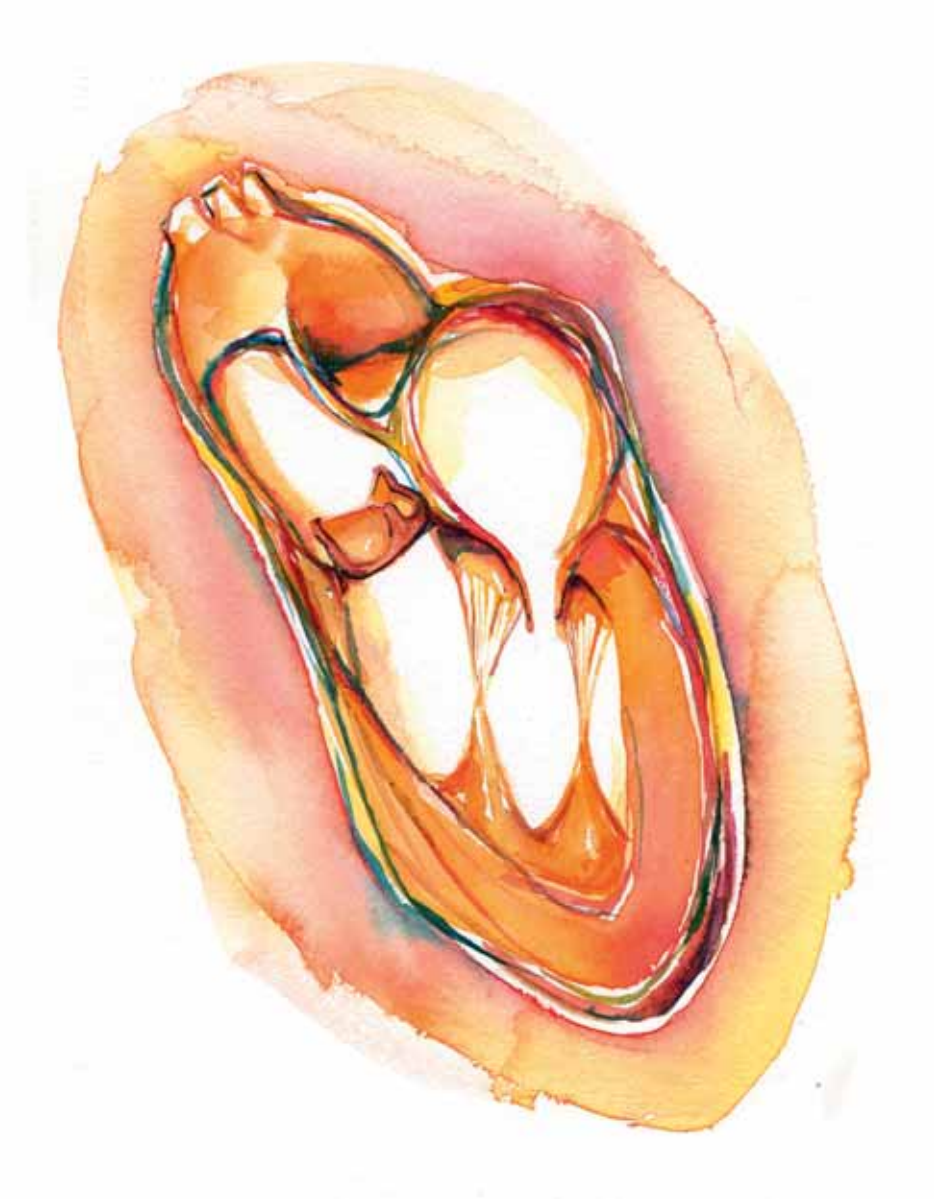

HEMODYNAMIC CONCEPTS IN AORTIC VALVE REPLACEMENT

BART J. J. VELDERS

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Hemodynamic Concepts in Aortic Valve Replacement
PhD Thesis, Leiden University, Leiden, The Netherlands

Cover design:	Kaitlin Walsh | Lyon Road Art
Layout:	Anna Bleeker | persoonlijkproefschrift.nl
Printing:	Ridderprint | ridderprint.nl

ISBN: 978-94-6506-926-5

Publication of this thesis was kindly supported by: Nederlandse Vereniging voor Thoraxchirurgie, Hartonderzoek Nederland, Weefsel Uitname Organisatie Nederland, Stichting ETB-BISLIFE, Krijnen Medical, and ChipSoft.

The financial and data support provided by Medtronic for several studies presented in this thesis is gratefully acknowledged.

HEMODYNAMIC CONCEPTS IN AORTIC VALVE REPLACEMENT

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof. dr. ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 20 maart 2025
klokke 16.00 uur

door

Bart Josephus Johannes Velders

geboren te Voorschoten
in 1995

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1

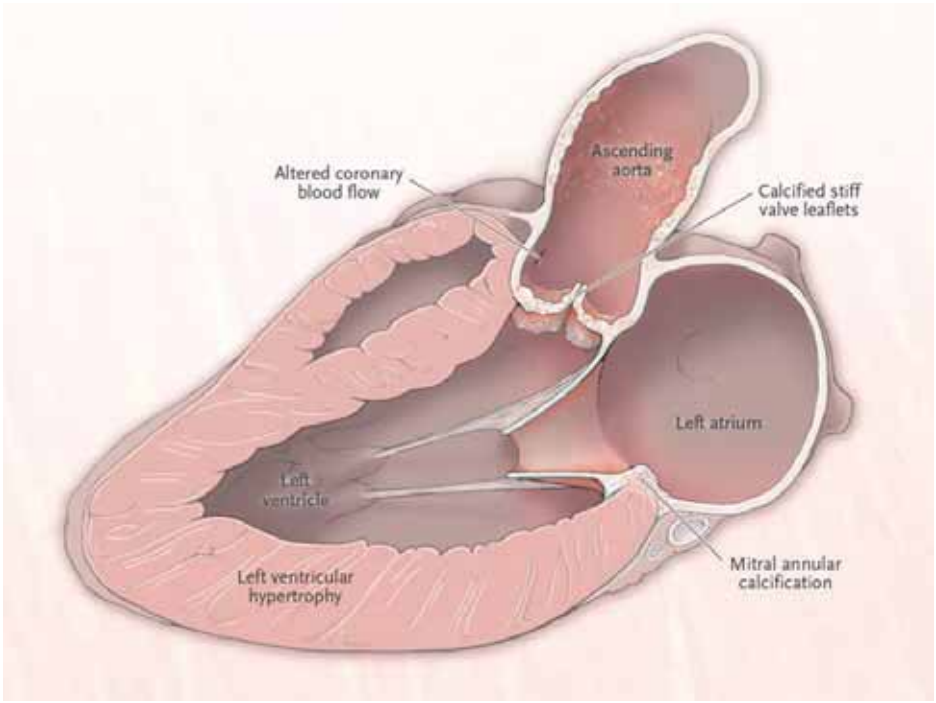
INTRODUCTION AND GENERAL OUTLINE OF THE THESIS

NORMAL AND ABNORMAL FUNCTION OF THE AORTIC VALVE

The aortic valve forms the gate between the heart and systemic circulation. It needs to open and close properly to prevent hemodynamic obstruction and guarantee unidirectional blood flow: from the left ventricle to the aorta. Valve motion is driven by pressure differences between these compartments during the cardiac cycle. The opening and closing properties rely on functional and anatomical aspects such as valve leaflet morphology, mobility and coaptation.

Aortic stenosis (AS) refers to a state in which the valve's opening property is diminished. AS is one of the most prevalent valvular heart diseases in adults in the Western world [1] and is present in around 2.8% of people aged 75 years and older [2]. It is a progressive condition predominantly of degenerative nature and mechanistically related to atherosclerosis [1-3]. The pathophysiological process is mainly driven by calcification, along with fibrosis and inflammation. Pediatric valvular heart disease is very different and falls outside the scope of this thesis. Risk factors for AS in adults include age, dyslipidemia, diabetes mellitus, hypertension and smoking, among others. Bicuspid aortic valve, a congenital abnormality in which one commissure is either absent or underdeveloped, is an important risk factor and is present in about 1-2% [1,2] of patients with AS. In contrast to degenerative or senile AS, bicuspid AS develops much earlier in life. In AS, obstruction at the level of the valve could lead to insufficient cardiac output and pressure overload of the left ventricle (LV) resulting in adverse remodeling and heart failure *(Figure 1)*. In contrast, aortic regurgitation or insufficiency emerges when the valve closes inadequately allowing blood to leak back to the heart [4]. Aortic regurgitation (AR) shares certain risk factors with AS such as bicuspid aortic valve. In developing countries, rheumatic disease is the main cause of AR. In sporadic instances, aortic dissections or endocarditis result in acute regurgitation which requires urgent intervention. AR mainly leads to volume overload which negatively impact LV function and inherently increase the risk of mortality and morbidity. The primary focus of this thesis is hemodynamic obstruction, i.e., stenosis, rather than regurgitation.

Figure 1. Sequelae of severe aortic stenosis.



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AORTIC VALVE REPLACEMENT

The indications for intervention on the aortic valve are based on hemodynamic severity of aortic valve disease, symptoms and LV function [5,6]. The main idea is to intervene on the valve before other components of the heart are irreversibly damaged. After the onset of severe aortic valve disease, the prognosis rapidly deteriorates if no intervention is performed [7]. Potential interventions can be divided into surgical and transcatheter aortic valve replacement (SAVR and TAVR, respectively). The first SAVR procedure was described by Hufnagel *et al.* in 1954 [8]. Since then, the surgical techniques, perioperative management, and the prosthetic heart valves have drastically improved. For the latter, a distinction is made between mechanical and biological valves with porcine or bovine pericardial leaflets. Surgical biological valves can be further subdivided into stented, stentless and sutureless bioprostheses. Homografts or pulmonary autografts, used in the Ross procedure, are additional options but these are rarely used in acquired aortic valve disease in older adults [9]. SAVR can be performed through a full sternotomy or by using less invasive access routes, like upper hemi-sternotomy, right anterior or axillary thoracotomy (so-called mini-AVR). An even less invasive interventional alternative to SAVR, without the use of extra corporeal

circulation techniques is transcatheter TAVR which was first described by Cribier *et al.* in 2002 [10]. While this treatment was initially proposed for high-risk individuals, it is currently offered to patients across the entire range of surgical risk [5,6]. In contemporary practice, way more TAVR than SAVR procedures are annually performed [11]. The choice for specific interventions and prosthetic valves for individual patients is based on patient characteristics, prosthetic valve durability and, importantly, patient preference [5,6].

THE ROLE OF ECHOCARDIOGRAPHY IN AORTIC VALVE REPLACEMENT

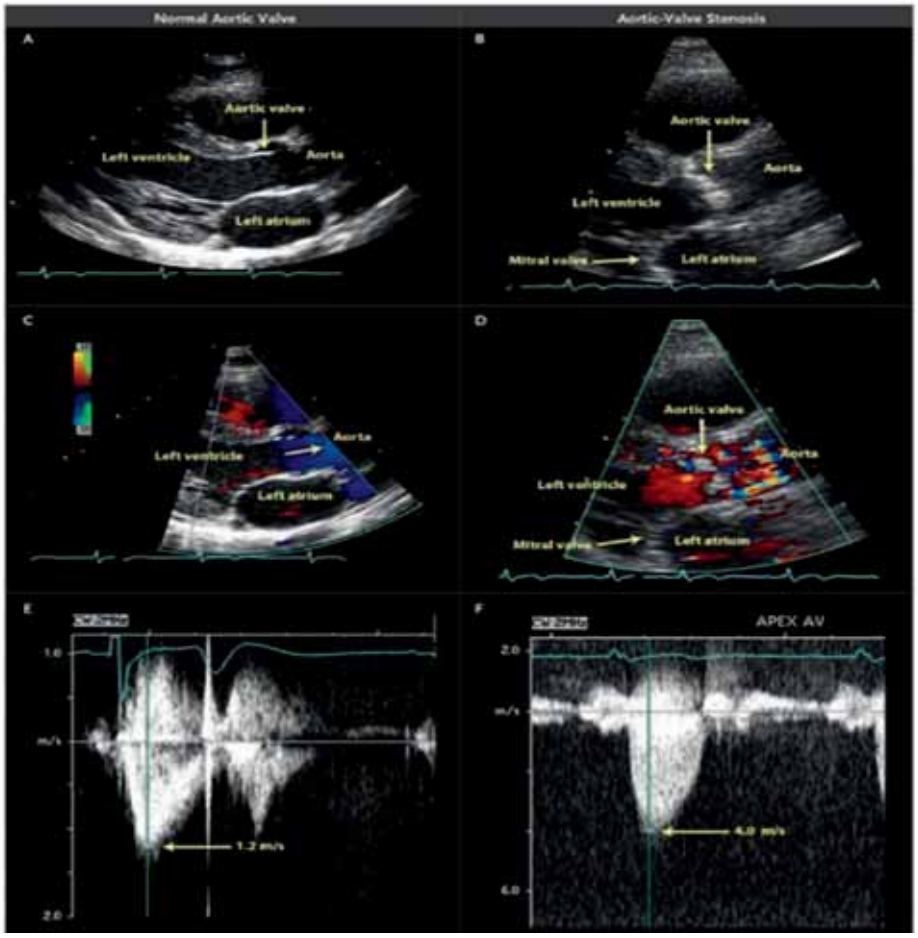
Echocardiography plays a central role in the assessment of the performance of the aortic valve. It guides the indication for intervention on the native aortic valve as well as the evaluation of prosthetic heart valves, both after implantation and during follow-up. This imaging tool, based on ultrasound, could provide quantitative information such as the opening area of the valve as well as qualitative insights like leaflet mobility and the presence of paravalvular leak in a quick examination. Before the era of echocardiography, valvular performance was assessed via cardiac catheterization [12]. Pioneers like Liv Hatle, Catherine Otto, and Jae Oh demonstrated that non-invasive estimation of hemodynamic parameters like the pressure gradient and the aortic valve area corresponded well to invasive catheterization measurements [13-16]. To note, it is good to realize that current hemodynamic measurements are based on complex fluid dynamics fundamentals [17]. Several pragmatic assumptions are made to simplify the clinical assessments [18]. For example, the behavior of fluids like blood is expressed by the Navier-Stokes equation which forms the base of the Bernoulli equation, and in clinical practice, the simplified Bernoulli equation is used to determine the transvalvular gradient.

Preoperative assessment

In preoperative care, the severity of AS is categorized as mild, moderate or severe using three primary echocardiographic parameters: the peak aortic jet velocity, the mean pressure gradient, and the aortic valve area [19]. To measure these parameters, blood velocity during the cardiac cycle needs to be recorded at the level of the aortic valve and in the left ventricular outflow tract (LVOT), of which geometric measurements like the LVOT diameter are also required *(Figure 2)*. In addition, various physiological and geometrical assumptions are made for pragmatic reasons. Next to these primary parameters, many other exist [19], however, current international guidelines lack any recommendations for AVR based on them [5,6]. In asymptomatic patients, the indication for intervention relies solely on echocardiography which underscores its pivotal role even more. The natural history of asymptomatic AS is not benign [20,21], and asymptomatic patients with "very severe" stenosis seem to benefit from early intervention [22,23]. In a reasonable amount of patients, the primary echocardiographic parameters are discordant [24]. The diagnosis of AS is challenging when the mean pressure gradient and aortic valve area depict different levels of disease severity. Even in case of preserved left ventricular ejection fraction, flow alterations are thought to play a crucial role in explaining

this discrepancy. Hence, a classification based on flow-gradient patterns was proposed to improve the diagnosis of true severe AS [25]. Many uncertainties remain regarding the accuracy of this diagnostic classification, and the characteristics, prognosis, and optimal interventional strategy for these flow-gradient groups [24-26].

Figure 2. Echocardiographic evaluation of a normal and stenotic aortic valve.



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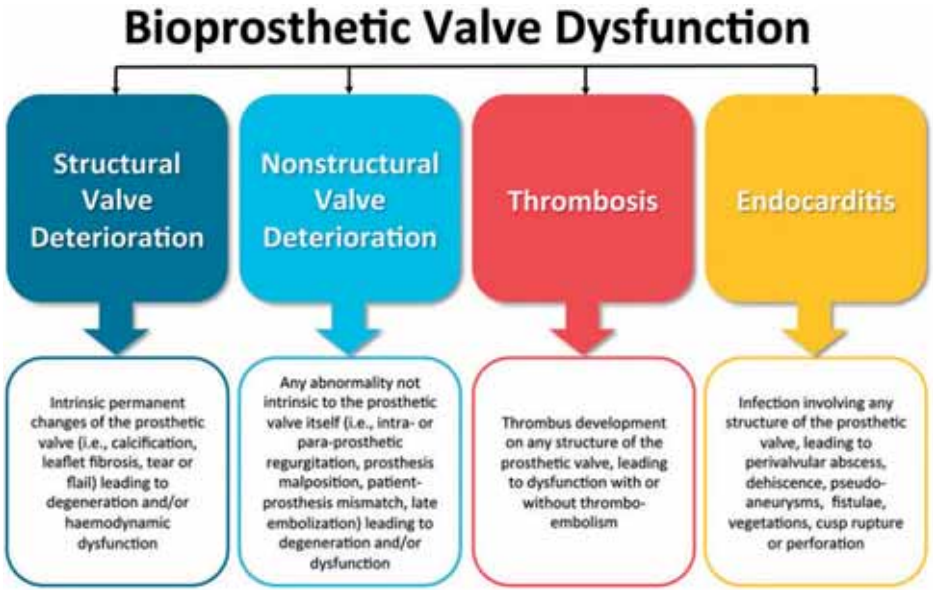
Perioperative management

In perioperative care, echocardiography is used to assess the technical success of prosthetic valve implantation and motion of the leaflets. Especially, the presence of paravalvular leak is carefully evaluated since it is associated with worse outcomes [27]. Specific interventional strategies or surgical approaches could affect hemodynamic outcomes such as paravalvular leak or the effective orifice area after implantation, for example through the prosthetic valve type or the suturing technique.

Postoperative assessment

In postoperative care, quantitative echocardiographic measurements are performed to investigate whether the prosthetic valve is sufficient for the patient's hemodynamic requirements. Because prosthetic valves are placed inside the aortic annulus / root, and most prostheses contain a sewing ring and struts, they could hinder the blood flow and generate some hemodynamic obstruction themselves [28,29]. If there is considerable hemodynamic obstruction after an intervention, this is called prosthesis-patient mismatch (PPM). This problem is currently defined by echocardiographic thresholds for the effective orifice area indexed to body surface area (BSA) [30]. PPM after AVR seems to be associated with increased mortality in most studies [31-33], however, the current definitions have been challenged for the appropriateness of the cut-offs and the validity of BSA indexation [34,35]. Up to now, no other echocardiographic parameters have been considered for the definition of PPM. Bioprosthetic valve dysfunction due to PPM or paravalvular leak are categorized as non-structural valve deterioration [30,36] *(Figure 3)*. The performance of prosthetic valves could also be hampered as a result of endocarditis, valve thrombosis, or structural valve deterioration (SVD). The latter is defined as irreversible damage to intrinsic components of the prosthesis such as the leaflets or the struts, and is caused by mechanical wear and immunological processes [30,36]. Durability remains a major, if not the most important, concern for biological heart valves. To detect prosthetic degeneration early, preferably at times that redo surgery or valve-in-valve reintervention could still be performed, new echocardiographic definitions have been proposed for hemodynamic SVD [30,36,37]. These definitions have been developed based on theory and their accuracy and clinical utility have yet to be explored.

