Percutaneous coronary intervention is *encircled*. SAVR, Surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

severity requiring intervention. Other risk factors of CAD, like hypertension and diabetes, were not associated with revascularization in our multivariable analysis, although this may be the result of a relatively low sample size in our study.

Of the patients who underwent revascularization, 16 patients had single-vessel disease and 8 patients 2-vessel disease. There were no patients with left main or 3-vessel disease. Considering the current guidelines for revascularization, the majority of patients would be referred for PCI on the basis of the complexity of coronary disease.¹² Eight patients with more complex coronary disease underwent CABG during follow-up.

These data are important in the era of expanding indications for TAVR. Recently, 2 randomized controlled trials showed significant benefit of TAVR compared with SAVR in the low-risk population.^{5,6} Revascularization with PCI after TAVR can be associated with multiple technical challenges related to transcatheter heart valve platform, coronary access, with potential consequences of (1) damaging the prosthetic heart valve, (2) dissecting the coronary artery, (3) acute kidney injury related to increased contrast usage, and (4) an unsuccessful procedure.¹³ Because CAD is present in 40% to 75% of patients undergoing TAVR,¹⁴ algorithms on obtaining coronary access have already been developed from experiences during concomitant or staged TAVR and PCI procedures.⁷ The presence of CAD in the younger population undergoing TAVR is not well known, as studies mostly consist of elderly patients. Therefore, this study is the first to systematically assess the long-term rate of revascularization after aortic valve intervention in low-risk patients without CAD. Although our population consists exclusively of isolated SAVR procedures, it provides evidence on rates of revascularization that may be extrapolated

to an overall TAVR population of low- to high-risk patients. Yet, literature also suggests that a proportion of patients might benefit from revascularization in the setting of acute coronary syndrome post-TAVR, and therefore greater incidences of revascularization could be expected in patients who initially would have been treated with medical therapy, when TAVR will expand toward the younger population.¹⁵

Of note, the mean age of our population was 57 years old as opposed to the current TAVR population with an advanced age, but a subgroup analysis according to age showed that the long-term rate of revascularization was comparable in patients younger or older or equal to 65 years. Expanding indication to lower-risk patients may have consequences for valve choice, given the younger age, and considering that coronary access is more challenging with a supra-annular TAVR than an intra-annular TAVR.⁷

Limitations

This is a retrospective study that has inherent shortcomings related to data collection, changes in definitions of comorbidities, and patients being lost to follow-up. However, we included only patients who were followed after SAVR at our own outpatient clinic to minimize this risk. The multivariable analyses to identify predictors of revascularization may have been underpowered due to the small number of patients that needed a revascularization procedure and the unavailability of all known risk factors for coronary artery disease. Furthermore, although the decision was made not to include patients undergoing SAVR with concomitant CABG in this cohort, we did not have any information on the presence and degree of nonsignificant CAD that may increase the risk of coronary revascularization during followup as a result of progression of disease.

CONCLUSIONS

In this retrospective analysis of patients who underwent isolated SAVR, the rate of requiring coronary revascularization at 20-year follow-up was relatively low. However, the rate was greater in patients who had undergone previous revascularization at the time of SAVR. These data provide some insights into requirements for coronary revascularization that may be relevant for the TAVR population. Future, larger studies are required on surgical and transcatheter cohorts to provide more insights into which patients are at particular risk of requiring coronary revascularization after aortic valve intervention.

Conflict of Interest Statement

Dr van Mieghem has received institutional research grant support from Boston Scientific, Medtronic, and Abbott and is an advisor to Medtronic and Boston Scientific. Dr Head is

an employee of Medtronic, plc. Prof Kappetein is also an employee of Medtronic, plc. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

CENTRAL MESSAGE

In a large SAVR cohort, the rate of coronary revascularization was 6.9% after 20-year followup. Previous revascularization was an independent predictor of revascularization after SAVR during follow-up.

PERSPECTIVE

Coronary revascularization rates after SAVR can be used to predict the need for revascularization after TAVR, should TAVR further expand into younger, lower-risk populations. Dedicated studies are required to address the incidence, predictors, and feasibility of revascularization after TAVR.

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9

Discussion

The aim of this thesis was to facilitate the unbiased comparison of different prosthetic valves and to study the outcomes and trends of surgical and transcatheter treatment of aortic valve disease. In this last chapter, the findings of this thesis are discussed from a broader perspective. Firstly, the characteristics and pitfalls of the assessment of surgical prosthetic valves, and efforts to achieve uniform prosthetic valve labeling will be summarized. Secondly, the past, present, and potential future of aortic valve interventions, and several important outcomes after aortic valve replacement are discussed. Furthermore, directions for future research and improvements are given.

Information for optimal surgical prosthetic heart valve choice

Intraoperative prosthetic heart valve choice during surgical aortic valve replacement is of paramount importance to ensure optimal short- and long-term postoperative outcomes. This choice must be based on thorough knowledge of prosthetic heart valve characteristics, including physical dimensions, fit to the patient's annulus, predicted hemodynamic performance and long-term durability. According to European and North American regulations, manufacturers are obliged to provide this information in a complete, standardized manner (1, 2). The amount and quality of data available on surgical prosthetic heart valves are repeatedly proven to be suboptimal (3).