Figure 3. Sources of bioprosthetic valve dysfunction.



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CHALLENGES IN ECHOCARDIOGRAPHIC IMAGING

Echocardiographic parameters are proxies for valvular performance, the underlying construct that we aim to measure, but they are also affected by physiological elements like LV function, vascular function and biological variability as well as non-physiological sources such as measurement error. These factors complicate the interpretation of valvular performance. Examples of challenging situations comprise assessment in patients with irregular contraction patterns or altered flow states. This thesis is in part devoted to distinguishing valvular performance from other disturbing sources to improve the interpretation of echocardiography and aid clinical decision-making by cardiologists and cardio-thoracic surgeons concerning the native and bioprosthetic aortic valve. The main challenges regarding hemodynamic concepts in aortic valve replacement that are addressed in this thesis are summarized in Table 1.

Table 1. The main challenges addressed in this thesis regarding hemodynamic concepts in aortic valve replacement.

Aortic Valve Replacement	Main challenge addressed in this thesis
Preoperative assessment	• The diagnosis of severe aortic stenosis in asymptomatic patients • The diagnosis of severe aortic stenosis in low-flow patients
Perioperative management	• The surgical strategy to optimize hemodynamic performance • The research methods to determine optimal surgical strategies
Postoperative assessment	• The prognostic value of prosthesis-patient mismatch and other parameters for residual hemodynamic obstruction • The diagnosis of hemodynamic structural valve deterioration

GENERAL OUTLINE OF THE THESIS

The overall aim of this thesis is to improve the evaluation of the native and bioprosthetic valve by cardiologists and cardio-thoracic surgeons to optimize clinical management. This thesis is delineated in chronological order starting at the onset of native aortic valve disease via the implantation of the tissue valve to end with bioprosthetic valve degeneration. While the primary focus lies on the clinical content, special attention is paid to the application of various epidemiological methods for measurement error, causality, predictive analytics, missing data, and longitudinal data analysis.

Part I is dedicated to hemodynamic performance of the native aortic valve, specifically aortic stenosis. In **Chapter 2**, the impact of measurement error in the echocardiographic assessment of AS severity is investigated in context of current thresholds for intervention in international guidelines [5,6]. In **Chapter 3 and 4**, the accuracy and clinical utility of the flow-gradient classification of severe AS are explored. The main pitfall of this classification is echocardiographic estimation of stroke volume; hence, experts have stressed that corroboration with other methods is essential [24-26]. In **Chapter 3**, the robustness of the flow-gradient classification is analyzed by studying reclassification due to different echocardiographic stroke volume measurements and measurement error. In **Chapter 4**, the impact of BSA on the classification of paradoxical low-flow severe AS is investigated. In the definition of this classification, BSA is used twice to index both stroke volume and aortic valve area [25], therefore it might disproportionally affect the probability to be classified as paradoxical low-flow stenosis. **Chapter 5** describes the differences in echocardiographic assessment of the native and bioprosthetic valve between a central core laboratory and clinical centers.

Part II focusses on the role of interventional strategies and surgical approaches regarding hemodynamic performance of bioprosthetic valves. In **Chapter 6**, outcomes after minimally invasive procedures such as right anterior thoracotomy and hemisternotomy are compared to conventional sternotomy. In **Chapter 7**, the effect of suturing techniques with pledgets is contrasted with techniques without pledgets in a cohort study. **Chapter 8** is a systematic review and meta-analysis on the same topic summarizing all available evidence. **Chapter 9** describes a step-by-step surgical tutorial of the implantation of a stentless aortic bioprosthesis. In **Chapter 10**, perioperative care differences of SAVR between North America and Europa are described to examine the generalizability of region-specific study results. These continents have separate guidelines [5,6] but the extent of practical differences is unknown. **Chapter 11** zooms in on methodological practice of studies on the optimal interventional strategy. The quality of reporting and conduct regarding confounding adjustment is investigated in observational studies not only on aortic valve procedures but on cardiothoracic interventions in general.

Part III addresses echocardiographic concepts in the postoperative phase. In **Chapter 12**, it is studied whether different postoperative echocardiographic parameters and the current thresholds for PPM [30] add prognostic value to a preoperative risk score for the prediction of all-cause mortality 5 years after SAVR. In **Chapter 13**, the reproducibility of the results of the previous study is examined in pooled data of three randomized controlled trials. Furthermore, the added prognostic value for cardiovascular mortality is also specifically targeted. Thereafter, the focus is shifted to the assessment of durability of bioprosthetic valves. In **Chapter 14**, the consistency of current definitions for hemodynamic SVD [30,36,37] is investigated.

This thesis ends with a summary of the main findings including a general discussion and outline of future perspectives on hemodynamic performance of the native and bioprosthetic aortic valve which is detailed in **Chapter 15.** A summary in Dutch is provided in **Chapter 16**.

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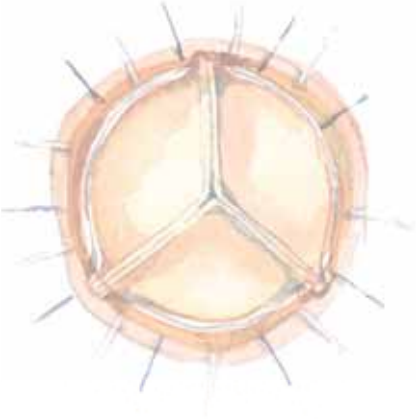


PART I

PREOPERATIVE ASSESSMENT

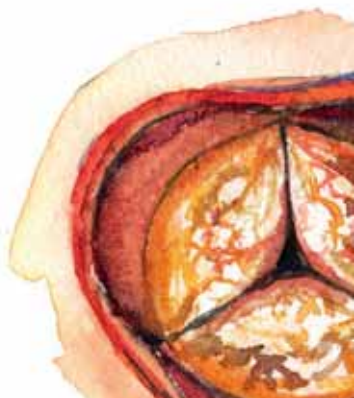
2

IMPROVING ACCURACY IN DIAGNOSING AORTIC STENOSIS SEVERITY: AN IN-DEPTH ANALYSIS OF ECHOCARDIOGRAPHIC MEASUREMENT ERROR THROUGH LITERATURE REVIEW AND SIMULATION STUDY

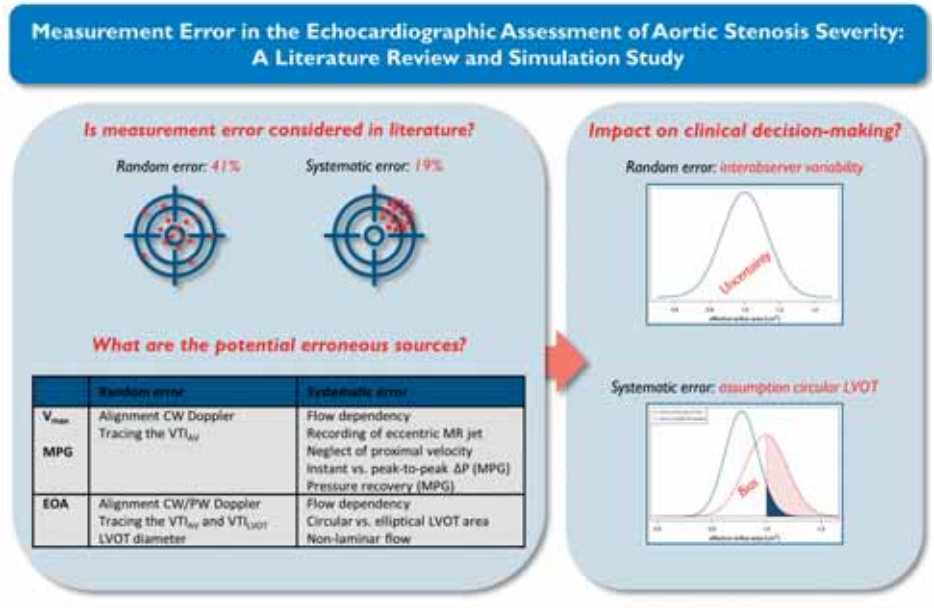
B.J.J. Velders, R.H.H. Groenwold, N. Ajmone Marsan, A.P. Kappetein, R.A.F. De Lind Van Wijngaarden, J. Braun, R.J.M. Klautz, M.D. Vriesendorp

Echocardiography 2023

Presented at the European Society of Cardiology 2022 congress, Barcelona, Spain



GRAPHICAL ABSTRACT



ABSTRACT

Aims: The present guidelines advise replacing the aortic valve for individuals with severe aortic stenosis (AS) based on various echocardiographic parameters. Accurate measurements are essential to avoid misclassification and unnecessary interventions. The objective of this study was to evaluate the influence of measurement error on the echocardiographic evaluation of the severity of aortic stenosis.

Methods and Results: A systematic review was performed to examine whether measurement errors are reported in studies focusing on the prognostic value of peak aortic jet velocity (V_{max}), mean pressure gradient (MPG), and effective orifice area (EOA) in asymptomatic patients with aortic stenosis. Out of the 37 studies reviewed, 17 (46%) acknowledged the existence of measurement errors, but none of them utilized methods to address them. Secondly, the magnitude of potential errors was collected from available literature for use in clinical simulations. Interobserver variability ranged between 0.9-8.3% for Vmax and MPG but was higher for EOA (range 7.7-12.7%), indicating lower reliability. Assuming a circular left ventricular outflow tract area led to a median underestimation of EOA by 23% compared to planimetry by other modalities. A clinical simulation resulted in the reclassification of 42% of patients, shifting them from a diagnosis of severe aortic stenosis (AS) to moderate AS.

Conclusions: Measurement errors are underreported in studies on echocardiographic assessment of AS severity. These errors can lead to misclassification and misdiagnosis. Clinicians and scientists should be aware of the implications for accurate clinical decision-making and assuring research validity.

INTRODUCTION

In the Western world, aortic stenosis (AS) is the most common primary valve disease and when severe requires surgical or transcatheter interventions (1). For the diagnosis of AS severity, clinicians depend primarily on the echocardiographic assessment, which includes different anatomical and hemodynamic parameters (2). Accurate definition of AS severity is of particular importance in asymptomatic patients where the decision to intervene is challenging and relies on the balance between operative risk and long-term survival benefit (3). In this decision-making, identification of patients with very severe, or critical AS who are at higher risk for mortality (4-9), is recommended (10, 11). The current guidelines give a class IIa indication for intervention solely based on a peak aortic jet velocity (V_{max}) of > 5 m/s or a mean transaortic pressure gradient (MPG) ≥ 60 mmHg (10, 11).

To prevent misclassification of the severity of AS, accurate echocardiographic measurements are crucial. However, as with any measurement, the echocardiographic assessment of AS is affected by measurement errors. The definition of measurement error used in this manuscript is provided in box 1. Even though previous studies have identified potential sources of measurement errors (2, 12), their effect on clinical practice and research outcomes is not yet fully understood. The objective of this study was threefold: 1) to examine the consideration of measurement error in echocardiography studies, 2) to determine the extent of different sources of measurement error, and 3) to simulate their effect on the present thresholds for intervention in patients with AS.

Box 1 – Measurement error definition.

Measurement errors lead to a difference between observed and true values (13, 102), and can be expressed in its simplest form as: observation = truth + error. Measurement errors can be classified as random or systematic. Random measurement errors consist of a zero average and a constant variance. A single observed value may be inaccurate, but the average observed value should be equal to the true value. In contrast, systematic measurement errors provide an observed variable that represents a biased variant of the true value thereby consistently leading to either over- or underestimation (13, 102). The term misclassification is used for measurement error in categorical variables. In these definitions, the truth or the true value is not defined by any imaging modality or gold standard but rather the target to be measured that one has in mind. An example of random measurement error in daily practice is for example, intraobserver or interobserver variability. Distinguishing these sources of variability from biological variation (e.g., due to circadian patterns) can be challenging.

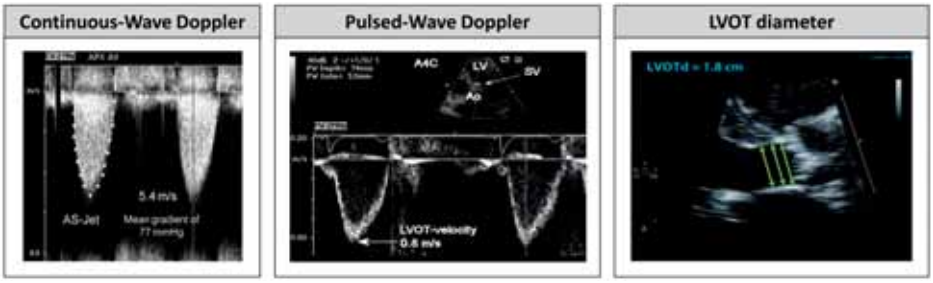
The term measurement error sometimes receives a negative connotation, as it can be inferred that some kind of mistake has been made. In this paper, measurement error is viewed from an epidemiological point of view as a cause of variability/uncertainty (random) or deviation from truth or an accepted reference (systematic). Hence, this manuscript is not a judgement of any author, clinician, or paper included in this manuscript, for it does not necessarily deal with human error.

METHODS

Systematic review

The reporting and correction of measurement errors in prognostic studies on echocardiography in AS were analyzed through a systematic review. We limited the analysis to studies in asymptomatic patients, where the accuracy of the measurements is of paramount importance and to limit the extent of the review analysis. Furthermore, the review only included papers on the three primary parameters used by the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE); V_{max}, MPG, and effective orifice area (EOA)/aortic valve area (AVA) (2). The required measurements to obtain these parameters are depicted in Figure 1.

Figure 1. Required measurements to obtain primary echocardiographic parameters.



The continuous-wave doppler is used to determine peak aortic jet velocity and mean transaortic pressure gradient derived from the velocity-time integral (VTI) across the aortic valve. Effective orifice area is calculated by the continuity equation which also uses the VTI across the aortic valve in combination with the VTI across the left ventricular outflow tract (LVOT), obtained by pulsed-wave doppler, and the LVOT diameter. All images are reproduced from Baumgartner et al. (103), with permission of Oxford University Press.

An electronic search in PubMed Central was performed on 03 September 2022. The complete search strategy and the inclusion/exclusion criteria can be found in the supplementary files. Two independent researchers (BV and MV) reviewed all potentially eligible articles by title and summary, and then conducted full-text reviews. In the event of inconsistencies, a third researcher (RG) repeated the screening, and a joint agreement was reached after a consensus meeting. The recommendations of the EACVI and ASE for echocardiographic assessment of AS (2), for example averaging three or more heartbeats for patients in sinus rhythm, and even more in case of irregular rhythms which is a method to reduce random error, were considered as the norm and residual measurement error was studied. Reporting on random measurement error was acknowledged if an article provided 1) calculations of agreement like intraobserver/ interobserver/ intervendor variability, or 2) textual coverage of parameter-specific coincidental variation. Similarly, reporting on systematic error was appointed if an article included discussion on the influence of 1) flow dependency/alterations, or 2) left ventricular outflow tract (LVOT) geometry alterations. All techniques to account for measurement error like stratification, regression calibration, multiple imputation, Bayesian

models, likelihood methods and bias analysis were recognized as correction methods (see Keogh *et al.* and Van Smeden *et. al* for more detailed examples (12, 13)).

Insights into the magnitude of erroneous sources

Potential erroneous sources for V_{max}, MPG, and EOA have been reported before, in echocardiographic guidelines and consensus statements (2, 14). These sources, classified as random and systematic measurement errors, are summarized in Table 1. In a scoping approach, information was gathered to provide *quantitative* insights into the magnitude of all potential erroneous sources. The sources for this information comprised the EACVI/ASE guidelines (2), the European and American guidelines on the management of valvular heart disease (10, 11), consensus statements (14), the studies included in our systematic review, and other relevant literature which was referred to in these papers. This quantitative information would serve as input for the simulations of the impact of measurement error which is outlined in the following section. If quantifications could not be made, erroneous sources were briefly explained and patient groups theoretically at risk for misclassification were introduced.

Table 1. Overview of potential erroneous sources in the echocardiographic assessment of aortic stenosis severity.

	Random measurement error	**Systematic measurement error**
V_{max}	• Alignment CWD • Tracing the CWD derived VTI_{AV}	• Flow dependency* • Recording of eccentric MR jet
MPG	• Alignment CWD • Tracing the CWD derived VTI_{AV}	• Flow dependency* • Recording of eccentric MR jet • Neglect of proximal velocity • Instantaneous vs. peak-to-peak pressure difference • Pressure recovery
EOA	• Alignment CWD • Tracing the CWD derived VTI_{AV} • Alignment PWD • Tracing the PWD derived VTI_{LVOT} • LVOT diameter	• Flow dependency* • Circular vs. elliptical CSA_{LVOT} • Non-laminar flow

** Flow dependency causes either underestimation (in case of reduced left ventricular function, regional wall motion abnormalities, concentric hypertrophy, mitral regurgitation, atrial fibrillation, or hypertension), or overestimation (in case of aortic regurgitation, sepsis, anemia, or hyperthyroidism). CWD; continuous-wave Doppler, EOA; effective orifice area, LVOT; left ventricle outflow tract, MPG; mean transaortic pressure gradient, MR; mitral regurgitation, PWD; pulsed wave Doppler, Vmax; peak aortic jet velocity, VTI; velocity-time integral.*

Impact of measurement error on current thresholds for intervention

The impact of measurement error was simulated based on echocardiographic indications for intervention recommended by the 2020 ACC/AHA and 2021 ESC/EACTS guidelines on valvular heart disease management (10, 11). We focused on interobserver variability (IOV), which reflects random measurement error, and the assumption of a circular LVOT area in 2-dimensional transthoracic echocardiography (2D-TTE) as a potential source of systematic measurement error. For the simulations, the IOV was set to values reported in the EACVI/ASE guidelines (2), 3.5% in V_{max}, and 13% in EOA, as the IOV described in

literature was heterogeneous (see results). The consequence of IOV was shown by uncertainty around observed parameters and the potential for misclassification of AS severity. The impact of assuming a circular LVOT shape was simulated using the median underestimation by 2D-TTE as compared to 3-dimensional transesophageal echocardiography (3D-TEE), computed tomography (CT), and cardiovascular magnetic resonance (CMR) planimetry reported in literature. By projecting this median underestimation on a hypothetical cohort of patients, the impact on the EOA and reclassification of AS severity were demonstrated. The EOAs of this cohort were based on a normal distribution using the mean and standard deviation of the surgical arm of the PARTNER 3 trial (15, 16). Data analysis and visualization were performed using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org). No original patient data were used in the simulations, and the R script is available in the supplementary files.

RESULTS

Systematic review

The initial search gave 203 articles of which 166 were excluded after a two-step screening approach (Figure S1). Eleven studies reported on V_{max} (8, 9, 17-25), six on MPG (6, 26-30), seven on EOA (31-37), and thirteen on multiple primary parameters (5, 7, 38-48). When all studies were pooled, any mention of error in measurement was made in less than half of the included studies (46%), with random measurement error (41%) more prevalent than systematic error (19%, Table 2). The studies on EOA discussed measurement error most frequently (57%), while reporting was absent in most studies on MPG. A comprehensive overview with all scoring categories is provided in the supplementary files in Table S1. Intraobserver or interobserver variability was most often described as the cause of random measurement errors. There was no correction for measurement error in all the studies included, even in studies that reported systematic measurement errors.

Table 2. Reporting of measurement error in studies on echocardiographic assessment of aortic stenosis severity.

	V_{max} n = 11	MPG n = 6	EOA n = 7	Combination n = 13	Total n = 37
Random measurement error	4 (36%)	0 (0%)	4 (57%)	7 (54%)	15 (41%)
Systematic measurement error	0 (0%)	1 (17%)	4 (57%)	2 (15%)	7 (19%)
Any measurement error	4 (36%)	1 (17%)	5 (71%)	7 (54%)	17 (46%)

Cells represent the number of studies (percentage). Note that the numbers do not necessarily add up because the numbers are expressed by study and studies can report random and systematic measurement errors. EOA; effective orifice area, MPG; mean transaortic pressure gradient, multiple parameters; any combination of Vmax/MPG/EOA, Vmax; peak aortic jet velocity.

Insights into the magnitude of erroneous sources

Peak aortic jet velocity (Vmax)

V_{max} is measured directly from the velocities across the aortic valve obtained via continuous-wave Doppler (CWD) (2). The highest value of measurements from different acoustic windows is determined. Doppler interrogation with windows outside of apical position is important since the highest velocity is often obtained from the right parasternal window (49, 50), however, this window is only used in 52% (51).

Random errors can occur in acquiring data, e.g., imperfect parallel alignment of CWD with the aortic jet, or in measuring data, i.e., selecting the peak of the velocity curve (2, 14). In addition, a combination of the previously mentioned errors can result in random variation on observer level. In literature, intraobserver and interobserver variability ranged from 0-4% (2, 38, 41, 52-55) and 0.9-8.3% (2, 18, 45, 52, 53, 55-57), respectively. In Table S2, a complete overview is provided.

Mean transaortic pressure gradient (MPG)

The MPG, mathematically expressed as ΔP, is calculated from the simplified Bernoulli equation (2): $\Delta P = 4\,v^2$. By averaging the instantaneous gradients over the ejection time, using the velocity-time integral across the aortic valve (VTI_{AV}), the MPG is derived (2). Since the CWD is used for calculating MPG and Vmax, the potential sources for measurement error are equal, though errors in velocity measurement are squared in Bernoulli's formula. Intraobserver and interobserver variability in literature ranged from 2.5-10.7% (38, 41, 53) and 3.9-7.0% (53, 56, 58), respectively (Table S2).

Other sources of measurement error are unique to MPG. The simplified Bernoulli equation, in contrast to the "non-simplified" Bernoulli equation, ignores the proximal velocity as this velocity is <1 m/s in most patients. However, consistent overestimation may occur in patients with hypertrophic cardiomyopathy or other types of subvalvular narrowing (2, 14, 59). Another source of overestimation of Doppler-derived MPG compared to catheterization measurements is due to the concept of pressure recovery (PR). PR is the hemodynamic phenomenon where beyond a narrowed area (the valve), kinetic energy (velocity) can be converted to potential energy (pressure) due to deceleration of blood (60). Recovery occurs in the proximal ascending aorta; however, as Bernoulli's formula uses the velocity across the valve as input, the pressure drop could be overestimated. In a pulsatile flow model, Niederberger and colleagues found constant overestimation of Doppler gradients with differences up to 66 mmHg in patients with a small aortic diameter of 1.8 cm (61). In a clinical study, Baumgartner *et al.* observed an average overestimation of MPG of 11 mmHg (20%) due to PR (62). In larger studies comprising 697 and 1563 patients, comparable overestimations ranging from 14-26% were observed (63, 64). Overestimation due to PR increased with smaller aortic diameters in all studies, especially when proximal aortic dimensions were below 3.0-3.5 cm (62-64).

Effective orifice area (EOA)

The EOA is calculated using the continuity equation (2): $EOA = \frac{LVOT\ area \times VTI\ L}{VTI\ AV}$. The continuity equation requires three different measurements; the PWD-derived VTI_{LVOT}, the CWD-derived VTI_{AV}, and the LVOT diameter functioning as an argument to calculate the cross-sectional area (CSA) assuming a circular shape; $CSA\ LVOT = \pi\left(\frac{D}{2}\right)^2$. Like the CWD, potential errors exist in PWD alignment and VTI_{LVOT} tracing (2, 14). Intraobserver and interobserver variability ranged from 1.1-5.0% (41, 53, 65-69) and 7.67-12.7% (53, 65, 66, 70), respectively (Table S2).

As measurement errors in LVOT diameter are squared in the calculation of EOA, its potential impact is amplified (2). While obtaining the LVOT diameter, random measurement errors can occur on one hand. On the other hand, assuming a circular geometry of the LVOT may result in a systematic underestimation, as a more elliptical shape is frequently observed (2, 14, 71). The anteroposterior diameter, which is measured by 2D-TTE, often serves as the smallest diameter (71). Several studies quantified the underestimation by 2D-TTE as summarized in Table 3 (65, 72-78). Median underestimation 2D-TTE was 20%, 28%, and 22% compared to 3D-TEE (72-76), CT (72, 73, 75-77), and CMR planimetry (65, 78), respectively. The maximum reported underestimation was 46% (75).

Additionally, in the calculation of EOA, the flow patterns in the LVOT and across the aortic valve are assumed to be laminar with a spatially flat flow profile (2). However, in case of increased subaortic flow velocities, for example in patients with septal hypertrophy, the profile becomes skewed leading to an overestimation of the VTI_{LVOT} (2). In accordance, the VTI_{AV} is also overestimated in patients with AS when laminar flow is assumed as shown by Donati *et al.* (79). The final direction of systematic measurement error depends on the impact on the ratio VTI_{LVOT}/VTI_{AV}. To our knowledge, literature is absent on the impact of the assumption of laminar flow on EOA calculation.

Table 3. Quantification of discrepancy in LVOT area reported in literature.

		2D-TTE vs. 3D-TEE planimetry
Study	**Mean underestimation**	**EOA**
Norum et al. 2020	8%	0.7 ± 0.2 cm^2
Teixeira et al. 2017	17%	0.62 ± 0.20 cm^2
Mehrotra et al. 2015	15%	0.6 ± 0.13 cm^2
Stähli et al. 2014	39%	0.48 ± 0.04 cm^{2*}
Ng et al. 2010	21% §	0.69 ± 0.18 cm^2
		2D-TTE vs. CT planimetry
Study	**Mean underestimation**	**EOA**
Norum et al. 2020	29%	0.7 ± 0.2 cm^2
Teixeira et al. 2017	24%	0.62 ± 0.20 cm^2
Stähli et al. 2014	46%	0.48 ± 0.04 cm^{2*}
Gaspar et al. 2012	15%	0.92 ± 0.44 cm^2
Ng et al. 2010	26% §	0.69 ± 0.18 cm^2
		2D-TTE vs. CMR planimetry
Study	**Mean underestimation**	**EOA**
Maes et al. 2017	24%	0.76 ± 0.17 cm^{2*}
Garcia et al. 2011	20%	1.53 ± 0.67 cm^2

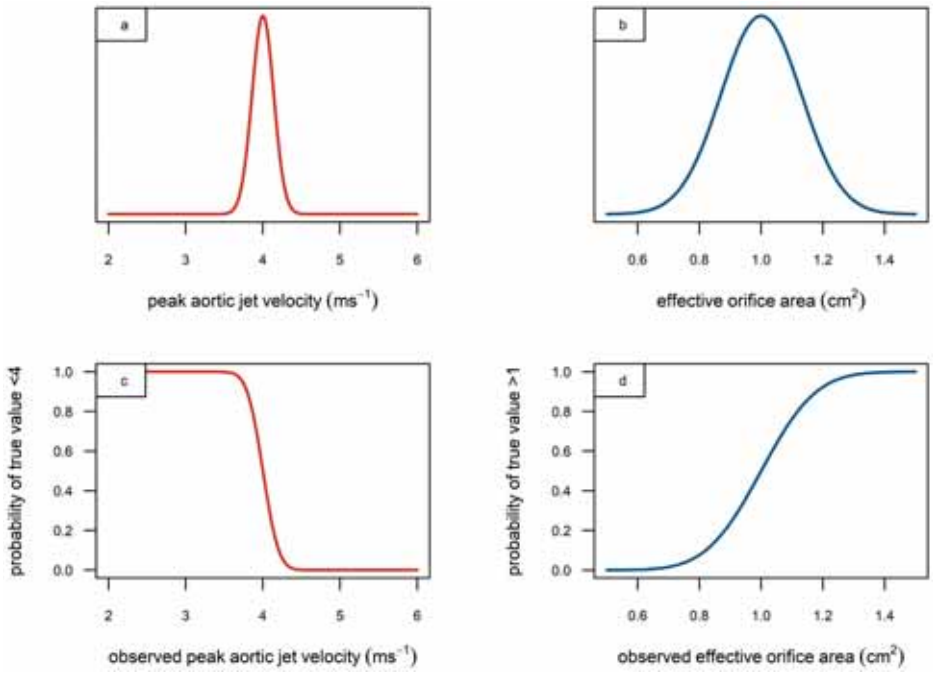
** The mean EOA was approximated to enhance readability by multiplying the mean EOA index by the mean BSA as reported by the specific study. § These studies used 2-dimensional TEE instead of TTE. EOA is presented as mean ± standard deviation calculated by the continuity equation. BSA; body-surface area, EOA; effective orifice area, CMR; Cardiovascular magnetic resonance, CT; Computed tomography, LVOT; Left ventricle outflow tract, TEE; Transesophageal echocardiography, TTE; transthoracic echocardiography.*

Impact of measurement error on current thresholds for intervention

Random measurement error

In the 2020 ACC/AHA and 2021 ESC/EACTS guidelines (10, 11), severe AS is defined as a $V_{max} \geq 4.0$ m/s, MPG ≥ 40 mmHg, and an EOA ≤ 1.0 cm^2. The impact of interobserver variability when these cut-off values are observed, is shown in Figure 2. For example, when one measures an EOA of 1.0 cm^2, the true EOA could well be in the range between 0.8 and 1.2 cm^2, or even more extreme (2b). The uncertainty around V_{max} is much smaller (2a) due to lower IOV (as the x-axes represent similar ranges). When one observes an EOA of 0.84 cm^2, there is a 10% chance (probability of 0.1) that the true EOA is greater than 1.0 cm^2 (2d), and the patient is misclassified due to IOV.

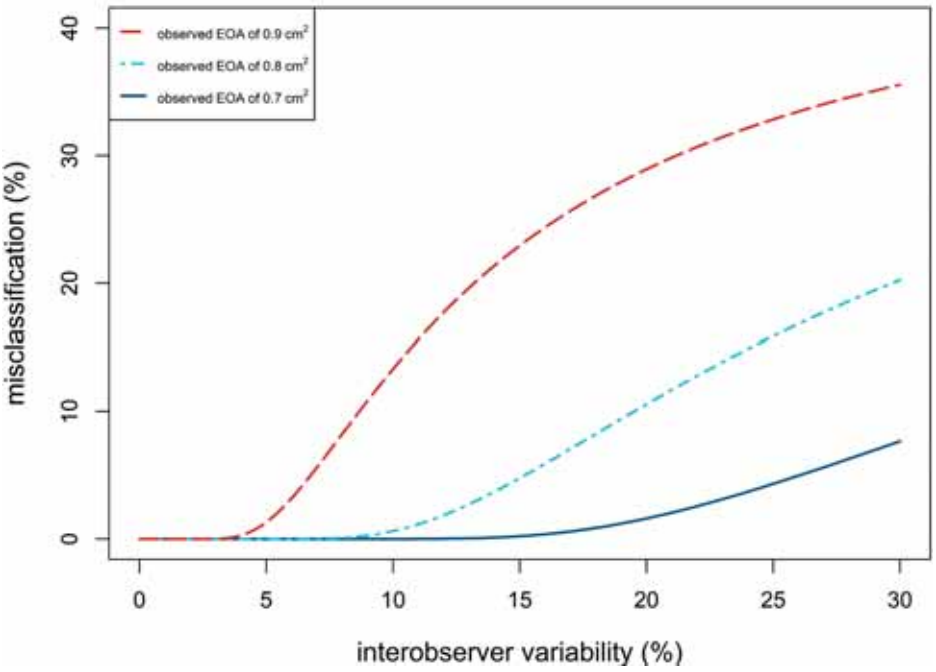
Figure 2. The impact of interobserver variability on observed echocardiographic values.



Panels 2a-b present the uncertainty due to interobserver variability around cut-off values for severe aortic stenosis in the guidelines (10, 11) for peak aortic jet velocity (a), and effective orifice area (b), respectively. Panels 2c-d show the chance the true value lies within the moderate aortic stenosis range due to interobserver variability for increasing values of peak aortic jet velocity (c), and effective orifice area (d), respectively.

The effect of increasing IOV on misclassification is shown in Figure 3. The chance of a true value higher than 1.0 cm^2 due to interobserver variability is plotted here for patients with an observed EOA of 0.9 (interrupted red line), 0.8 (dot/dashed light blue line), and 0.7 (solid dark blue line) cm^2. For the patients with an observed EOA of 0.7 cm^2, their value is not close to the cut-off separating severe from moderate AS, and an IOV of less than 15% rarely leads to misclassification. However, for an observed EOA of 0.9 cm^2, the same 15% leads to misclassification in approximately 25% of patients.

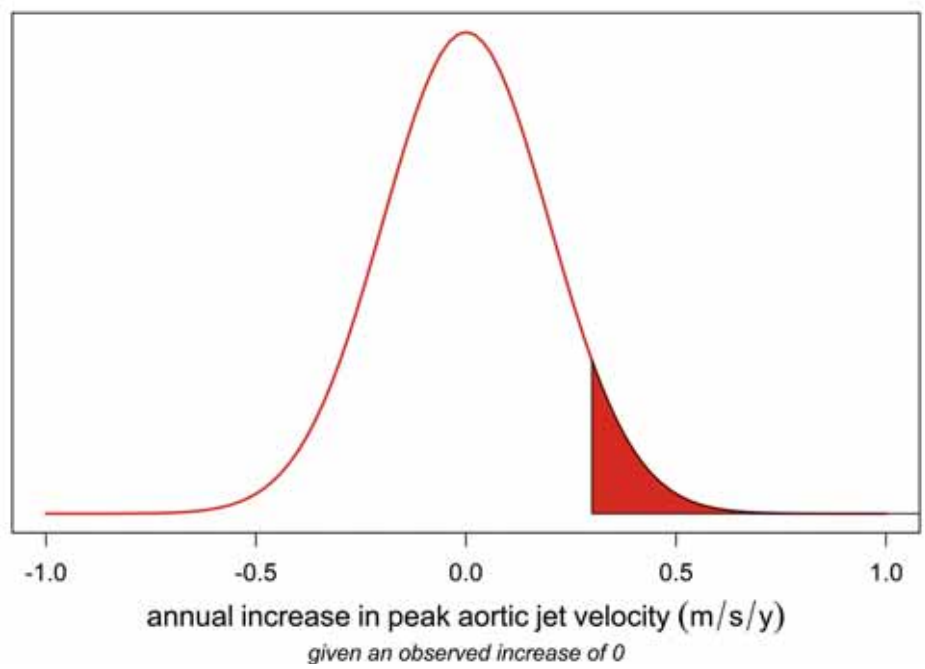
Figure 3. Impact of increasing interobserver variability in effective orifice area on misclassification.



The figure shows the chance the true EOA value lies within the moderate aortic stenosis range according to increasing interobserver variability. The colored lines represent percentage of misclassification for patients with different observed values for EOA. EOA; effective orifice area.

The latest guidelines (10, 11) introduced a new class IIa indication for intervention when the annual increase in peak aortic velocity was ≥ 0.3 m/s/year in combination with severe valvular calcifications. This parameter requires two measurements of V_{max} both of which may be affected by random measurement error such as IOV. This impact is shown in Figure 4: when an annual increase of 0 m/s/year is observed, the true progression is ≥ 0.3 m/s/y in 6.5%, indicating unjustly withholding of intervention in 1 in 16 patients due to IOV.

Figure 4. Impact of interobserver variability on annual increase in peak aortic jet velocity

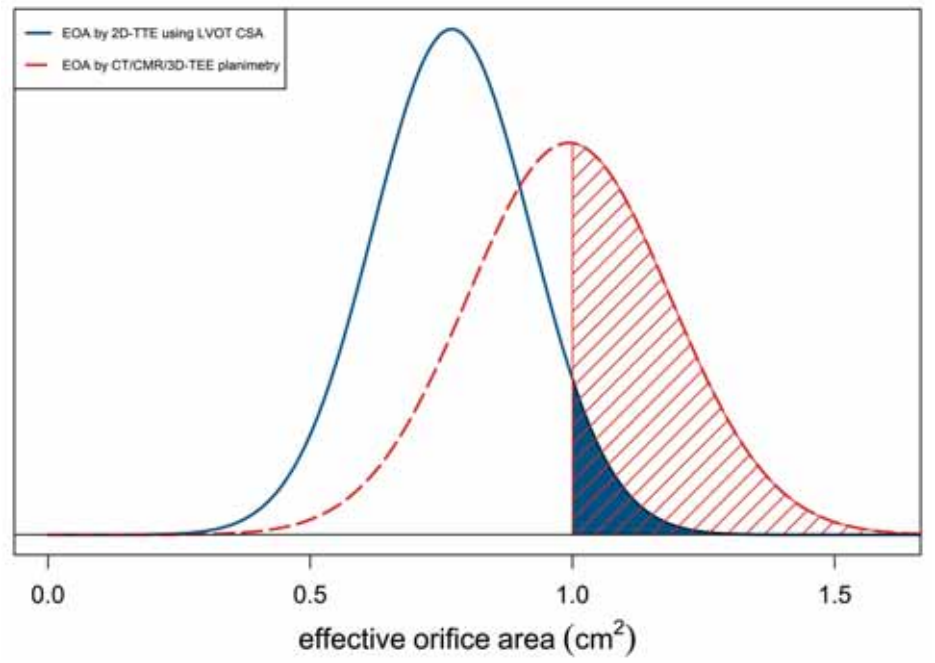


The red lines show the distribution of true annual increase in peak aortic jet velocity when a 0 m/s/year increase is observed. The highlighted area under the curve (6.5%) represents the patients with a true annual increase ≥ 0.3 m/s/y (having an indication for intervention) who are not detected due to interobserver variability.