To explore solutions, leading European and American surgical societies, the European Association for Cardio-Thoracic Surgery (EACTS), the Society of Thoracic Surgeons (STS) and the American Association for Thoracic Surgery (AATS) established a Task Force, composed by delegates of the Societies, cardiologists, engineers, representatives of the International Organization for Standardization (ISO), European and American regulators, and representatives of all major valve manufacturers. The Task Force produced a series of documents (**Chapter 2** and **Chapter 3**), in which the background of surgical heart valve labeling and the current practice of prosthetic heart valve assessment are analyzed. Furthermore, these documents formulate comprehensive recommendations for providing information on surgical prosthetic heart valves in transparent, uniform, and comparable manner.

In **Chapter 2**, the background and current practice of prosthetic heart valve assessment, sizing and labelling is summarized, and several key issues are identified. Firstly, it is concluded that the reporting of physical dimensions of prosthetic valves is non-uniform. Technical standards of the ISO are one of the cornerstones of premarket assessment both in the European Union and in the United States (1, 4). These standards provide guidance on the preclinical and clinical assessment of prosthetic valves including in vitro durability and hydrodynamic testing, reporting of physical dimensions and product labelling. Although continuously updated, these standards are not conclusive. One of the shortcomings is that the set of physical dimensions provided in ISO to describe prosthetic valves is incomplete, which leads to non-uniform reporting (5). Secondly,

the definition of labelled valve size is unclear, and inconsistencies exist between the dimensions of valve sizers and labelled valve size. ISO defines labelled valve size as “the size of the patient tissue annulus where the valve fits”, but does not standardize valve sizers (5). This lack of standardization led to the widely known sizer-labelled size discrepancies, which prohibits the direct comparison of similarly sized valves as they might not fit in the same annulus (6-8). Thirdly, information on in vivo hemodynamic performance of prosthetic valves is limited in the Instruction for Use (IFU) leaflets and is lacking on package labels. Prosthetic heart valves must undergo thorough in vitro hydrodynamic testing. Importantly, in vitro hydrodynamic testing cannot reliably predict actual in vivo hemodynamic performance. Furthermore, results of in vitro testing can be different between testing centers or pulse duplicator models for the same valve (9, 10). Lastly, this uncertainty around exact hemodynamic performance prohibits designing reliable tools to assess and prevent prosthesis-patient mismatch (PPM) (11).

In **Chapter 3**, problems listed in Chapter 2 are revisited and comprehensive recommendations are formulated to improve surgical prosthetic heart valve labeling. Firstly, a complete, standardized set of physical dimensions is proposed that should be reported by manufacturers for all valves. This set completes the existing ISO dimensions and gives clear definitions (5). Secondly, a solution is proposed to de-cypher the meaning of labelled valve size. As prostheses with similarly sized sizing tools fit in the same annulus, we suggest that besides prosthesis dimensions, manufacturers should also provide the exact diameters of valve-related sizers. This is a directly available parameter and having this dimension for all valves would immediately solve the decade-long confusion and frustration caused by being unable to compare valves based on labelled size. Thirdly, recommendations are formulated on the quality and extent of hemodynamic data on prosthetic heart valves. In line with applicable guidelines, we suggest the use of echocardiographically determined mean transprosthetic gradients and effective orifice area for this purpose (12, 13). Measurements should be performed between 30 days and 1 year after implant and determined in a large enough ($n \geq 30$) reference population, for each corresponding valve size. To avoid “cherry-picking” of favorable study results, we propose that besides the data, relevant study characteristics should also be reported, and core laboratory adjudicated data should be used, whenever possible. Fourthly, a novel tool is suggested to assess the probability of prosthesis-patient mismatch (PPM). In this new PPM chart, the percentage probability of predicted severe PPM is displayed, based on the distribution of reference EOA data, patient characteristics and widely accepted PPM cut-offs. Lastly, in **Chapter 3** we suggest that all this information should be made available on standardized sheets, on so-called “Valve Charts”. Consulting these charts would provide a complete overview of prosthesis characteristics and would allow quick, direct and unbiased comparison of valves from different manufacturers, solving the current situation without drastically changing existing product labeling.