Systematic measurement error

In literature, the median underestimation of the LVOT area by 2D-TTE as compared to all other modalities was 22.5% (Table 3). The impact of this underestimation on the classification of AS is shown in Figure 5. The distributions represent the EOA values obtained by 2D-TTE (solid dark blue line), and by planimetry of the LVOT area (interrupted red line), of a hypothetical cohort of patients based on the PARTNER 3 trial (15, 16). The proportion with non-severe AS increased by 42% when the LVOT area is measured by planimetry (48% compared to 6% by 2D-TTE).

Figure 5. Underestimation of EOA by 2D-TTE compared to CT / CMR / 3D-TEE planimetry



The solid dark blue line represents the EOA distribution of patients determined by the continuity equation using the LVOT CSA. The interrupted red line illustrates the EOA distribution of the same patients if the LVOT area is measured by CT, CMR, or 3D-TEE planimetry. The areas under the curve show the number of patients with non-severe AS. An increase in patients of 42% is observed when EOA is measured by planimetry. AS; Aortic stenosis, CT; Computed tomography, CMR; Cardiovascular magnetic resonance, CSA; cross-sectional area, EOA; effective orifice area, LVOT; left ventricular outflow tract, 2D-TTE; 2-dimensional transthoracic echocardiography, 3D-TEE; 3-dimensional transesophageal echocardiography.

DISCUSSION

This study showed that the potential of measurement errors in echocardiographic assessment of AS severity is underreported in literature. It also detailed mechanisms and magnitudes of random and systematic errors, including subgroups of patients prone to AS severity misclassification.

The European and American guidelines on valvular heart disease management have broadened recommendations for aortic valve interventions in AS patients based solely on abnormal echocardiographic parameters (10, 11). Both guidelines include indications for asymptomatic patients with severe AS. Furthermore, thresholds for intervention in asymptomatic patients with severe AS and LV dysfunction are lowered from an ejection fraction below 50% to 55% (11). Besides, patients with discordant primary parameters, for example in case of low-flow low-gradient severe AS, are also considered to be candidates for aortic valve replacement (10, 11). With these expanding echocardiography-based

recommendations, it is crucial to acknowledge the presence and magnitude of measurement error and its implications to adequately refer AS patients to undergo an intervention. Most importantly, interventions on unjustly indicated patients must be avoided.

The 46% consideration of measurement error found in this study, was identical to its reporting in high-impact journals (80). Brakenhoff and colleagues stated that in most articles uninformative claims about the impact of measurement errors were made without quantitative data support. Our experience is similar, apart from calculations of observer agreement, as the impact of errors was only vaguely addressed and phrased like 'we must take measurement error into account', without further explanation (21).

A systematic measurement error may partially fix the discrepancy between the current cut-off values for severe AS demonstrated in several studies (81-83). In a large group of AS patients with preserved ejection fraction, Minners *et al.* (81) found that 30% had an EOA < 1 cm^2 despite a MPG < 40 mmHg. In that study, a MPG of 40 mmHg corresponded to an EOA of 0.75 cm^2. However, when correcting for systematic underestimation by the continuity equation, that value would shift closer toward the cut-off of 1 cm^2. Other flow-dependent factors, such as low stroke volume, also contribute to this discrepancy (81).

Interestingly, Mehrotra *et al.* (74) found that the underestimation of the LVOT area by TTE compared to CT was more profound in patients with severe AS than in controls (20% vs. 12%). They hypothesized that pressure overload caused by AS induces LV remodeling, specifically increased interventricular septal thickness, upper septal hypertrophy, and calcifications. These secondary effects can increase LVOT stiffness reducing its ability to expand during systole (74). This would mean that a decrease in EOA leads to less LVOT expansion, which consequently causes an increase in underestimation. In Table 3, the mean EOA was shown next to the underestimation rates to investigate this hypothesis. Unfortunately, our data were too limited to draw firm conclusions. Further research on this topic is of interest, as different EOA cut-off values will be needed when underestimation of the LVOT area is truly dependent on patient features such as AS severity. The potential utilization of 3D-TTE for optimizing LVOT measurements presents an attractive alternative to invasive methods such as TEE, contrast-enhanced CT, or CMR. However, the feasibility of implementing 3D-TTE is hindered by challenges posed by image quality and the presence of calcifications, which can impact its accuracy and reliability (72, 77).

The severity thresholds for aortic stenosis were selected based on their link with clinical outcomes. Therefore, studies on the prognostic implications of systematic measurement errors would be valuable to clinical practice. Unfortunately, these are rare. Clavel *et al.* performed a head-to-head LVOT comparison and AVA recalculation by CT vs. echocardiography and found no superiority of CT, just a higher threshold of 1.2 cm^2 that was associated with poor survival (84). Considering these results, the clinical relevance of the 42% reclassification of AS severity in our simulation would be diminished.

We have not yet discussed a potential source of systematic measurement error that could occur in all primary echocardiographic parameters is their dependence on flow (85-91). General quantitative claims about the impact of flow are hard to make as flow widely varies between and within patients. Flow dependency could either lead to overestimation of echocardiographic parameters in case of an increased flow state, for instance in patients with aortic regurgitation (AR), anemia, hyperthyroidism, or sub/supravalvular obstruction (2, 14, 92, 93). On the contrary, a decreased flow state leads to underestimation of echocardiographic measurements, for example in patients with reduced left ventricular (LV) function/heart failure, regional wall motion abnormalities, concentric LV hypertrophy, mitral regurgitation, atrial fibrillation, or hypertension (14). As the presence of these conditions will increase with age, elderly patients especially might be prone to an altered flow state, and therefore unreliable flow-dependent parameters (94). Using body surface area (BSA) as an index to account for flow dependency is suggested for EOA. Theoretically, the EOA index (EOAi) should be less influenced by flow compared to EOA alone. However, multiple studies have demonstrated that BSA is an inadequate proxy for cardiac output, both in normotensive individuals (95, 96) and patients with severe aortic stenosis (97, 98). This limitation could potentially result in inaccurate classification, such as in EOAi-based concepts like prosthesis-patient mismatch after AVR (97, 98).

Echocardiographic parameters play a crucial role in clinical practice by aiding in diagnosis and prognosis, relying on accurate measurement and true associations. Precision in measurement is vital for treatment decision-making in individual patients. Among the primary parameters explored in this review, Vmax demonstrated the least variability between observers, requiring minimal assumptions. However, its reliability diminishes in patients with altered flow states. Additional echo parameters exist beyond the primary ones (2). Doppler velocity/dimensionless index and velocity ratio (LVOT V_{max}/AV V_{max}) are more flow-independent and relatively easy to measure but are only applicable when there is no LVOT obstruction. Recent studies highlight the importance of focusing on myocardial parameters and incorporating multimodality imaging (99). These advancements show promise, but further research is necessary to optimize diagnostic processes and determine the ideal intervention threshold for AS patients.

Implications for clinical practice and scientific research

The measurement methods utilized in routine clinical practice are mostly comparable to those used in the studies that serve as the basis for guidelines, and they likely exhibit similar degrees of measurement error. Therefore, current cut-off values should be correct, even though the observed values might not be the true values. A problem arises though if measurement errors are unequally distributed among patients compromising uniform cut-off values.

Clinicians should be aware of potential misclassification due to (random) measurement error, especially when an echocardiographic observation is close to the cut-off value. Assessment can be repeated (after a short time) reducing the impact of random errors, but not that of systematic

errors. Moreover, a combination of parameters should be considered, not only hemodynamic measures, but also functional status, valvular calcification, LV function, and LV hypertrophy, as advised in the guidelines (10, 11). Clinicians should recognize differential systematic measurement errors that depend on patient characteristics, such as flow alterations in reduced LV function, aortic regurgitation, or anemia. Such sources of error must be minimized to accurately classify patients. If this is not possible, observed values should be carefully interpreted.

In scientific research, measurement error can affect estimates of exposure-outcome relationships, including randomized controlled trials (100, 101). Its presence can lead to over- and underestimation of the true exposure-outcome relationship, even in case of random measurement error because statistical assessment depends on sampling variability (12, 13). Echocardiographic assessments at baseline or during follow-up can be repeated (in a short time) to enhance the credibility of obtained values. If continuous echocardiographic values are dichotomized to compare with decision thresholds, patients may be misclassified and therefore improperly treated. To reduce measurement errors, researchers must identify, assess, and correct them. Reporting errors is crucial, and collaborating with epidemiologists or statisticians can improve research validity, especially since many clinical researchers may not be familiar with correction techniques.

Limitations

Two factors could compromise our findings. First, exposure and results can be measured more precisely in clinical research than in routine daily practice. Therefore, the results of the magnitude of erroneous sources in this study could be conservative. Second, reporting certain measurement errors was unclear. Intraobserver and interobserver variability were frequently reported as percentage without specification of methodology or reliability coefficients (Table S2). As both intraobserver and interobserver variability are random measurement errors, the reported percentages were therefore interpreted as distributed around the observed mean value. Lastly, the simulations showed simplified clinical scenarios in which only one random or systematic measurement error was present. In daily clinical practice, the sum of all errors together determines whether the observed echocardiographic parameters are reliable and unbiased.

CONCLUSIONS

With expanding recommendations for intervention on abnormal echocardiographic parameters, understanding the various sources of measurement errors in assessing AS and how to handle them is crucial. This will improve clinical decision-making and ensure research validity. We (re-)encourage clinicians and researchers to not rely exclusively on (single) echocardiographic parameters for the diagnosis of severe AS.

Acknowledgements: We thank dr. Jae K. Oh and dr. Howard C. Herrmann for reviewing the manuscript and providing feedback on the content.

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SUPPLEMENTARY FILES

Available at https://doi.org/10.1111/echo.15664.

3

THE ROBUSTNESS OF THE FLOW-GRADIENT CLASSIFICATION OF SEVERE AORTIC STENOSIS

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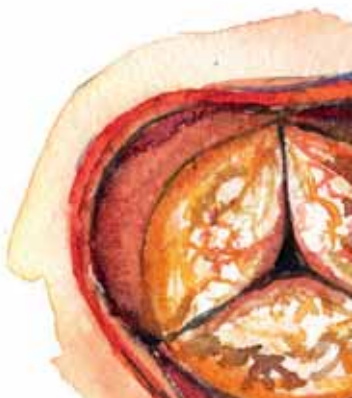
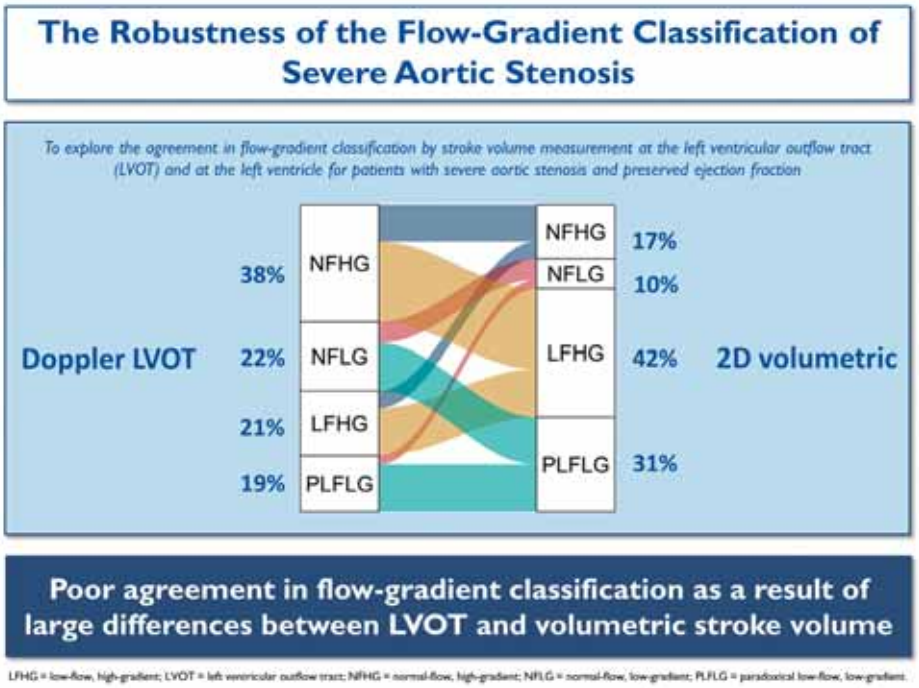
JTCVS Open 2023

Presented at the 2023 annual meeting of the Heart Valve Society, Malaga, Spain



GRAPHICAL ABSTRACT



ABSTRACT

Background: A flow-gradient classification is used to determine the indication for intervention for severe aortic stenosis (AS) patients with discordant echocardiographic parameters. We investigated the agreement in flow-gradient classification by stroke volume (SV) measurement at the left ventricular outflow tract (LVOT) and at the left ventricle.

Methods: Data were used from a prospective cohort study and severe AS patients ($AVAi \leq 0.6 cm^2/m^2$) with preserved ejection fraction (>50%) were selected. SV was determined by an echocardiographic core laboratory at the LVOT and by subtracting the 2-dimensional left ventricle end-systolic from the end-diastolic volume (volumetric). Patients were stratified into four groups based on SV index (SVi, 35 mL/m^2) and mean gradient (40 mmHg). The group composition was compared and the agreement between the SV measurements was investigated using regression, correlation, and limits of agreement. In addition, a systematic LVOT diameter overestimation of 1 mm was simulated to study flow-gradient reclassification.

Results: Of 1118 patients, 699 were eligible. The group composition changed considerably as agreement on flow-state occurred in only 50% of the measurements. LVOT SV was on average 15.1 mL (95% limits of agreement -24.9:55.1 mL) higher than volumetric SV. When a systematic 1 mm LVOT diameter overestimation was introduced, the low-flow groups halved.

Conclusions: There was poor agreement in the flow-gradient classification of severe AS as a result of large differences between LVOT and volumetric SV. Furthermore, this classification was sensitive to small measurement errors. These results stress that parameters beyond the flow-gradient classification should be considered to ensure accurate recommendation for intervention.

INTRODUCTION

The diagnosis of severe aortic stenosis (AS) is challenging when echocardiographic parameters such as the mean pressure gradient (MPG) and the aortic valve area (AVA) are discordant. Even in case of preserved left ventricular ejection fraction (LVEF), flow alterations are thought to play a crucial role in explaining this discrepancy [1]. Hence, a classification based on flow-gradient patterns was proposed [2]. Patients with a MPG ≤40 mmHg are still considered to have severe AS in case of a small AVA index (AVAi) and low-flow state (stroke volume index [SVi] ≤35 mL/m^2). This classification is important to the heart team as it determines the indication for aortic valve replacement (AVR) in the guidelines [3,4]. The main pitfall for this classification is SV measurement, determined at the left ventricular outflow tract (LVOT) [1,2,5]. Therefore, corroboration with volumetric echocardiographic methods such as the Simpson's was initially advised [2,5]. Although fair agreement between these SV methods was reported by some studies [6,7], several other studies found poor agreement [8,9,10]. The consequences for the flow-gradient classification, which are directly relevant to clinic practice, are still unclear.

Hence, this study aimed to investigate the agreement in flow-gradient classification by LVOT and volumetric SV for severe AS patients with preserved LVEF. The secondary aim was to study the agreement between the SV measurements themselves. The overarching goal is to provide information to improve decision-making by the heart team for AS patients with discordant echocardiographic parameters.

PATIENTS AND METHODS

Study data

Data from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve (www.clinicaltrials.gov, NCT02088554) were used. The PERIGON Pivotal Trial is a single-armed prospective observational follow-up study to examine the safety and performance of the Avalus bioprosthesis (Medtronic, Minneapolis, Minnesota, USA). The design of the trial was formerly outlined in detail [11]. In the PERIGON Pivotal Trial, patients with a clinical indication for AVR due to AS or aortic regurgitation (AR) were enrolled. More than mild mitral- or tricuspid regurgitation was an exclusion criterion. Specifically for the current study, patients with AR or a mixed primary indication with more than mild regurgitation were also excluded. Moreover, only the patients with an AVAi ≤0.6cm^2/m^2 and preserved LVEF (>50%) were selected. The study was conducted at 38 centers across North America and Europe at which local institutional review boards or ethics committees provided study approval (see supplementary files Klautz *et al.* [12] for number and date per center). Furthermore, written informed consent was obtained from all patients. All deaths and valve-related events were adjudicated by an independent clinical events committee (Baim Institute for Clinical Research, Boston, MA, USA).

2-Dimensional and Doppler echocardiography

An independent core laboratory (MedStar Health Research Institute, Washington, DC, USA) assessed all echocardiograms. MPG and AVA were determined using the simplified Bernoulli equation and the continuity equation, respectively. SV was calculated according to two independent methods. The first was the LVOT method (SV_{LVOT}) in which the velocity-time integral (VTI) was multiplied by the LVOT cross-sectional area under the assumption of a circular shape. The second was the volumetric method ($SV_{volumetric}$) in which the 2D left ventricle (LV) end-systolic volume was subtracted from the LV end-diastolic volume using biplane data, conforming to the modified Simpson's rule. When two orthogonal views were not adequate for measurement, a single plane measurement was used. LVEF was also calculated from the LV end-systolic and end-diastolic volume conform the modified Simpson's rule. When this continuous parameter was not available (which was the case in 21%), a categorical variable was used that indicated whether LVEF was good (>50%), moderate (31-50%), poor (21-30%), or very poor (≤ 20%) based on visual inspection. Indexed parameters were constituted by dividing them by BSA (according to the DuBois formula [13]).

Patients were stratified by flow-gradient pattern according to the criteria of Dumesnil *et al.* [2]; low-flow was defined as SV ≤35 mL/m^2, and low gradient as MPG ≤40 mmHg. This resulted in four groups: normal-flow, high-gradient (NFHG); normal-flow, low-gradient (NFLG); low-flow, high-gradient (LFHG); and paradoxical low-flow, low-gradient (PLFLG).

Statistical analysis

Numerical data were presented either as mean ± standard deviation or median [interquartile range] depending on their distribution, and categorical data were presented as counts (percentages). Missing baseline data were present only for $SV_{volumetric}$ (in 20%), and were assumed to be missing at random (MAR) [14]. Therefore, multiple imputation was performed based on all available patient characteristics, preoperative echocardiographic parameters, and survival status using predictive mean matching with 50 iterations to create 10 imputed datasets. Estimates and corresponding variances were pooled according to Rubin's rules [14]. To pool correlation coefficients, a Fisher Z transformation was used [15]. A sensitivity analysis was carried out in patients with complete data.

First, the proportion of patients per flow-gradient group was determined according to each SV method. Subsequently, the agreement between these methods was investigated using linear regression and Pearson's correlation coefficient. Furthermore, the mean difference between the SV measurements, including 95% limits of agreement, was illustrated in a Bland-Altman plot [16]. Two Kaplan-Meier analyses were executed according to flow-gradient patterns determined by each SV method to investigate whether potential differences in group composition affected the corresponding survival rates. Follow-up started at the day of surgery and lasted until death, withdrawal, or stay in the study until the data pull, whichever came first.

Lastly, the clinical implication of measurement error in SV_{LVOT} was studied. An overestimation of the LVOT diameter by 1 mm was simulated, after which the SV and AVA were recalculated and the consequences for the flow-gradient classification were assessed.