One of the most important questions after aortic valve replacement is whether the hemodynamic properties of the implanted prosthesis can fulfil the circulatory requirements of the patient. In other words, that PPM is avoided (14). PPM is associated with worse long-term survival and impaired prosthesis durability (15-19). Historically, valve manufacturers provided indexed effective orifice area (EOAi) charts to forecast the presence of PPM after valve replacement. Although these charts are undeniably attractive due to their simplicity, they are also proven to be unreliable in predicting PPM (11, 20, 21). In **Chapter 4** we discuss and highlight the differences between the traditional EOA charts, and the novel PPM chart suggested by the EACTS-STAS-AATS Valve Labeling Task Force. Although both charts are based on the widely accepted EOAI cutoff for severe PPM ($\text{EOAI} < 0,65 \text{ cm}^2/\text{m}^2$), the novel PPM chart provides a probability of PPM based on the distribution of reference EOAs, instead of classifying PPM as a binary (“present” or “absent”) outcome. This method is more accurate and helps surgeons to better understand the ambiguity of predicting PPM based on EOAI cutoffs. This creates more space for individualized treatment decisions where the predicted risk of PPM can be individually weighed against the risks of an additional annular enlargement procedure (22) or TAVI implantation. Importantly, the novel PPM chart cannot be considered as the ultimate solution for preventing PPM as it gives only a probability, and it does not say in which cases PPM will certainly occur. Indeed, the use of predicted EOAI cutoffs is unlikely to be able to exclusively prevent PPM, and novel methods are needed to be developed to forecast the scenario when the implanted valve will actually be too small for the individual patient (23).

The past and future of aortic valve interventions

The landscape of aortic valve interventions has rapidly changed in the last decade. Until recently, surgical aortic valve replacement was the standard of care for the treatment of severe aortic valve stenosis. In the last decade, however, TAVI has challenged the ultimate role of SAVR and became an established alternative in selected patient populations (24-30). This makes ever more important to critically investigate the trends and outcomes of different treatment modalities, as these factors have a major influence on treatment allocation in the clinical practice.

Although TAVI is undeniably attractive due to its minimally invasiveness, surgical aortic valve replacement has earned its place in the clinician’s armamentarium, with excellent long-term outcomes (31). In **Chapter 5**, we analyzed the long-term outcomes after SAVR in the Erasmus MC over the past three decades. We found that, despite the continuously increasing comorbidity burden and patient complexity, the relative survival of patients undergoing primary isolated SAVR was excellent, 92,4% (CI: 89,4 – 95,5%) at 10 years and remained as high as 73% (CI: 67,1 – 81,1%) at 20 years after the index procedure. These findings reinforce the role of SAVR in the treatment of younger,

low-risk patients having aortic valve disease, although also highlights the fact that SAVR cannot completely restore life-expectancy in patients having aortic valve disease (32). The question of whether this loss in life expectancy depends on the age of the patients, remains to be answered.

Another important finding of our study was that the population undergoing surgical aortic valve replacement has changed during the last decades, with a larger group of patients between 70 – 80 years being treated for aortic valve disease. In the last years, this group became the majority of patients undergoing SAVR. Among other factors, this shift partially explains the considerable increase in bioprostheses use, a trend also observed in several Western countries (33, 34). Importantly, the group of younger patients remains constant, and these patients receive mostly mechanical valves (35).

After a constant grow, annual SAVR numbers became stagnating or slightly decreasing in the most recent period. This is due to the introduction of TAVI and the increasingly overlapping indications of TAVI and SAVR in clinical practice guidelines (36, 37). Of note, the dramatic increase of TAVI numbers in the recent years also lead to a parallel increase in the total number of patients treated for aortic stenosis. This suggest that TAVI and SAVR are not directly competitive but rather complementary therapies, although expansion of TAVI to the surgical population is inevitable (38). Previously, our group performed a modelling study which analyzed the prevalence of aortic stenosis in the elderly. This study demonstrated that historically, approximately 40% of patients with aortic valve stenosis did not undergo surgery which provided predictions for the cumulative number of potential candidates in Western countries (39). We repeated this study (**Chapter 6**) with a different methodology to estimate the actual yearly number of TAVI candidates in different European and North American countries. Data derived from epidemiological studies and large registries were collated with population statistics in each country and the incidence rate of severe aortic stenosis were estimated. Our results show the annual number of TAVI candidates could be as high as approximately 3.600/year in the Netherlands (CI: 2185 - 5481), 20.000/year in Germany (CI: 12.237 – 31.180) or 52.000/year in the United States (CI: 31.357 – 78.241). The validity of these estimations has already been confirmed by data on actual yearly TAVI numbers from large registries reflecting actual clinical practice (40, 41). Our study also considered several alternative scenarios. One of these scenarios was the prediction of the number of potential TAVI candidates if also elderly, low risk patients would be considered for TAVI instead for SAVR. This hypothetical scenario might become reality soon, considering the change in age thresholds recommended for treatment allocation in aortic stenosis in the latest European clinical practice guidelines (42).

Beside the number of annual candidates, yearly TAVI procedures per country are influenced by several other factors (43). In some patients, who might otherwise be candidates for TAVI, an intervention might be simply futile due to extreme comorbidity burden

with no real chance for recovery or for an acceptable quality of life. Moreover, societal factors, access to care and reimbursement also play a critical role (44). This mandates the careful adaption of international clinical practice guidelines into national recommendations as their societal expectations and health-care systems differ considerably between countries (45). Furthermore, the long-term durability and the cost-effectiveness of TAVI compared to SAVR in patients with longer life expectancy are at this moment unknown. Implanting TAVI valves in younger patients could lead to a higher rate of reinterventions due to prosthesis degeneration at the long-term (31, 46-49).

Cerebrovascular accidents (CVAs) are considered as one of the most important outcomes after heart valve interventions. CVAs cause substantial excess mortality and have a major impact on quality-of-life (50). Both TAVI and SAVR have several inherent factors that can increase the risk of a periprocedural CVA. The SURTAVI randomized controlled study compared surgical and transcatheter aortic valve replacement in intermediate-risk patients (27). This study employed a strict protocol of neurological examinations that allowed the in-depth analysis of CVAs occurring in the periprocedural period. We performed a study (**Chapter 7**) to analyze the incidence, characteristics, and consequences of neurological events in patients enrolled in the SURTAVI trial. In this analysis, we found that more strokes occurred after SAVR than after TAVI in the early post-procedural period (3,3% vs 5,4% $p=0,031$), although at one year the rate of stroke was not statistically different (5,2% vs 6,9%, $p=0,136$, for TAVI and SAVR, respectively). Of note, the use of embolic protection devices was not allowed in the SURTAVI study. When positioned in the aortic arch, these devices can filter out debris coming loose during aortic valve interventions (51). Embolic protection devices have been investigated in both TAVI and SAVR and although their use seems logical, no convincing evidence was found to date to prove their efficacy (52, 53).

Another important aspect of this study was to investigate the quality of life, with special emphasis on patients suffering a periprocedural stroke. Besides survival, quality of life is the most important measure of procedural success after any intervention from the patient's perspective. We found that at baseline, patients waiting for an aortic valve intervention have a lower generic health status than the general population when evaluated with the Medical Outcomes Study Short Form (SF-36), which improved faster after TAVI than after SAVR (54). Importantly, despite periprocedural stroke, measured quality of life improved equally after TAVI and SAVR and was better than at baseline after 1 year after the index procedure.

A not negligible proportion of patients requiring aortic valve replacement also have coronary artery disease. Coronary revascularization can be easily performed during SAVR or performed in a staged fashion before TAVI. However, some patients may need coronary revascularization at a later moment. Recent studies have demonstrated that acute coronary syndromes, especially a STEMI after TAVI is associated with considerable

excess mortality (55, 56). Access to the coronary arteries can be challenging after implantation of a transcatheter valve, as the stent frame or the leaflets of the native valve can partially block the coronary ostia (57). Since long-term follow up after TAVI in younger patients is lacking, we performed a study (**Chapter 8**) on a large cohort of patients undergoing SAVR to assess the magnitude of this problem. Our study demonstrated that the revascularization rate after isolated aortic valve replacement was low, 4,1% and 6,9% at 10 and 20 years, respectively. However, the rate of coronary revascularization at long-term (at 15 years) was higher in patients who already underwent revascularization before aortic valve replacement (22,1 vs 3,7% $p < 0,001$) and in those with documented hypercholesterolemia (14,2% vs 4,1% $p = 0,002$). These data might be a useful adjunct for decision making in patients with severe AS who have a relatively long life expectancy.

Conclusions

The landscape of aortic valve interventions is rapidly changing. Informed prosthetic heart valve choice has a key role in ensuring optimal patient outcomes. In this thesis, we analyzed the current practice and shortcomings of surgical prosthetic heart valve labelling and investigated the most important outcomes and trends of aortic valve replacement. We concluded that despite continued efforts in the last decades, optimal selection and unbiased comparison of surgical prosthetic valves remain cumbersome. To solve these issues, combined effort and cooperation of all stakeholders are required. In this thesis, we provided comprehensive recommendations on how the current situation can be improved and suggested a novel tool to assess the probability of patient-prosthesis mismatch. We demonstrated that although SAVR have excellent very long-term outcomes, short-term survival and neurological outcomes after TAVI and SAVR are comparable. In the recent decades, an increasing number of elderly patients are considered for aortic valve replacement which predicts a further increase in annual TAVI numbers. Importantly, although outcomes after aortic valve interventions are overall well-studied, there are still evidence gaps that mandates further research.

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10

Summary

The aim of this thesis was to facilitate the unbiased comparison of different prosthetic valves and to study the outcomes and trends of surgical and transcatheter treatment of aortic valve disease.

Chapter 1 provides a general introduction to the topics discussed in this thesis. Furthermore, the aims and an outline of the studies included in this thesis are given.

Chapter 2 is the first consensus document of the EACTS-STS-AATS Valve Labelling Task Force, which focuses on the present problems around the selection of surgical prosthetic heart valves. The following major issues are identified: (i) the reporting of physical dimensions of prosthetic valves is non-uniform and often incomplete; (ii) the definition of labelled valve size is unclear and inconsistencies exist between the dimensions of valve-related sizes and labelled valve size; (iii) information on in vivo hemodynamic performance of prosthetic valves is limited in the Instruction for Use leaflets and is lacking on package labels; (iv) no reliable tools are available to prevent patient-prosthesis mismatch (PPM).

Chapter 3 is the second consensus document of the EACTS-STS-AATS Valve Labelling Task Force, which answers the questions raised by Chapter 2, and provides recommendations on how a better-informed prosthesis choice and an improved comparability between prosthetic valves can be achieved. In this chapter, the introduction of a standardized Valve Chart is suggested, which contain comprehensive information on surgical heart valve dimensions, implant position and hemodynamic performance in a uniform manner. Furthermore, a novel tool to assess the probability of PPM is introduced for valves in the aortic position.