All analyses were performed using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org).

RESULTS

Patient characteristics according to flow-gradient patterns

Out of 1118 patients in the PERIGON Pivotal Trial, 699 were eligible (supplementary files *Figure S1*). The baseline characters are presented according to flow-gradient patterns determined by SV_{LVOT} (*Table 1*). The low-flow groups comprised more males. The LFHG group had the lowest median Society of Thoracic Surgeons predicted risk of mortality (STS PROM), whereas the PLFLG had the highest. The average AVA and AVAi were smallest in the LFHG group, and largest in the NFLG group. There were large discrepancies in SV_{LVOT} and $SV_{volumetric}$, and PLFLG patients had the smallest average indexed LV end-diastolic volume (LVEDV). Mild mitral regurgitation was relatively uncommon in the PLFLG group. Coronary artery disease and concomitant coronary artery bypass grafting were more common in the low-gradient groups as compared to the high-gradient groups. Lastly, atrial fibrillation (AF) was frequently present in PLFLG patients.

In *Table S1*, the baseline characteristics per flow-gradient group are presented, stratified by SV method. When $SV_{volumetric}$ was used, the normal-flow groups comprised more male patients than the low-flow groups. Furthermore, the lowest STS PROM was observed for the NFHG group, and the largest discrepancies in SV were present in the low-flow groups. Except for these differences, the group characteristics remained rather similar to the scenario using SV_{LVOT}.

Table 1. Baseline characteristics of severe aortic stenosis patients by flow-gradient patterns based on LVOT SV measurement.

	NFHG	**NFLG**	**LFHG**	**PLFLG**
	N = 267 (38%)	**N = 156 (22%)**	**N = 148 (21%)**	**N = 128 (19%)**
Patient characteristics				
Age (years)	71.3 ± 8.3	70.8 ± 8.1	70.0 ± 7.0	70.7 ± 7.6
Male	188 (70%)	110 (71%)	116 (78%)	96 (75%)
Body surface area (m^2)	1.93 ± 0.19	1.98 ± 0.22	2.07 ± 0.21	1.99 ± 0.20
Body mass index (kg/m^2)	28.6 ± 4.8	29.9 ± 5.0	30.6 ± 5.4	30.1 ± 5.6
STS score (%)	1.54 [1.06,2.46]	1.68 [1.10,2.38]	1.43 [0.98,2.13]	1.77 [1.15,2.45]
Diabetes mellitus	56 (21%)	51 (33%)	61 (41%)	42 (33%)
Hypertension	200 (75%)	130 (83%)	116 (78%)	95 (74%)
Chronic obstructive pulmonary disease	28 (10%)	15 (10%)	18 (12%)	11 (9%)

1. Continued

	NFHG	NFLG	LFHG	PLFLG
	N = 267 (38%)	N = 156 (22%)	N = 148 (21%)	N = 128 (19%)
Coronary artery disease	106 (40%)	76 (49%)	57 (39%)	65 (51%)
Concomitant CABG	76 (28%)	62 (40%)	35 (24%)	56 (44%)
Atrial fibrillation	24 (9%)	9 (6%)	14 (9%)	17 (13%)
New York Heart Association class III/IV	116 (43%)	68 (44%)	66 (45%)	53 (41%)
Stroke	13 (5%)	7 (4%)	7 (5%)	4 (3%)
Peripheral vascular disease	16 (6%)	13 (8%)	11 (7%)	11 (9%)
Renal insufficiency	30 (11%)	13 (8%)	14 (9%)	18 (14%)
Echocardiography				
Peak aortic jet velocity (ms^{-1})	4.7 ± 0.5	3.8 ± 0.4	4.6 ± 0.4	3.6 ± 0.4
Mean pressure gradient (mmHg)	55 ± 13	33 ± 6	55 ± 10	31 ± 7
Aortic valve area (cm^2)	0.71 ± 0.15	0.90 ± 0.14	0.57 ± 0.11	0.74 ± 0.15
Aortic valve area index (cm^2/m^2)	0.37 ± 0.07	0.46 ± 0.07	0.28 ± 0.05	0.37 ± 0.08
Doppler velocity index	0.23 ± 0.08	0.29 ± 0.08	0.20 ± 0.08	0.25 ± 0.08
LVOT SV (mL)	84.9 ± 15.2	83.0 ± 12.9	63.2 ± 8.1	61.0 ± 9.4
LVOT SV index (mL/m^2)	44.0 ± 7.0	42.1 ± 5.5	30.6 ± 3.0	30.6 ± 3.5
Volumetric SV (mL)	62.9 ± 18.8	62.6 ± 18.7	61.8 ± 17.6	53.5 ± 17.3
Volumetric SV index (mL/m^2)	32.4 ± 8.7	31.8 ± 8.1	30.0 ± 7.9	26.8 ± 7.4
Heart rate (bpm)	65 ± 10	64 ± 11	71 ± 12	70 ± 12
LV end-diastolic volume index (mL/m^2)	52.0 ± 13.4	51.7 ± 13.4	49.4 ± 12.8	43.6 ± 11.7
LV end-systolic volume index (mL/m^2)	19.9 ± 6.3	20.0 ± 6.4	19.5 ± 6.4	16.2 ± 5.6
Left ventricular ejection fraction (%)	62 ± 6	62 ± 5	61 ± 6	62 ± 6
Left ventricular hypertrophy	120 (45%)	42 (27%)	63 (43%)	43 (34%)
Mild mitral regurgitation	100 (37%)	54 (35%)	58 (39%)	26 (20%)
Mild tricuspid regurgitation	101 (38%)	43 (28%)	38 (26%)	39 (30%)

Data are either presented as mean ± standard deviation, median [interquartile range] or counts (percentages). CABG = coronary artery bypass grafting; LFHG = low-flow, high-gradient; LVOT = left ventricular outflow tract; NFHG = normal-flow, high-gradient; NFLG = normal-flow, low-gradient; PLFLG= paradoxical low-flow, low-gradient; STS PROM = Society of Thoracic Surgeons; SV = stroke volume.

The agreement in flow-gradient classification and SV measurement

Using SV_{LVOT}, the NFHG group comprised 267 (38%) patients, the NFLG group 156 (22%), the LFHG group 148 (21%), and the PLFLG group 128 (19%). The group composition changed when $SV_{volumetric}$ was used (*Figure S2*); the NFHG group consisted of 111 (17%) patients, the NFLG group of 53 (10%), the LFHG group of 227 (42%), and the PLFLG group of 168 (31%). Both SV methods agreed on low-flow in 31%, and normal-flow in 19%, while they disagreed in the other 50% (*Figure 1*). Furthermore, an increase in LVOT

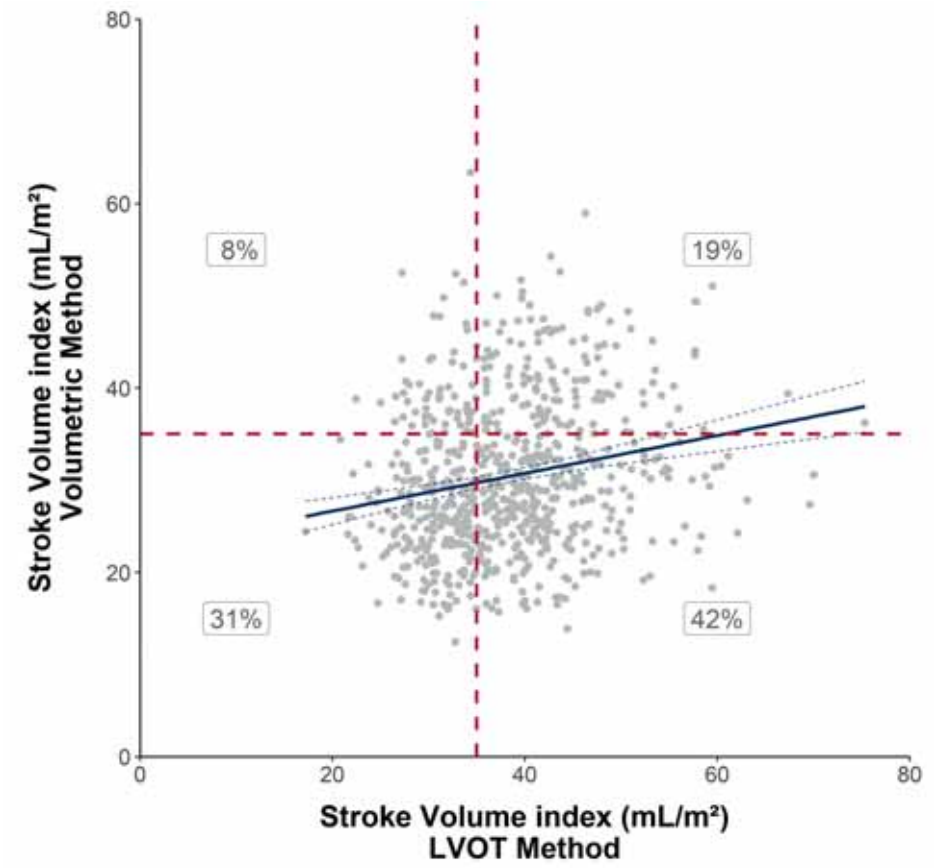
SVi of 1 mL/m^2 resulted on average in an increase in volumetric SVi of 0.22 mL/m^2 (95% confidence interval [CI] 0.14:0.29 mL/m^2). The correlation between the SV methods was 0.33 (95% CI 0.26:0.40). SV_{LVOT} was on average 15.1 mL higher than $SV_{volumetric}$ with 95% limits of agreement ranging from -25.0 to 55.1 mL (*Figure 2*). For the entire cohort, the median follow-up time was 1785 days. The discrepancy in flow-gradient classification also yielded alterations in survival (*Figure 3*). If SV was obtained via the LVOT method, the NFHG patients showed the worst survival; with a Kaplan-Meier survival rate of 87% (95% CI 82-91%) at 5 years of follow-up. However, when using volumetric SV, the LFHG group had the worst survival (Kaplan-Meier survival rate 88%, 95% CI 84-93%), and the survival curves for all patient groups changed.

The results of the above-mentioned analyses based on partly imputed data were similar to the results of the sensitivity analysis in patients with complete data (*Table S2, Figure S3 and S4*).

Clinical implication of measurement error in LVOT SV

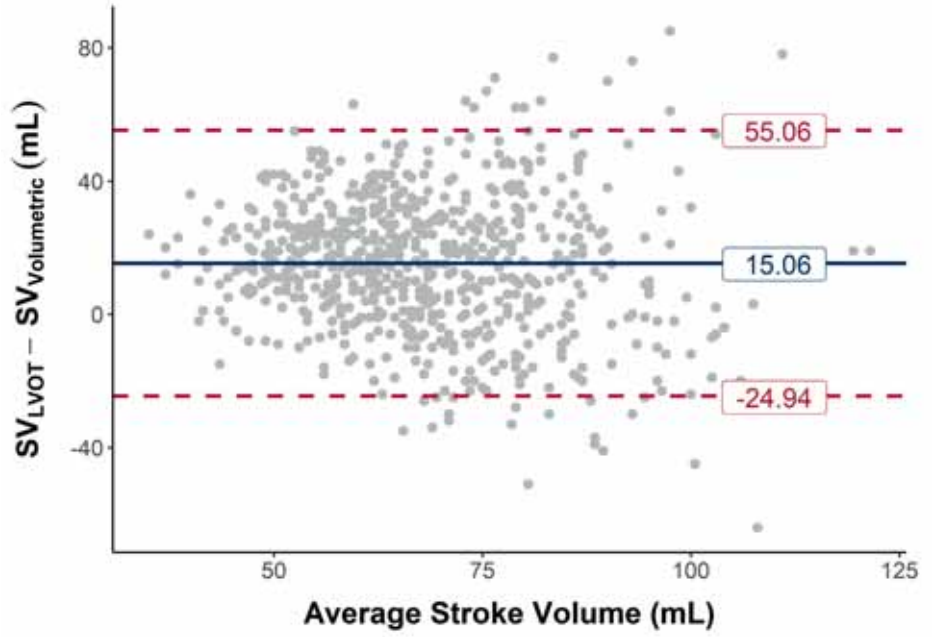
A 1 mm overestimation of the LVOT diameter resulted in an increase in mean SV_{LVOT} index from 38.3 to 42.7 mL/m^2 and in mean AVAi from 0.37 to 0.43 cm^2. Consequently, while 40% were originally in low-flow, only 20% remained in this state after the introduction of the 1mm overestimation (*Figure 4, Figure S5)*. In absolute numbers, the LFHG group drecreased from 148 to 79 patients, and the PLGLG group from 128 to 64, i.e., the low-flow groups almost halved. Furthermore, 43 (6%) patients were reclassified to moderate AS due to an AVAi > 0.6 cm^2/m^2.

Figure 1. Agreement between the LVOT and the volumetric method to determine indexed stroke volume in patients with severe aortic stenosis.



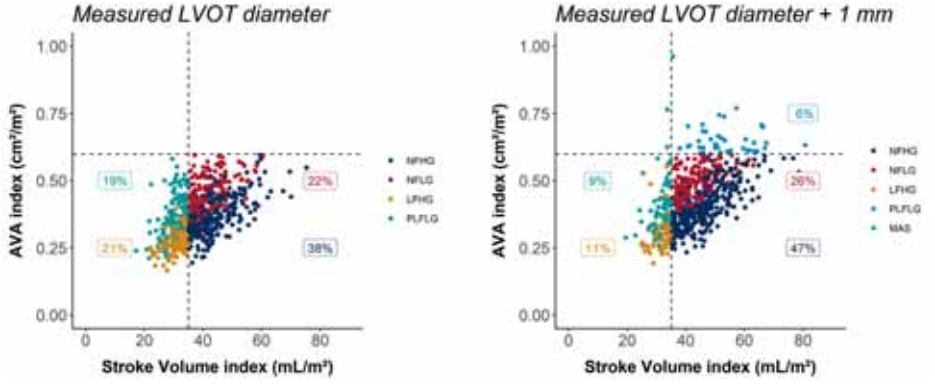
The blue lines displays the relation using linear regression including corresponding 95% confidence intervals. The horizontal and vertical dashed red lines are placed at the threshold for low-flow. LVOT = left ventricular outflow tract.

Figure 2. Bland-Altman plot: agreement between LVOT and the volumetric stroke volume measurements in patients with severe aortic stenosis.



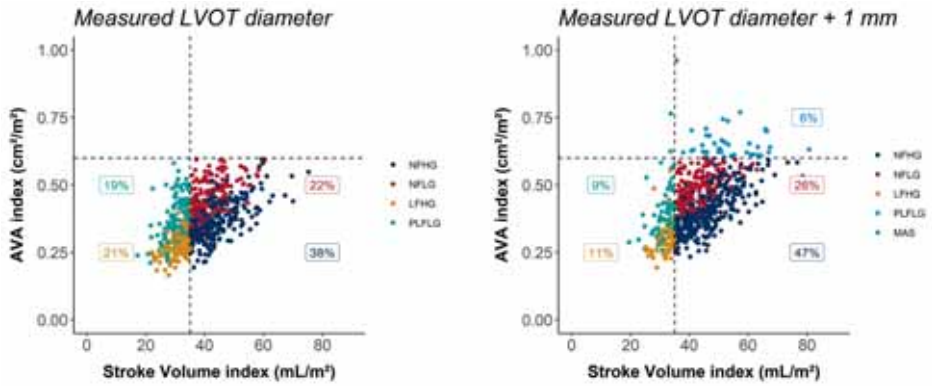
The lines represents the mean difference between the two measurements including the 95% limits of agreement. LVOT = left ventricular outflow tract; SV = stroke volume.

Figure 3. Kaplan-Meier survival analysis according to flow-gradient patterns of patients who underwent aortic valve replacement.



Censoring is indicated by the "+" sign. For the left Kaplan-Meier analysis, the survival rates were 86.5% (95% CI 82.3-91.0%) for NFHG, 91.4% (95% CI 86.7-96.2%) for NFLG, 91.5% (95% CI 86.7-96.6%) for LFHG, and 90.0% (95% CI 84.4-96.0%) for PLFLG. For the right Kaplan-Meier analysis, the survival rates were 90.7% (95% CI 85.4-96.4%) for NFHG, 96.3% (95% CI 89.4-100%) for NFLG, 88.1% (95% CI 83.5-92.9%) for LFHG, and 89.8% (95% 85.2-94.7%) for PLFLG. CI = confidence interval; LFHG = low-flow, high-gradient; LVOT = left ventricular outflow tract; NFHG = normal-flow, high-gradient; NFLG = normal-flow, low-gradient; PLFLG = paradoxical low-flow, low-gradient; SVi = stroke volume index.

Figure 4. Clinical implication of overestimation of LVOT diameter by 1 mm for the flow-gradient classification of severe aortic stenosis.



The vertical line represents the threshold for low-flow and the horizontal line for severe aortic stenosis. AVA = aortic valve area; LFHG = low-flow, high-gradient; LVOT = left ventricular outflow tract; MAS = moderate aortic stenosis; NFHG = normal-flow, high-gradient; NFLG = normal-flow, low-gradient; PLFLG = paradoxical low-flow, low-gradient.

DISCUSSION

In this analysis of 699 severe AS patients with preserved LVEF, there were large differences in flow-gradient classification as a result of poor agreement between LVOT and volumetric SV measurement (*Figure 5*). $SV_{volumetric}$ was systematically lower than SV_{LVOT}. Furthermore, SV_{LVOT} was very sensitive to small measurement error; when a systematic 1mm LVOT diameter overestimation was simulated, the low-flow groups halved.

The flow-gradient classification was proposed to enhance the confirmation of severe AS, specifically for patients with discordant echocardiographic parameters [2]. The patient characteristics that distinguish the flow-gradients patterns are moderately understood and the reported features are quite heterogeneous [17]. Bavishi and colleagues [18] reported high incidences of coronary artery disease in the low-flow groups, and frequent AF and a small indexed LVEDV in PLFLG patients. For the LFHG group, Eleid *et al.* [19] found that the AVA and AVAi was smallest, and that the incidence of diabetes mellitus was relatively high. In our study, we identified similar characteristics.

Previous studies have stated that SV corroboration with other methods is essential for accurate flow-gradient classification [2,5]. In the first study concerning PLF severe AS, the SVs derived from the LVOT and the Simpson's method were comparable [6], which was also found in a more recent study comprising mild to severe AS patients [7]. Conversely, a significantly lower SV by the biplane Simpson's method was observed by Stähli *et al.* [8], by Iwataki *et al.* [9], and by the World Alliance of Societies of Echocardiography [10] in 1450 healthy adult volunteers. In the current study, $SV_{volumetric}$ was expected to approximate the forward SV_{LVOT} since patients with more than mild mitral or tricuspid regurgitation were

excluded. However, a lower SV was observed using the volumetric method. In the absence of substantial backward flow, it is difficult to physiologically explain this discrepancy. Moreover, in a post-hoc analysis we excluded patients who underwent concomitant CABG to rule out the potential influence of LV wall motion abnormalities and the results (which are not reported) remained unchanged. Since both methods require multiple measurements and geometrical assumptions, measurement errors are a likely cause.