Chapter 4 compares the PPM chart suggested by the EACTS-STS-AATS Valve Labelling Task Force with the existing indexed effective orifice area (EOAi) charts. The novel PPM provides a percentage probability of severe PPM and could better inform surgeons and guide prosthetic valve selection than the classical EOAI charts.

Chapter 5 describes the trends in the utilization of surgical aortic valve replacement (SAVR) in the Erasmus Medical Center in the last three decades. Also, the long term-survival after SAVR is investigated according to three distinct, ten-years periods. Our data show an excellent long-term survival after SAVR compared that of the age-matched population, despite increasing patient complexity and comorbidities across the last three decades.

Chapter 6 is a modelling study which estimates the annual number of potential candidates for transcatheter aortic valve implantation (TAVI) in Europe and Northern America using data generated by epidemiological studies. Different scenarios of TAVI adoption based on estimated surgical risk and patient age were considered. We estimated that the annual number of patients eligible for TAVI could be as high as approximately 3.600/year in the Netherlands, 20.000/year in Germany or 52.000/year in the United States.

Chapter 7 investigates the rate and characteristics of neurological complications after SAVR and TAVI in patients with intermediate surgical risk enrolled in the SURTAVI randomized-controlled trial. The results of this study, which employed a strict protocol for neurological follow-up, show that the rate of cerebrovascular events at 30-days were lower after TAVI than after SAVR, although this difference disappears at 1-year follow up.

Chapter 8 investigates the incidence of interventions on the coronary arteries in patients who previously underwent SAVR in the Erasmus Medical Center between 1987 and 2015. Our results show that after aortic valve replacement, the rate of coronary interventions is low, however, in patients with previous coronary revascularization had a higher revascularization rate (22.1% vs 3.7%,) at 15 years.

Chapter 9 is the general discussion of the results presented in this thesis.

SAMENVATTING

Het doel van dit proefschrift was om de vergelijking van verschillende chirurgische hartklepprothesen te vergemakkelijken en om de uitkomsten en trends van chirurgische en transkatheterbehandeling van de aandoeningen van de aortaklep te bestuderen.

Hoofdstuk 1 bevat de algemene introductie van het onderwerp van deze thesis. Verder worden de doelstellingen geformuleerd en er wordt een overzicht gegeven van de studies die in dit proefschrift zijn opgenomen.

Hoofdstuk 2 is het eerste consensus document van de EACTS-STAS-AATS Valve Labeling Task Force, dat zich richt op de huidige problemen met betrekking tot de selectie en labelling van chirurgische hartklepprothesen. De volgende problemen zijn geïdentificeerd: (i) rapportage van de afmetingen van chirurgische hartklepprothesen is niet uniform en is vaak onvolledig; ii) de definitie van "labelled valve size" is onduidelijk en er zijn inconsistenties tussen de afmetingen van sizers en labelled valve size; iii) informatie over in vivo hemodynamische prestaties van hartklepprothesen is beperkt in de bijsluiters en is niet aanwezig op de verpakking; (iv) er zijn geen betrouwbare hulpmiddelen beschikbaar om patient-prothesis mismatch (PPM) te voorkomen.

Hoofdstuk 3 is het tweede consensus document van de EACTS-STAS-AATS Valve Labelling Task Force, dat de vragen van Hoofdstuk 2 beantwoordt. Tevens worden aanbevelingen gegeven met betrekking tot een beter geïnformeerde hartklepkeuze. In dit hoofdstuk wordt een gestandaardiseerde "Valve Chart" voorgesteld, die informatie presenteert op een uniforme manier over de afmetingen, beoogde positie in de annulus en hemodynamische prestaties van verschillende chirurgische hartklepprothesen om de vergelijkbaarheid van klepprothesen te verbeteren. Bovendien wordt er een nieuw hulpmiddel geïntroduceerd om de kans van PPM te evalueren na een aortaklepverving.

Hoofdstuk 4 vergelijkt de nieuwe PPM chart voorgesteld door de EACTS-STAS-AATS Valve Labelling Task Force met de bestaande indexed effective orifice area (EOAi) charts. De nieuwe PPM chart toont de procentuele kans op ernstige PPM na chirurgische aortaklepverving. De nieuwe PPM chart zou chirurgen beter kunnen informeren over een mogelijke PPM dan de bestaande, klassieke EOAI-charts.

Hoofdstuk 5 beschrijft de trends van chirurgische aortaklepverving (SAVR) in het Erasmus Medisch Centrum in de afgelopen drie decennia en onderzocht de lange termijn overleving na SAVR, vergeleken met de op leeftijd gematchte populatie. Deze studie toont aan dat ondanks de toenemende complexiteit en co-morbiditeiten van patiënten, de lange termijn overleving na SAVR uitstekend is.