Derivation of $SV_{volumetric}$ via the biplane Simpson's method demands capturing the complex LV geometry in two-dimensional images. Errors could arise in tracing the endocardial borders, from the inability to track the entire LV volume for example due to anatomical constraints, geometrical assumptions, and (apical) foreshortening [10, 20]. Small variability in 2D measurements can lead to larger distortions when translated to the volumetric scale. Foreshortening happens when the echo beam does not capture the true apex and results in underestimation of the LV volume. This problem arises from the image acquisition and cannot be solved by image analysis despite the use of an experienced core lab. Hence, foreshortening could contribute to the SV discrepancy in our study.

While the LVOT method is most commonly applied, this measurement is also susceptible to measurement error. The VTI_{LVOT} could be mismeasured due to probe malalignment or due to a spatially non-uniform velocity profile in the LVOT [21], whereas the LVOT area is often underestimated as a result of the assumption of a circular shape [1]. Considering the latter, SV_{LVOT} would increase; hence, the apparent difference would even be larger. The sensitivity to small errors in the LVOT diameter is a drawback of the LVOT method. To exemplify, a 1 mm overestimation of the LVOT diameter resulted in a reduction in the proportion of low-flow patients of about 50% in our simulation. This has important implications not only for scientific research, in which patients could be misclassified to incorrect flow-gradient groups, but also for clinical practice since recommendations for intervention only exist for specific flow-gradient groups [3,4].

From our data, we cannot conclude that $SV_{volumetric}$ is a systematic underestimation of the SV_{LVOT}, or vice versa. Although this was not the aim of this study, the optimal SV method for the flow-gradient classification of severe AS is hard to determine due to the lack of a gold standard for non-invasive SV measurement. However, as studies including imaging modalities such as 3-dimensional echocardiography [10, 22], computed tomography (CT) [8] or cardiovascular magnetic resonance (CMR) [7,23] also indicate different (usually larger) SVs, it seems that neither method is completely interchangeable. To avoid ambiguity, we encourage guideline authors to at least specify the SV measurement method in recommendations for interventions specific flow-gradient patterns. Furthermore, more consideration of the clinical relevance of using echocardiographic SV to categorize AS patients might be needed. Theoretically, it makes sense to assess SV when a low gradient is observed. However, the benefit of correctly identifying low-flow patients who would benefit from AVR needs to be weighed against the harms of misclassification due to measurement variability and error.

Recent research endeavors suggest to shift the focus to the myocardium to optimize diagnostic pathways and the timing of intervention [24]. The main idea is to intervene before structural components of the heart are irreversibly damaged. Modern echocardiographic parameters such as global longitudinal strain and myocardial work indices but also multimodality imaging like fibrosis assessment using CMR could be helpful to achieve this, however, robust evidence on their superiority is needed before these will be part of standard clinical practice. For now, the results of this analysis reinforce the guideline recommendations [3,4] that for the confirmation of true severe AS, an integrated approach is crucial. Especially in cases of conflicting primary parameters, other echocardiographic measurements, such as DVI, functional status, and anatomical parameters like valvular calcification on CT should also point in the direction of severe AS [3,4].

Strengths and limitations

The study population consisted of patients who were at low surgical risk, which could reduce the generalizability of the observed differences in SV to high-risk severe AS patients who are scheduled for transcatheter AVR. Nevertheless, while all patients had a primary indication for valve replacement based on their AVAi, common concomitant procedures like CABG were allowed, which boosts overall representativeness to the entire severe AS population. In addition, the study was executed in an international multicenter setting with prospective data gathering. The current analysis included relatively large patient groups, especially the LFHG and PLFLG group when compared to previous studies [18]. Unfortunately, no information on anatomical AS severity such as valve calcification was present due to the lack of routine CT assessments.

Differences between SV_{LVOT} and $SV_{volumetric}$ have been described before [6-10], however, we directly related these to the flow-gradient classification of AS which is essential to decision-making by the heart team. For this classification, we also demonstrated the sensitivity to small measurement errors. The outline of these implications for clinical practice is the novelty of the current study.

CONCLUSIONS

In this analysis, there were large differences in flow-gradient classification as a result of poor agreement between LVOT and volumetric SV measurement. Furthermore, this classification was sensitive to small measurement errors. These results stress that the heart team should consider multiple hemodynamic, anatomical, and clinical parameters beyond the flow-gradient classification to ensure accurate recommendations for intervention for AS patients with discordant echocardiographic parameters.

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SUPPLEMENTARY FILES

Available at https://doi.org/10.1016/j.xjon.2023.08.022.

4

THE IMPACT OF BODY SURFACE AREA ON THE CLASSIFICATION OF PARADOXICAL LOW-FLOW SEVERE AORTIC STENOSIS

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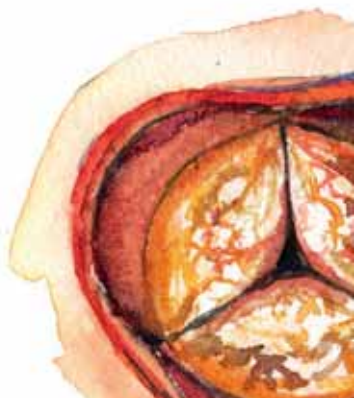
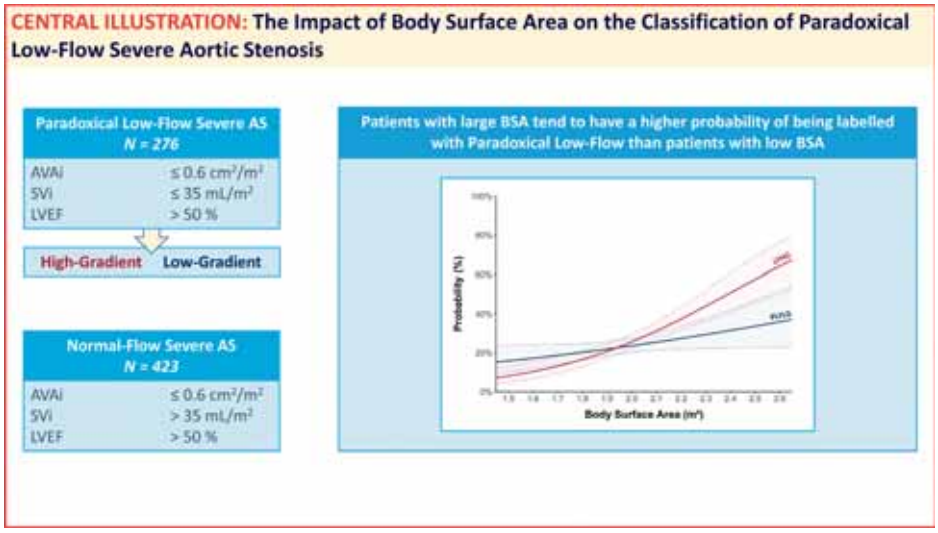
Submitted

Presented at the 2023 annual meeting of the Heart Valve Society, Malaga, Spain



GRAPHICAL ABSTRACT



ABSTRACT

Background: In the classification of paradoxical low-flow (PLF) severe aortic stenosis (AS), body surface area (BSA) is used to normalize both the aortic valve area index (AVAi) and stroke volume index (SVi).

Objective: To investigate whether BSA disproportionally affects the classification of PLF.

Methods: Patients with severe AS (AVAi≤0.6 cm^2/m^2) and preserved ejection fraction who received an aortic valve in a prospective cohort study were identified. Thresholds of ≤35 mL/m^2 for SVi and >40 mmHg for mean pressure gradient (MPG) were used to define PLF and its subgroups of low-flow, high-gradient (LFHG) and PLF, low-gradient (PLFLG). Their relationships with BSA, per 0.1 m^2 increase, were investigated using binary and multinomial logistic regression, for which normal-flow served as reference group.

Results: Of 1118 who received a study valve, 699 patients met the criteria for this analysis, of which 276 (39%) had PLF. Increasing BSA was associated with an increase in the probability of being classified with PLF (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.12:1.31) and with its subcategories of LFHG (OR 1.32, 95% CI 1.20:1.46) and PLFLG (OR 1.10, 95% CI 1.00:1.22). These associations remained after adjustment for age and gender.

Conclusions: The classification of PLF seems dependent on BSA, which could induce misclassification of the flow-gradient and subsequently mistreatment. Especially when the AVAi and MPG are discordant, it is of utmost importance to consider multiple hemodynamic, anatomical, and clinical parameters to decide whether AS is truly severe and the patient will benefit from valve replacement.

INTRODUCTION

Some patients with severe aortic stenosis (AS) based on their aortic valve area (AVA) present with relatively low stroke volume (SV) despite a preserved left ventricular ejection fraction (LVEF). This paradoxical low-flow (PLF) severe AS has been defined as an indexed AVA to body surface area (AVAi) ≤ 0.6 cm^2/m^2, indexed SV (SVi) ≤35 ml/m^2, and LVEF > 50% [1]. By handling an additional threshold for mean pressure gradient of ≤ 40 mm Hg, patients can be further stratified to paradoxical low-flow, low-gradient (PLFLG) and low-flow, high-gradient (LFHG) [2]. The apparent discrepancy in echocardiographic parameters complicates the identification of true severe AS [3].

In the classification of PLF, body surface area (BSA) is used to standardize both AVA and SV, which may disproportionally affect the probability of being labelled with PLF [4]. We therefore studied the impact of BSA on the classification of PLF stenosis.

METHODS

Study data

Data from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve (www.clinicaltrials.gov, NCT02088554) were used. This single-arm observational follow-up study examined the performance of the Avalus bioprosthesis (Medtronic, Minneapolis, Minnesota, USA) [5]. Patients with a clinical indication for valve replacement due to AS or regurgitation (AR) were enrolled. For the current analysis, only the patients with an AVAi ≤ 0.6 cm^2/m^2 and preserved LVEF (> 50%) were included, and patients with AR as primary indication or a mixed indication with more than mild regurgitation were excluded. The study was conducted at 38 centers across North America and Europe, at which local institutional review boards or ethics committees provided study approval (see supplementary files in Klautz *et al.* [6] for approval number and date per center). Furthermore, written informed consent was obtained from all patients. As this analysis investigated the classification of PLF, baseline data (prior to aortic valve replacement) were used exclusively.

Echocardiography

An independent core laboratory (Cardiovascular Core Laboratories, MedStar Health Research, Institute, Washington DC, USA) assessed all echocardiographic parameters. Mean pressure gradient (MPG) and AVA were determined using the simplified Bernoulli equation and the continuity equation, respectively. By dividing the velocity-time integral (VTI) of the left ventricular outflow tract (LVOT) by the VTI of the aortic valve, the Doppler velocity index (DVI) was derived. Stroke volume was determined by multiplying the velocity-time integral across the LVOT (VTI_{LVOT}) by the corresponding cross-sectional area. LVEF was calculated from the left ventricle end-systolic and end-diastolic volume using biplane data, conforming to the modified Simpson's rule. When this continuous parameter

was not available (which was the case in 21%), a categorical variable was used indicating whether LVEF was >50%, 31-50%, 21-30%, or ≤20% based on visual inspection. Indexed parameters were constituted by dividing the specific parameters by BSA (according to the DuBois formula: BSA = 0.007184 * height$^{0.725}$ * weight$^{0.425}$ [7]). PLF was defined according to the criteria of Dumesnil *et al.* [2], consisting of an AVAi ≤ 0.6 cm^2/m^2, SVi ≤ 35 mL/m^2, and LVEF > 50%. PLF patients were further stratified to low-flow high-gradient (LFHG) or PLF low-gradient (PLFLG), based on the mean pressure gradient (MPG) > or ≤ a threshold of 40 mmHg, respectively.

Statistical analysis

Numerical data were presented either by mean ± standard deviation or median [interquartile range] depending on their distribution, and categorical data were presented as counts (percentages). Data were compared using the independent samples t-test, Mann-Whitney U test, or Chi-square test, respectively.

The relations between BSA and PLF, LFHG, and PLFLG were investigated using binary and multinomial logistic regression analysis with and without adjustment for age and sex. The assumptions of linearity between the log odds of PLF, LFHG, and PLFLG and the continuous parameters BSA and age were checked with restricted cubic splines plots. In addition, the likelihood ratio test was used to study whether logistic models, including an additional square root or quadratic term, modelled the relation with the outcome better than a model with the continuous variables BSA or age alone. The assumption of linearity was met for BSA (supplementary files, Figure S1) but not for age. Hence, we chose to add the term age^2 next to age and sex as a covariate in the adjusted analyses.

The impact of BSA on the separate components of the PLF definition, such as AVAi, SVi, MPG, and LVEF, were investigated using linear regression, again, with and without adjustment for age and sex. The assumption of linearity between the separate components and the continuous parameters BSA and age was checked by visual inspection of scatter plots and was met for all variables (Figure S2). The associations between BSA and the separate components of the PLF definition were also expressed by means of Pearson's correlation coefficients. All analyses were performed using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org).

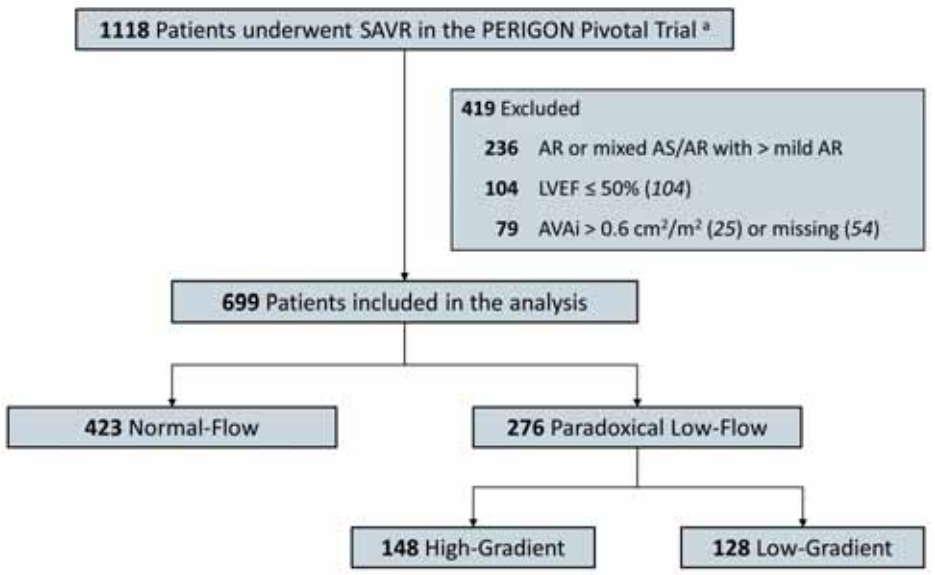
RESULTS

Characteristics of PLF patients

Of the 1118 patients enrolled in the PERIGON Pivotal Trial, 699 met the criteria for the current analysis, of which 423 (61%) had normal flow (NF) and 276 (39%) had PLF (*Figure 1)*. The PLF group comprised the LFHG group (n=148, 21%) and the PLFLG group (n=128, 18%). *Table 1* demonstrates the baseline characteristics of patients with NF and PLF. PLF patients had on average higher BSA and BMI. Furthermore, male sex, diabetes mellitus, and

atrial fibrillation (AF) were more frequent in this group. The AVAi and SVi were lower in the PLF group. In addition, other flow-dependent echocardiographic parameters were lower, too. In *Table S1* in the supplementary files, the baseline characteristics of the PLF patients were further stratified to LFHG and PLFLG. Differences between these subgroups consisted of smaller BSA, higher median Society of Thoracic Surgeons predicted risk of mortality (STS PROM), more frequent coronary artery disease, and smaller LV end-diastolic and end-systolic volume index for the PLFLG patients. Moreover, left ventricular hypertrophy (LVH), larger LV end-diastolic volume index and associated mild mitral regurgitation were more frequent in the LFHG group.

Figure 1. CONSORT diagram for patients with severe aortic stenosis and preserved ejection fraction.



[a] Baseline data were used from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve (Medtronic, Minneapolis, Minnesota, USA). AR; aortic regurgitation, AS; aortic stenosis, AVAi; aortic valve area index, CONSORT; Consolidated Standards Of Reporting Trials, LVEF; left ventricular ejection fraction, SAVR; surgical aortic valve replacement.

Relation between BSA and PLF

The probability to be classified with PLF significantly increased with increasing BSA (odds ratio [OR] of 1.21, 95% confidence interval [CI] 1.12:1.31, per 0.1 m^2 increase, *Table 2*). Furthermore, increasing BSA was associated with an increase in the probability to be classified with LFHG (OR 1.32, 95% CI 1.20:1.46) and PLFLG (OR 1.10, 95% CI 1.00:1.22, *Figure 2*). When these relations were adjusted for the confounding factors age and sex, the ORs were comparable in both magnitude and direction (PLF: 1.23 [1.12:1.35], LFHG: 1.35 [1.21:1.51], PLFLG: 1.09 [0.97:1.23]).

Relation between BSA and the separate components of PLF

For the separate components in the definition of PLF, a negative association was observed between BSA and AVAi and between BSA and SVi (*Table 3*). On the contrary, no association was present with either MPG or LVEF. After adjustment for age and sex, these relations remained similar in magnitude and direction. The correlation coefficients were in line with the results from the linear regression analysis (*Figure 3*): BSA negatively correlated with AVAi (r = -0.19 [-0.26:-0.12]) and SVi (r = -0.23 [-0.30:-0.15]), while BSA did not correlate with MPG and LVEF (r = 0.01 [-0.06:0.09] and r = -0.04 [-0.12:0.04], respectively).

Table 1. Baseline characteristics for patients with normal-flow and paradoxical low-flow severe aortic stenosis and preserved ejection fraction.

	NF n = 423	**PLF n = 276**	**p-value**
Demography			
Age (years)	71.1 ± 8.2	70.3 ± 7.3	0.162
Male	298 (70%)	212 (77%)	0.078
Body surface area (m^2)	1.95 ± 0.20	2.03 ± 0.20	<0.001
Body mass index (kg/m^2)	29.1 ± 4.9	30.4 ± 5.5	0.002
STS PROM (%)	1.60 [1.08:2.44]	1.60 [1.04:2.31]	0.377
Diabetes mellitus	107 (25%)	103 (37%)	<0.001
Hypertension	330 (78%)	211 (76%)	0.696
Chronic obstructive pulmonary disease	43 (10%)	29 (11%)	0.986
Coronary artery disease	182 (43%)	122 (44%)	0.819
Atrial fibrillation	33 (8%)	31 (11%)	0.161
NYHA class III/IV	184 (43%)	119 (43%)	0.982
Stroke	20 (5%)	11 (4%)	0.781
Peripheral vascular disease	29 (7%)	22 (8%)	0.685
Renal Dysfunction/Insufficiency	43 (10%)	32 (12%)	0.637
Echocardiography			
Peak aortic jet velocity (ms^{-1})	4.3 ± 0.6	4.1 ± 0.7	<0.001
Mean transaortic pressure gradient (mmHg)	46.6 ± 15.1	43.6 ± 14.7	0.010
Effective orifice area (cm^2)	0.78 ± 0.20	0.65 ± 0.20	<0.001
Effective orifice area indexed by BSA (cm^2/m^2)	0.40 ± 0.10	0.32 ± 0.10	<0.001
Doppler velocity index	0.25 ± 0.10	0.23 ± 0.10	<0.001
Velocity-time integral aortic valve (cm^2)	106.4 ± 20.1	97.7 ± 20.9	<0.001
Velocity-time integral LVOT (cm^2)	25.7 ± 4.5	21.1 ± 3.6	<0.001
Cardiac output (L/min)	5.4 ± 1.1	4.4 ± 1.0	<0.001
Stroke volume (mL)	84.2 ± 14.4	62.2 ± 8.8	<0.001

Table 1. Continued

	NF n = 423	**PLF n = 276**	**p-value**
Stroke volume indexed by BSA (mL/m^2)	43.3 ± 6.6	30.6 ± 3.3	<0.001
Heart rate (bpm)	66 ± 10	70 ± 12	<0.001
LV end-diastolic volume index (mL/m^2)	51.9 ± 13.4	46.8 ± 12.7	<0.001
LV end-systolic volume index (mL/m^2)	19.9 ± 6.3	18.3 ± 6.2	0.002
Left ventricular ejection fraction (%)	61.9 ± 5.9	61.2 ± 5.9	0.205
Left ventricular hypertrophy	162 (38%)	106 (38%)	>0.99
Mild mitral regurgitation	154 (36%)	84 (30%)	0.122
Mild tricuspid regurgitation	144 (34%)	76 (28%)	0.086

Table 2. The relationship between body surface area and PLF, LFHG, and PLFLG for patients with severe aortic stenosis and preserved ejection fraction.

	Unadjusted odds ratio BSA (95% CI)	**p-value**	**Adjusted [a] odds ratio BSA (95% CI)**	**p-value**
PLF	1.21 (1.12:1.31)	<0.001	1.23 (1.12:1.35)	<0.001
LFHG	1.32 (1.20:1.46)	<0.001	1.35 (1.21:1.51)	<0.001
PLFLG	1.10 (1.00:1.22)	0.048	1.09 (0.97:1.23)	0.131

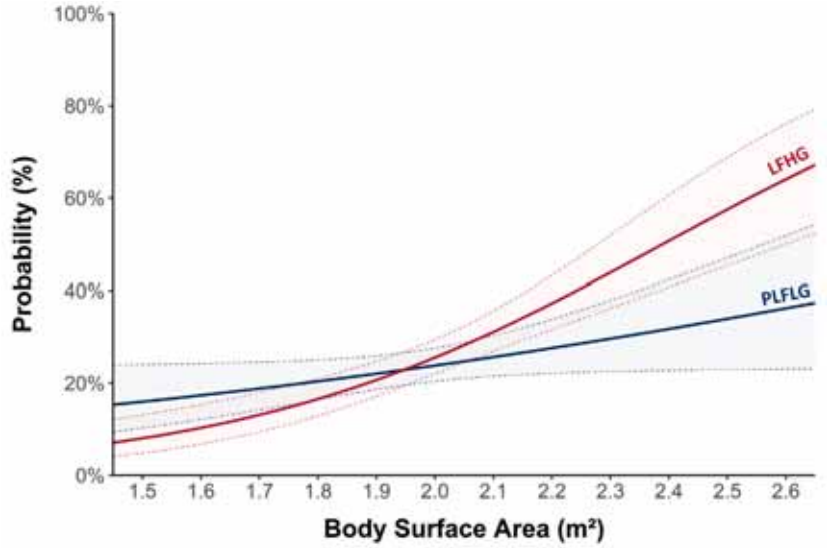
Normal-flow serves as the reference category in all analyses. Note that LFHG and PLFLG are subgroups of PLF. The scales for the odds ratios of BSA are per 0.1-m2 increase. a Adjusted for age, age2, and sex. BSA; body surface area, CI; confidence interval, LFHG; low-flow high-gradient, PLF; paradoxical low-flow, PLFLG; PLF low-gradient.

Table 3. The relationship between body surface area and the separate components in the definition of paradoxical low-flow for patients with severe aortic stenosis and preserved ejection fraction.

	Unadjusted β BSA (95% CI)	**p-value**	**Adjusted [a] β BSA (95% CI)**	**p-value**
Aortic valve area index	-0.008 (-0.011:-0.005)	<0.001	-0.010 (-0.014:-0.007)	<0.001
Stroke volume index	-0.889 (-1.173:-0.604)	<0.001	-0.979 (-1.324:-0.634)	<0.001
Mean pressure gradient	0.093 (-0.435:0.621)	0.731	0.189 (-0.452:0.830)	0.564
Left ventricular ejection fraction	-0.123 (-0.367:0.120)	0.321	0.051 (-0.242:0.344)	0.733

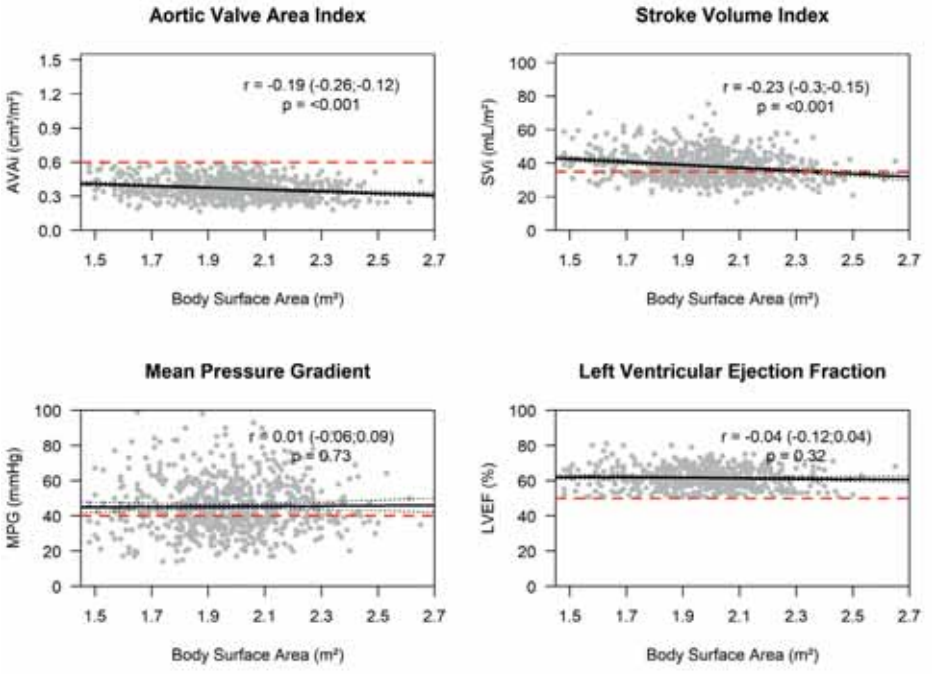
The scales for the regression coefficients of BSA are per 0.1-m2 increase. a Adjusted for age and sex. BSA; body surface area, CI; confidence interval, β; regression coefficient.

Figure 2. The relation between BSA and the probability of being classified with LFHG and PLFLG for patients with severe aortic stenosis and preserved ejection fraction.



The dashed lines represent the 95% confidence interval. Normal-flow serves as the reference category for both LFHG and PLFLG. BSA; body surface area, LFHG; low-flow high-gradient, PLFLG; paradoxical low-flow low-gradient.

Figure 3. The relation between the separate components in the definition of paradoxical low-flow and body surface area for patients with severe aortic stenosis and preserved ejection fraction.



The solid black lines demonstrate the relation between the variables using linear regression. The dashed black lines represent the 95% confidence interval. The dashed red line depicts the thresholds for severe aortic stenosis, low-flow, low-gradient, and preserved ejection fraction, respectively. The Pearson correlation coefficient (r), including 95% confidence interval and p-value, is also reported. AVAi; aortic valve area index, LVEF; left ventricular ejection fraction, MPG; mean pressure gradient, SVi; stroke volume index.

DISCUSSION

In this analysis of 699 patients with severe AS and preserved ejection fraction, higher BSA increased the probability of being classified as PLF, LFHG, and PLFLG. These associations remained after adjusting for age and sex. Of the separate parameters required for defining these groups, specifically the indexed parameters AVAi and SVi were dependent on BSA, while the unindexed parameters MPG and LVEF were not.

Understanding the limitations of indexed valve area and volume calculations requires understanding the absence of scientific validation behind the concept of BSA. Meeh *et al.* first published an equation for BSA after marking shapes on a body, followed with tracing the shapes on paper to calculate an area [8]. A total of only 16 subjects were studied at the time (10 adults, 6 children). This formula was changed and reiterated to a surface area calculation by the DuBois brothers in 1915, after studying 19 body measurements in a limited study of 5 subjects. In a subsequent publication, the database was expanded to an

additional 7 subjects, who were wrapped in molds to determine their BSA, and subsequently a formula was developed to approximate this measure using weight and height [7]. Data were collected from a 'normal adult' subject; a 26 year old female model, deemed to be 'athletic and…muscles were well-developed,' a 21 month old infant with severe rickets measured 2 hours post-mortem, two male bilateral above the knee amputees and other individuals who had succumbed to premature death post-mortem due to disease [8]. Few have challenged the scientific expansion and broad application of incorporation of the BSA formula into modern patient care and its attempted role to serve as a surrogate for cardiac output. BSA has broadly been used for indexation of hemodynamic parameters, far from the original 'scientific' intent of its derivation from 12 study subjects in 1915. In 1993, Slone *et al.* [9] demonstrated that 'modern' BSA equations additionally erroneously assume the skin to be flat, and the impact of skin follicles and skin pores to be of negligible contribution to skin surface area. However, variations in follicle and pore density vary greatly between the adult and pediatric population, further negating the accuracy of BSA calculations.

BSA indexation is performed to achieve that the ratio of a hemodynamic parameter and BSA (i.e., parameter/BSA) is a constant which would allow for uniform use of indexed parameters. Thereby, it is implicitly assumed that hemodynamic parameters have a proportional relation to BSA. Previous studies have additionally demonstrated the fallacy of constant hemodynamic parameter/BSA ratios as this assumption does not hold in normotensive volunteers [10,11] or in patients with severe aortic stenosis who underwent surgical aortic valve replacement [12]. In the latter study, our group demonstrated that the violation of this proportionality assumption could lead to erroneous labelling of prosthesis-patient mismatch (PPM): that is, in patients with small BSA, PPM was underestimated, while in patients with large BSA, PPM was overestimated. A study that compared the incidence of PPM between an Asian and Western population [13] serves as a clear example of the clinical implications as described here [14]. The implications of erroneous BSA indexation will be important to any assessment of hemodynamic valvular performance, so also for the evaluation of TAVR in SAVR and valve-in-valve TAVR.

Similarly, for the flow-gradient classification of severe AS, patients with large BSA tend to be labelled with PLF and its subcategories more often due to the improper indexation of AVA and SV. Attempts at oversimplification of criteria for AS staging by establishing non-reproducible echocardiographic parameters negatively impact the understanding of natural progression of clinical staging of patients with symptomatic AS. Intense focus on calculated stroke volume index many times creates distraction from the apparent clinical diagnosis of negative left ventricular remodeling that has occurred with progression of symptomatic aortic stenosis, and the inability of the left ventricle to mount any substantial forward stroke volume. This complicates decision-making in patients with apparent severe AS, because intervention is not indicated for all flow-gradient patterns in the both the American [15] and European [16] guidelines on the management of valvular heart disease. For example, certain PLFLG patients with very large BSA might potentially have an *unindexed* SV that is normal

for them but an *indexed* SV that falls below the threshold of low-flow due to disproportional BSA indexation. These patients might actually have NF low-gradient AS if BSA indexation had been proportional. Considering this scenario, these patients would not have had an indication for intervention.

Especially for LFHG patients, low (forward) SVi is physiologically hard to explain since both the LVEF is good and the MPG is high. In the PERIGON Pivotal Trial, patients with more than mild mitral- or tricuspid regurgitation were excluded, hence discrepancies from regurgitant flow were negated. Alternative explanations for low (forward) SVi in this group might be related to AF, though only present in 9% *(Table S1*), or the residual mitral regurgitation (MR). However, when adjusted for age, sex, AF, and mild MR in a post-hoc regression analysis (*Table S2*), the relation between BSA and LFHG remained unchanged. The contribution of non-physiological explanations such as disproportional BSA indexation or measurement error now become more reasonable. SVi estimation includes the measurement of the LVOT diameter, a parameter prone to error and large variability [3] that is squared in SV calculation ($LVOT\ VTI * \pi * \left[\frac{LVOT\ diameter}{2}\right]^2$).

Distortions of the flow-gradient classification caused by BSA should be prevented. Multi-disciplinary heart teams must not lose sight of modern day transcontinental scientific guidelines advocating for multi-pronged approach to diagnosis and management of valvular heart disease [15,16]. This multi-disciplinary heart team integrated approach evaluating multiple hemodynamic, anatomical, and clinical parameters are critical to patient centric care. In the setting of discordance between AVA(i) and MPG, complementary information on, for example, DVI, LVH, valvular calcification, and functional status is crucial to determine whether AS is truly severe and the patient would benefit from aortic valve replacement.

Strengths and limitations

The generalizability of our results can be diminished by the selection of participants for the study. Data were used from a prospective cohort study that included only low-risk patients who were deemed candidates for surgical AVR by the local heart teams. Hence, the results should be interpreted as hypothesis-generating and external validation is needed. In the enrollment period, which was 2014 and 2017 for all valve sizes and reopened in 2019 for the 29-mm valves to continue through early 2023, low-gradient severe AS might have been considered less often. Nevertheless, the current analysis was based on prospectively collected data with consistent assessment of echocardiographic parameters by an independent core laboratory. Moreover, the sample size of the study was relatively large, especially for the LF subgroups. The allowance of concomitant procedures like coronary artery bypass grafting and the international multicenter setting boosted the overall generalizability to other patients with severe AS.

CONCLUSIONS

The classification of PLF seems dependent on BSA. Patients with large BSA tend to have a higher probability of being labelled with PLF than patients with small BSA. This BSA dependency could induce misclassification, and subsequently mistreatment, as not all flow-gradient patterns have an indication for intervention in current guidelines [15,16]. Especially when the AVA(i) and MPG are discordant, it is of utmost importance to consider multiple hemodynamic, anatomical, and clinical parameters to decide whether AS is truly severe.

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SUPPLEMENTARY FILES

Table S1. Baseline characteristics for patients with severe aortic stenosis stratified to low flow high-gradient and paradoxical low-flow low-gradient.

	LFHG n = 148	**PLFLG n = 128**	**p-value**
Demography			
Age (years)	70.0 ± 7.0	70.7 ± 7.6	0.431
Male	116 (78%)	96 (75%)	0.557
Body Surface Area (m^2)	2.07 ± 0.21	1.99 ± 0.20	0.002
Body Mass Index (kg/m^2)	30.6 ± 5.4	30.1 ± 5.6	0.402
STS PROM (%)	1.43 [0.98,2.13]	1.77 [1.15,2.45]	0.023
Diabetes Mellitus	61 (41%)	42 (33%)	0.222
Hypertension	116 (78%)	95 (74%)	0.461
Chronic Obstructive Pulmonary Disease	18 (12%)	11 (9%)	0.468
Coronary Artery Disease	57 (39%)	65 (51%)	0.073
Atrial fibrillation	14 (9%)	17 (13%)	0.393
NYHA class III/IV	66 (45%)	53 (41%)	0.582
Stroke	7 (5%)	4 (3%)	0.729
Peripheral Vascular Disease	11 (7%)	11 (9%)	0.867
Renal Dysfunction/Insufficiency	14 (9%)	18 (14%)	0.295
Echocardiography			
Peak aortic jet velocity (ms^{-1})	4.6 ± 0.4	3.6 ± 0.4	<0.001
Mean transaortic pressure gradient (mmHg)	54.7 ± 10.1	30.8 ± 6.5	<0.001
Effective orifice area (cm^2)	0.57 ± 0.11	0.74 ± 0.15	<0.001
Effective orifice area index (cm^2/m^2)	0.28 ± 0.05	0.37 ± 0.08	<0.001
Doppler velocity index	0.20 ± 0.08	0.25 ± 0.08	<0.001
Velocity-time integral aortic valve (cm^2)	111.1 ± 16.3	82.1 ± 13.5	<0.001
Velocity-time integral LVOT (cm^2)	21.7 ± 3.6	20.4 ± 3.4	0.002
Cardiac output (L/min)	4.4 ± 0.9	4.3 ± 1.0	0.272
Stroke volume (mL)	63.2 ± 8.1	61.0 ± 9.4	0.032
Stroke volume index (mL/m^2)	30.6 ± 3.0	30.6 ± 3.5	0.943
Heart rate (bpm)	70 ± 11	70 ± 12	0.713
LV end-diastolic volume index (mL/m^2)	49.4 ± 12.8	43.6 ± 11.7	<0.001
LV end-systolic volume index (mL/m^2)	19.5 ± 6.4	16.2 ± 5.6	0.001
Left ventricular ejection fraction (%)	60.9 ± 5.7	61.6 ± 6.2	0.342
Left ventricular hypertrophy	63 (43%)	43 (34%)	0.190
Mild mitral regurgitation	58 (39%)	26 (20%)	0.001

Table S1. Continued

	LFHG n = 148	PLFLG n = 128	p-value
Mild tricuspid regurgitation	38 (26%)	39 (30%)	0.650

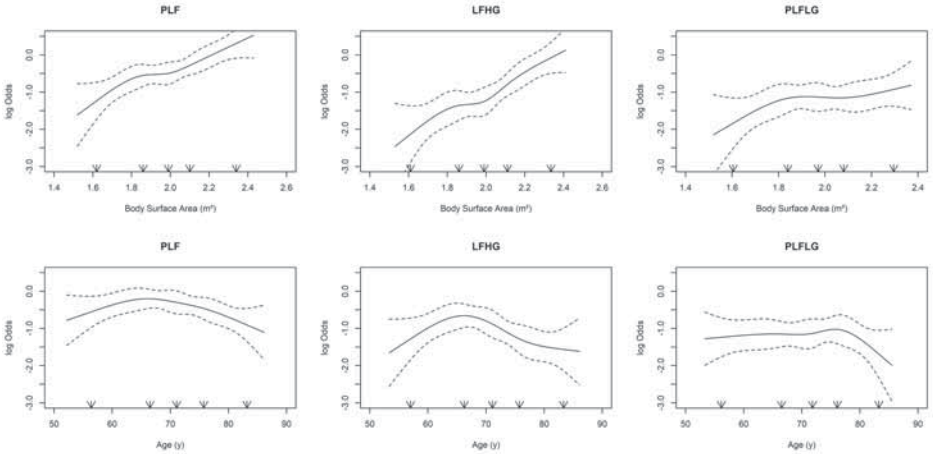
Numerical data are presented as mean ± standard deviation or median [interquartile range] according to their distribution, and categorical data are summarized as counts (percentages). Data were compared using the independent samples t-test, Mann-Whitney U test, or Chi-square test, respectively. BSA; body surface area, LFHG; low-flow high-gradient, LVOT; left ventricular outflow tract, NYHA; New York Heart Association, PLFLG; paradoxical low-flow low-gradient, STS PROM; Society of Thoracic Surgeons predicted rate of mortality.