Hoofdstuk 6 is een studie die het aantal jaarlijkse kandidaten voor transkatheter aortaklepiimplantatie (TAVI) in Europa en Noord-Amerika schat met behulp van data uit epidemiologische studies. Deze studie schetst verschillende scenario's van mogelijke

TAVI-adoptie gebaseerd op het geschatte chirurgische risico en de leeftijd van de patiënten. We schatten dat het jaarlijkse aantal patiënten dat in aanmerking kan komen voor een TAVI zou kunnen oplopen tot ongeveer 3.600 per jaar in Nederland, 20.000 per jaar in Duitsland of 52.000 per jaar in de Verenigde Staten.

Hoofdstuk 7 heeft de frequentie en kenmerken van neurologische complicaties na SAVR en TAVI vergeleken bij patiënten met een gemiddeld chirurgisch risico die deelnamen aan de SURTAVI randomised controlled trial. De SURTAVI study had een strikt protocol voor neurologische evaluatie en follow-up. De resultaten tonen aan dat de frequentie van beroerte binnen 30 dagen na operatie lager was na TAVI dan na SAVR, echter, dit verschil verdween na 1 jaar.

Hoofdstuk 8 beschrijft de incidentie van interventies aan de kransslagaderen bij patiënten die eerder een aortaklepvervangning ondergingen in het Erasmus Medisch Centrum tussen 1987 en 2015. Hoewel de frequentie van coronaire interventies na een chirurgische aortaklepvervangning laag is, komt revascularisatie bij patiënten met eerdere interventies op de coronairen op lange termijn aanzienlijk vaker voor (22,1% versus 3,7%, na 15 jaar).

Hoofdstuk 9 is de bespreking van de resultaten die in dit proefschrift worden gepresenteerd.

11

List of publications

1. Long-term outlook for transcatheter aortic valve replacement.
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Trends Cardiovasc Med. 2018 Apr;28(3):174-183.
2. Long-term survival after surgical aortic valve replacement: expectations and reality.
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3. Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections.
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6. Characteristics of surgical prosthetic heart valves and problems around labeling: a document from the European Association for Cardio-Thoracic Surgery (EACTS) – The Society of Thoracic Surgeons (STS) – American Association for Thoracic Surgery (AATS) Valve Labeling Task Force.
Durko AP, Head SJ, Pibarot P, Atluri P, Bapat V, Cameron DE, Casselman FPA, Chen EP, Dahle G, Ebels T, Elefteriades JA, Lancellotti PA, Prager RL, Rosenhek R, Speir A, Stijnen M, Tasca G, Yoganathan A, Walther T, De Paulis R; EACTS–STS–AATS Valve Labeling Task Force. *Eur J Cardiothorac Surg*. 2019 Jun 1;55(6):1025-1036, *J Thorac Cardiovasc Surg*. 2019 Oct;158(4):1041-1054., *Ann Thorac Surg*. 2019 Jul;108(1):292-303
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Durko AP, Pibarot P, Atluri P, Cameron DE, De Paulis R; European Association for Cardio-Thoracic Surgery; Society of Thoracic Surgeons; American Association for Thoracic Surgery Valve Labelling Task Force *J Thorac Cardiovasc Surg.* 2020 Jun;159(6):e332-e333.
 10. The devil is in the details (of definitions).
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 14. Coronary revascularization after surgical aortic valve replacement
Çelik M, **Durko AP**, Head SJ, Mahtab EAF, van Mieghem NM, Cummins PA, Kappetein AP, Bogers AJJC. *JTCVS Open* doi: <https://doi.org/10.1016/j.xjon.2020.05.005>
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16. Anticoagulation after mechanical aortic valve implantation: is it time to act after PROACT?
Çelik M, **Durko AP**, Head SJ. *Ann Transl Med*. 2018 Nov;6(Suppl 1):S16.
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Çelik M, Milojevic MM, **Durko AP**, Oei FBS, Bogers AJJC, Mahtab EAF. *Interact Cardiovasc Thorac Surg*. 2020 Nov 1;31(5):587-594.
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Çelik M, Milojevic M, **Durko AP**, Oei FBS, Bogers AJJC, Mahtab EAF. *Eur J Cardiothorac Surg*. 2021 Jun 14;59(6):1191-1199.
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22. Challenges and satisfaction in Cardiothoracic Surgery Residency Programmes: insights from a Europe-wide survey.
Cerqueira RJ, Heuts S, Gollmann-Tepeköylü C, Syrjälä SO, Keijzers M, Zientara A, Jarral OA, Jacob KA, Haunschild J, Ariyaratnam P, **Durko AP**, Muller P, Myers PO, Sadaba JR, Lehtinen ML. *Interact Cardiovasc Thorac Surg*. 2021 Jan 22;32(2):167-173.
23. How should I treat an Edwards SAPIEN 3 aortic valve embolisation during a transaortic transcatheter aortic valve implantation?
Fournier S, Monney P, Roguelov C, Ferrari E, Eeckhout E, Muller O, **Durko A**, Van Mieghem NM, Kappetein AP, Margey R. *EuroIntervention*. 2017 Jul 20;13(4):495-498.

Bookchapters:

1. Mechanical complications of acute myocardial infarction.
Durko AP, van Leeuwen WJ, Kappetein AP. *The Interventional Cardiology Training Manual* 2018 Aug; Springer. Editors: Aung Myat, Sarah Clarke, Nick Curzen, Stephan Windecker, Paul A. Gurbel
2. Decision making and Heart Team: Conclusion and Future Perspectives.
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Surgical tutorials:

1. Conventional open harvesting of the great saphenous vein as a conduit for coronary artery bypass grafting.
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5. Technique of surgical aortic valve implantation using single interrupted annular sutures.
Çelik M, **Durko A**, Mahtab E, Schouten G, Bogers A. *Multimed Man Cardiothorac Surg*. 2020 Nov 3;2020. doi: 10.1510/mmcts.2020.059.
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Max SA, Çelik M, **Durko A**, Mahtab EAF. Multimed Man Cardiothorac Surg. 2021 Sep 13;2021. doi: 10.1510/mmcts.2021.038.

12

PhD portfolio

Name PhD candidate:	András Péter Durkó
Erasmus MC department:	Cardiothoracic Surgery
Research school:	COEUR
PhD period:	2016 - 2022
Title thesis:	Optimizing outcomes in aortic valve replacement
Promotor:	Prof. A.P. Kappetein / Prof. A.J.J.C. Bogers
Co-promotor:	Dr. E.A.F. Mahtab

	Year	ECTS
COURSES		(11,8)
General academic skills		
Research integrity Erasmus MC	2017	0,3
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	2021	1,5
Laboratory animal science		
Basic Laboratory animal science (UU Utrecht)	2018	3,0
Species-specific course on sheep (UU Utrecht)	2018	1,4
Species-specific course on pigs (UU Utrecht)	2018	1,4
Swiss EGA course (legislation) (UZH Zurich)	2018	0,2
Statistics and methodology		
NIHES Biostatistical Methods – Part A	2018	2,0
Basic introduction course on SPSS	2017	1,0
EndNote Workshop	2017	1,0
CONFERENCES		(10,2)
EACTS 30 st Annual Meeting, Barcelona, Spain	2016	1,2
EACTS 31 st Annual Meeting, Vienna, Austria	2017	1,2
Transcatheter Cardiovascular Therapeutics, Denver, CO, USA	2017	0,6
NVT/BACTS Annual Meeting, Antwerp, Belgium	2017	0,4
ICTEHV, Amsterdam, the Netherlands	2018	0,4
EACTS 32 nd Annual Meeting, Milan, Italy	2018	1,2
Aortic Live, Essen, Germany	2018	0,8
STS 55 th Annual Meeting, San Diego, CA, USA	2019	1,2
NVT Annual Meeting, Utrecht, the Netherlands	2019	0,4
EACTS 33 rd Annual Meeting, Lisbon, Portugal	2019	1,2
STS 56 th Annual Meeting, New Orleans, LA, USA	2020	1,2
NVT/NVA-CA/NeSECC Annual Meeting, Ede, the Netherlands	2021	0,4
PRESENTATIONS		(5,3)
Oral presentations		
EACTS 31 st Annual Meeting, Vienna, Austria (4 presentations)	2017	2,4
EACTS 32 nd Annual Meeting, Milan, Italy	2018	0,6
NVT Annual Meeting, Utrecht, the Netherlands	2019	0,6

EACTS 33 rd Annual Meeting, Lisbon, Portugal	2019	0,6
Poster presentations		
Transcatheter Cardiovascular Therapeutics, Denver, CO, USA	2017	0,6
NVT/BACTS Annual Meeting, Antwerp, Belgium	2017	0,6
SEMINARS AND WORKSHOPS		(5,3)
Local scientific meetings department of cardiothoracic surgery	2017-2019	3,0
Aneurysmal disease (COEUR)	2018	0,5
A(orta)-Team symposium (LUMC)	2018	0,4
Professional Leadership – EACTS, Windsor, United Kingdom	2018	1,0
12 th International Symposium on Biomechanics in Vascular Biology	2017	0,4
OTHER ACADEMIC AND TRAINING ACTIVITIES		(6,0)
Member, EACTS Residents Committee	2016-2019	3,0
Member, EACTS Vascular Disease Domain	2016-2019	3,0
EACTS Training Management system, assisting in development	2017 –	
MMCTS Core Skills tutorials for cardiothoracic surgery residents	2017 –	
EACTS Adult Cardiac Database, contact person University of Debrecen	2018 –	
Nederlands als Tweede Taal (NT2)	2018	
Taaltoets voor Medici uit EER	2018	
Peer reviewer Journal of American College of Cardiology		
Peer reviewer European Journal of Cardio-Thoracic Surgery		
Peer reviewer European Heart Journal		

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About the author

CURRICULUM VITAE

András Péter Durkó was born on 27th February 1986 in Budapest, Hungary. In 2005 he was admitted to the Faculty of Medicine, University of Debrecen in 2005, where he graduated summa cum laude in 2011. He started his clinical career in 2011 at the Department of Cardiac Surgery, Semmelweis University, Budapest and entered residency training in cardiac surgery in 2013, at the Department of Cardiac Surgery, University of Debrecen. In 2016, together with Dr. Károly Szabó, he won a cognitive skills competition organized by the Joint Council on Thoracic Surgery Education for European and North American residents. In 2016 November he paused his clinical training to start a PhD project at the Department of Cardiothoracic Surgery, Erasmus University Medical Center, under the supervision of Prof. A. P. Kappetein. During his years as a PhD candidate, he was actively involved in the European Association of Cardio-Thoracic Surgery as member of the Residents Committee and Vascular Disease Domain and had a coordinating role in the multi-society EACTS-STS-AATS Valve Labeling Task Force.



Parallel to finalizing his PhD, he re-started clinical work at the Erasmus MC in 2019. In 2020, he moved to the Amsterdam UMC where he resumed his residency training to become a cardiothoracic surgeon.

14

Acknowledgements

Finally, I would like to close this thesis with the words of sincere gratitude to those who helped me during my PhD years and beyond.

Dear Pieter. Little I know in 2015, when we first met in Amsterdam at the EACTS, what future will hold. I cannot thank you enough for your trust and for the countless opportunities you kept offering me during the past years, even though I did or could not take all of them.

Dear Professor Bogers. Thank you for your support and guidance during my years in the Erasmus MC.

Dear Edris. Thank you for your friendship and for your support during my PhD years and beyond.

Dear Ruben. Thank you for helping me with my first steps in Rotterdam and during the first years of my PhD.

I am grateful to Professor Bouten, Professor Duncker and Professor Klautz for accepting the invitation to be part of my doctoral committee. I would also like to thank all other members of the committee for accepting the invitation to be my opponents during the PhD defense.

Ruggero. Thank you for putting your trust in me. It was a real honor for me to collaborate with you in the Valve Labelling Task Force and in the Vascular Domain, and I hope I can continue learning from you in the future.

Mevlüt. Thank you for your help during the PhD years. You are a hardworking and honest person and I wish you very much success with your further career as a clinician.

Daan. Thank you for taking the risks of being my paranymph after our adventures together during the past years as PhD students. Most importantly, thank you for being a friend.

Károly. Együtt indultunk el azon az úton, ami először Amszterdamba, majd Phoenix-be, és végül ennek a könyvnek a végéhez is elvezetett. Hálás vagyok, hogy a barátok vagyunk és hogy elfogadtad a felkerést, hogy itt állj mellettem a védésen.

Milan. Thank you very much for offering me shelter in the first weeks of my stay in Rotterdam, and for your advice and help during the past years. I hope that we can see each other more frequently in the future.

Dear Rianne, thank you for your indispensable help and support during the last years: in Windsor, Rotterdam, Leiden and in Amsterdam.

During the past years, being part of the EACTS family gave me countless opportunities to develop myself as a clinician and as a researcher. Members of the Vascular Disease Domain, Residents Committee, and the Valve Labelling Task force: it was a real honor to collaborate with you and to learn from you. Dear Kathy, Stephanie, Sharon, Amanda, and Cori from the EACTS Office: thank you very much.

Colleagues from Rotterdam and fellow PhD students. Thank you very much for your support during my years at the Erasmus MC.

Dear colleagues at the Department of Cardiac Surgery from Amsterdam UMC. I am grateful that I can work with you and learn from you as a clinician. I would also like to thank you for your support and patience during the last phase of my PhD.

Kedves Szerafin Tanár úr. Köszönöm, hogy elindított a klinikai pályámon és mindig támogatott. Kitartása, precizitása és állhatatossága a beteg emberek érdekében példa a számomra. Remélem, hogy egyszer én is olyan orvos lehetek, akire úgy gondolnak majd a kollégái, ahogy én gondolok Önre.

Debreceni kollégák. Hálás vagyok, hogy veletek dolgozhattam és tanulhattam tőletek. Mindig szeretettel, és második otthonként gondolok a debreceni Szívsebészeti Klinikára, ahonnan elindulhattam, először mint orvostanhallgató, majd mint kolléga.

Lieve Marlous en de hele familie van Wijngen. Jullie waren mijn "Nederlandse familie" tijdens mijn jaren in Rotterdam. Beste Gerard, bedankt voor jouw goede adviezen en hulp. Lieve Marlous, bedankt voor je liefde, luisterend oor en steun.

Kedves jó testvérem, Gábor. Te magad is megtapasztaltad, hogy milyen egy PhD fokozatot szerezni, és neked sokkal nehezebb körülmények között is sikerült, ami nekem is erőt adott.

Lieve Ellen. Ik ben heel dankbaar dat ik jou mocht ontmoeten.

Kedves Mama és Papa. Végül nektek szeretném megköszönni, hogy idáig eljuthattam. A szavak igazából nem elegek arra, hogy elmondjam mennyire hálás vagyok azért, hogy szeretetben felneveltetek bennünket Gáborral, támogattatok és mindent megpróbáltatok megadni nekünk, ami csak az erőtökből kitelt.