Table S2. The relationship between body surface area and PLF, LFHG, and PLFLG adjusted for age, sex, atrial fibrillation, and mild mitral regurgitation for patients with severe aortic stenosis and preserved ejection fraction.

	Unadjusted odds ratio BSA (95% CI)	p-value	Adjusted [a] odds ratio BSA (95% CI)	p-value
PLF	1.21 (1.12:1.31)	<0.001	1.22 (1.12:1.34)	<0.001
LFHG	1.32 (1.20:1.46)	<0.001	1.35 (1.21:1.52)	<0.001
PLFLG	1.10 (1.00:1.22)	0.048	1.09 (0.96:1.22)	0.171

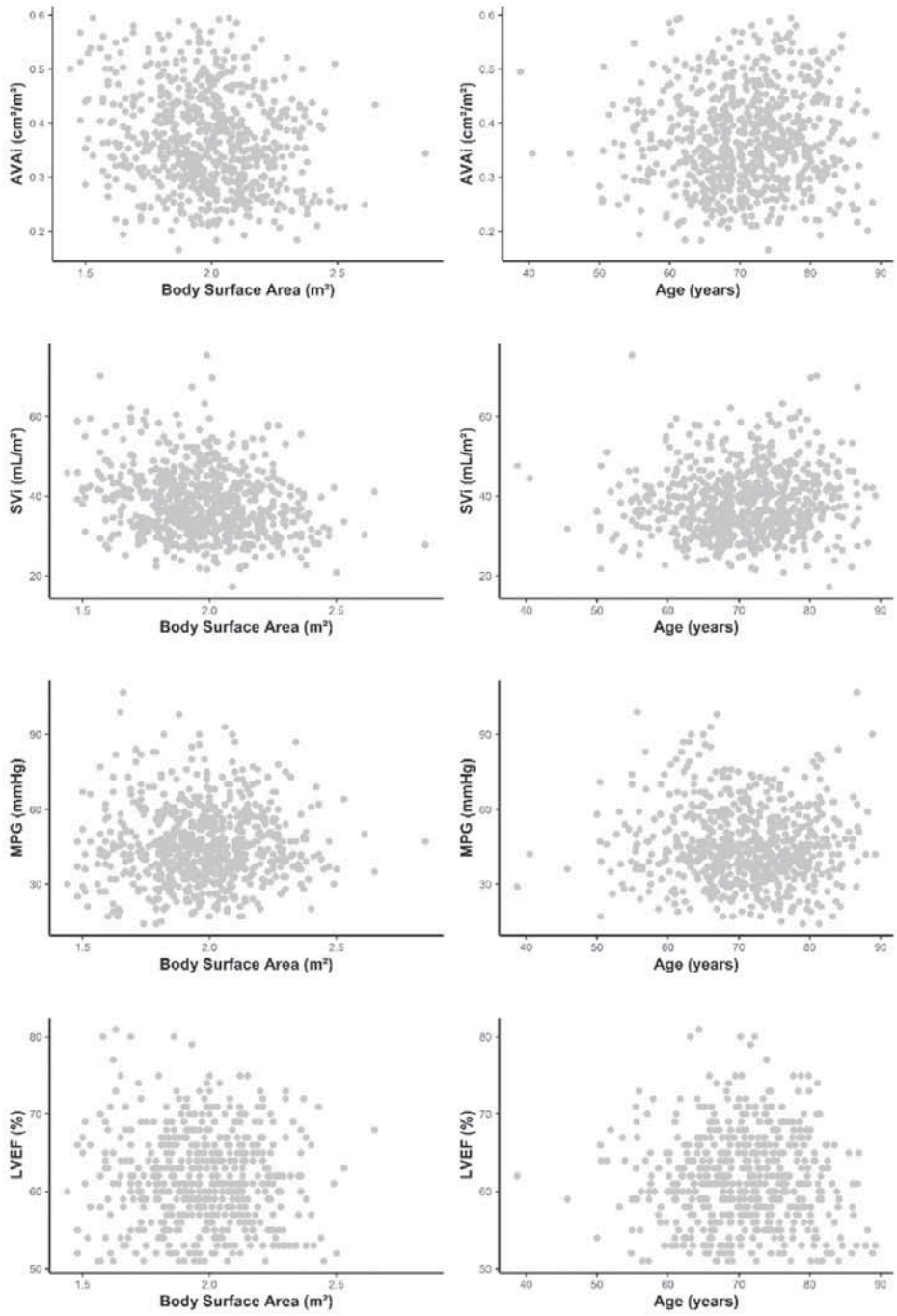
Normal-flow serves as the reference category in all analyses. Note that LFHG and PLFLG are subgroups of PLF. The scales for the odds ratios of BSA are per 0.1 m2 increase. a Adjusted for age, age2, sex, atrial fibrillation, and mild mitral regurgitation. BSA; body surface area, CI; confidence interval, LFHG; low-flow high-gradient, PLF; paradoxical low-flow, PLFLG; PLF low-gradient.

Figure S1. The relation between the log odds of PLF, LFHG, and PLFLG and the continuous variables body surface area and age for patients with severe aortic stenosis and preserved ejection fraction.



The solid black lines are restricted cubic splines representing the different relationships. The dashed black lines display the 95% confidence intervals. The downward-pointing arrows demonstrate data knots. LFHG; low-flow high-gradient, PLF; paradoxical low-flow, PLFLG; PLF low-gradient.

Figure S2. The relation between AVAi, SVi, MPG, and LVEF and the continuous variables body surface area and age for patients with severe aortic stenosis and preserved ejection fraction.



AVAi; aortic valve area index, LVEF; left ventricular ejection fraction, MPG; mean pressure gradient, SVi; stroke volume index.

5

CORE LABORATORY VERSUS CENTER-REPORTED ECHOCARDIOGRAPHIC ASSESSMENT OF THE NATIVE AND BIOPROSTHETIC AORTIC VALVE

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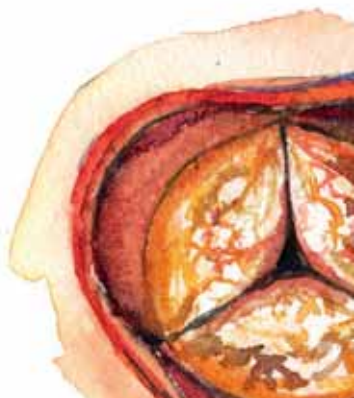
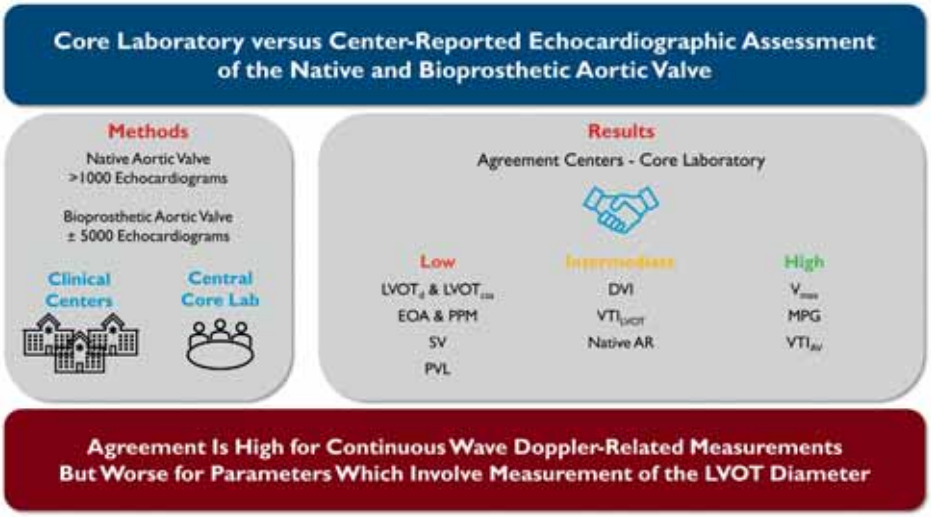
Echocardiography 2024

Presented at the 2024 European Society of Cardiology congress, London, United Kingdom



GRAPHICAL ABSTRACT



ABSTRACT

Background: Insights into quantitative differences between core laboratory and center-reported echocardiographic assessment of the native and bioprosthetic aortic valve are lacking. We aimed to explore clinically relevant differences between these evaluations.

Methods: Data were used from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve. In this trial, patients with an indication for surgical aortic valve replacement (SAVR) due to aortic stenosis or regurgitation (AR) were enrolled. Serial echocardiographic examinations were performed at each center and blindly reanalyzed by an independent echocardiographic core laboratory (ECL). For the bioprosthetic valve analysis, postoperative data throughout 5-year follow-up were pooled. Differences between the ECL and the centers in continuous parameters were quantified in mean differences, and intraclass correlation coefficients (ICCs). Agreement on AR, paravalvular leak (PVL), and prosthesis-patient mismatch (PPM) classification was investigated using Cohen's kappa coefficients.

Results: The analysis on the native aortic valve was performed on 1118 echocardiograms. The relative mean difference was largest for the left ventricular outflow tract (LVOT) area followed by stroke volume and effective orifice area (index) with center-reported values being 11-7% higher. High ICCs of around 0.90 were observed for the parameters peak aortic jet velocity, mean pressure gradient, and the velocity-time integral across the aortic valve. Over 5000 echocardiograms were available for the bioprosthetic valve analysis. Therein, comparable results were observed. The kappa coefficient was 0.59 (95% confidence interval [CI] 0.56, 0.63) for agreement on native AR, 0.28 (95% CI 0.18,0.37) for PVL, and 0.42 (95% CI 0.40, 0.44) for PPM.

Conclusions: There is high agreement between the ECL and clinical centers on continuous-wave Doppler-related measurements. In contrast, agreement is low for parameters that involve measurement of the LVOT diameter. These results provide important context for the interpretation of aortic valve performance in studies that lack central ECL evaluation.

INTRODUCTION

Hemodynamic performance of the native and bioprosthetic aortic valve is primarily evaluated by echocardiography (1-3). Variability in echocardiographic assessment can result not only from physiological fluctuation, for example, in circadian patterns, volumes, or heart rhythm, but also from variation within and between observers (4).

To minimize this type of variation in trials, the use of an echocardiographic core laboratory (ECL) has been advised (5). In clinical centers, uniform evaluation is not guaranteed, and often many observers with various experiences are involved. In contrast, central analysis of echocardiograms at an ECL allows for standardized and blinded assessment by a limited number of certified observers.

Quantitative differences between core laboratory and center-reported echocardiographic assessment have been investigated to a limited degree (6-9). Moreover, studies have focused only on left ventricular function or aortic dimensions and not on valvular heart disease. Quantitative insights could enhance the interpretation of hemodynamic data from studies that lack central echocardiographic assessment. Hence, the objective of this study was to explore differences between core laboratory and center-reported echocardiographic assessment of the native and bioprosthetic aortic valve.

METHODS

Study data

Data were used from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve (www.clinicaltrials.gov, NCT02088554). The PERIGON Pivotal Trial is a single-armed prospective observational follow-up study to examine the safety and performance of the Avalus bioprosthesis (Medtronic, Minneapolis, Minnesota, USA). The design of the trial was previously described in detail (10). In short, patients with a clinical indication for surgical aortic valve replacement (SAVR) due to aortic stenosis (AS) or regurgitation (AR) were enrolled. Local ethics committees or institutional review boards provided study approval, and all patients provided written informed consent (11). Echocardiographic parameters were assessed at each center and blindly reanalyzed by an independent ECL (MedStar Health Research Institute, Washington, DC, USA).

Echocardiography

All patients underwent transthoracic echocardiography prior to SAVR and peri-procedural transesophageal echocardiography. Thereafter, patients were scheduled for serial follow-up at hospital discharge (up to 30 days), 3 to 6 months, 1 year, and annually up to 5 years after SAVR. The ECL prespecified the required procedures, exams, and images required by study protocol, which are outlined below. Per the study protocol, training on image acquisition

was provided to all echocardiographers/sonographers listed on the designated task list at participating centers, at investigator meetings, as well as via training CD.

Measurements were performed at each center and by a specific measurement protocol in the ECL based on American Society of Echocardiography guidelines (1-3), described as follows: Peak aortic jet velocity (V_{max}) and the velocity-time integral across the aortic valve (VTI_{AV}) were measured with continuous-wave Doppler in the window with highest velocities. The mean pressure gradient (MPG) was determined by the simplified Bernoulli formula, and the effective orifice area (EOA), by using the continuity equation under the assumption of a circular cross-sectional area of the left ventricular outflow tract ($LVOT_{csa}$). The LVOT diameter ($LVOT_{d}$) was measured in mid-systole from inner edge to inner edge of the septal endocardium and the anterior mitral leaflet for the native aortic valve and immediately proximal to the inflow aspect of the sewing cuff for the bioprosthetic valve. The VTI across the LVOT (VTI_{LVOT}) was measured with pulsed-wave Doppler. The Doppler velocity index (DVI) was determined by dividing the VTI_{LVOT} by the VTI_{AV} and stroke volume (SV) by multiplying the $LVOT_{csa}$ by the VTI_{LVOT}. The EOA index (EOAi) was derived by indexing EOA to the patient's body surface area. An integrated approach including color flow, pulsed-wave and continuous-wave Doppler was used to assess the severity of native AR and paravalvular leak (PVL) in the parasternal long and short-axis, apical long-axis and 5-chambers view. These parameters were classified as none, trace, mild, moderate, or severe (12, 13).

Statistical analysis

All statistical analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org). Patient characteristics were reported as mean (± standard deviation) or median [interquartile range (IQR)] according to their distribution for numerical values and as counts (percentages) for categorical values. All cross-sectional analyses were performed on information that was complete for both the ECL and the center-reported assessment, i.e., a complete-case analysis was performed.

Native valves

For investigations on the native aortic valve, echocardiographic data at baseline (prior to surgery) were used and for these analyses patients with a failed bioprosthesis as primary indication (n = 6) were excluded. Cross-sectional differences between the ECL and the centers in continuous parameters were quantified in mean differences, relative mean differences, and intraclass correlation coefficients (ICCs, R package *irr*). Agreement on native AR classification was investigated using weighted Cohen's kappa coefficients with weights based on the equal-spaces method (R package *vcd*).

Prosthetic valves

For assessment of the bioprosthetic aortic valve, postoperative data throughout 5-year follow-up were stacked, though the discharge visit was analyzed separately since different image acquisition was expected. Hence, the units of observation for postoperative data were

echocardiograms instead of patients. Cross-sectional differences were determined with the same measures as described above and illustrated in Bland-Altman plots including 95% limits of agreement (14). Agreement in PVL at discharge and postoperative prosthesis-patient mismatch (PPM) according to the VARC-3 criteria (15) was analyzed using weighted Cohen's kappa coefficients. Likewise, the agreement in postoperative MPG ≥ 20 mmHg, used in definitions of hemodynamic structural valve deterioration (15, 16), was calculated using an unweighted Cohen's kappa coefficient. Differences between the 10 centers that implanted the most prostheses and the ECL were illustrated by plotting standardized mean differences. This restriction in centers was applied because data of low-enrolling centers were deemed less reliable and generalizable due to sampling variability.

In addition, longitudinal differences between the ECL and the centers were studied. The progression of echocardiographic values throughout 5-year follow-up was modelled for each individual patient using linear regression (see Figure S1 in the supplementary file for graphical illustration). This procedure was done twice, using data of the ECL and of the centers. For example, the models for MPG for each individual looked like $MPG_{center} = intercept + \beta \times time$ and $MPG_{ECL} = intercept + \beta \times time$ in which the intercept is the predicted ECL or center value at discharge for that individual. Time was fitted as a continuous variable in months. For this longitudinal analysis, we selected patients who had complete data at 3 follow-up visits or more and who had an equal number of measurements for the ECL and center-reported assessments. The mean residual, which depicts the average difference between the measured values and the predicted values based on linear regression (the distance marked with red lines in Figure S1), was determined for both the ECL and the center measurements.

RESULTS

All 1118 patients who received an implant in the PERIGON Pivotal Trial at the time of data analysis were included in the current analysis. The baseline characteristics of the study cohort are presented in Table S1. Patients were on average 70 years old, 75% were male, and 87% had preserved LV ejection fraction at baseline. Missing data in ECL and center measurement of the parameters studied in this analysis are reported in Table S2. The amount of missing ECL and center data was comparable for most parameters. The largest discrepancies in available data were observed in EOA, EOAi, and SV.

Native valves

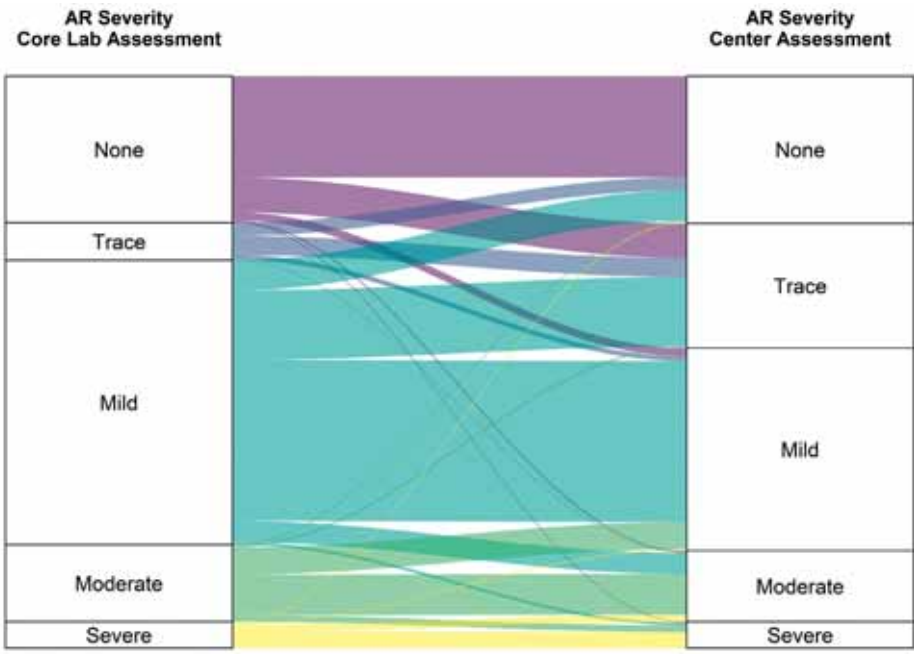
Agreement between center-reported and ECL assessment of the native aortic valve is presented in Table 1. The relative mean difference was largest for $LVOT_{csa}$ followed by SV, EOA, and EOAi with center-reported values being 11-7% higher on average. High ICCs of around 0.90 were observed for the parameters V_{max}, MPG, and VTI_{AV}. An overview of native AR classification by assessor is provided in Figure 1. The corresponding Cohen's kappa coefficient was 0.59 (95% confidence interval [CI] 0.56, 0.63), and AR classification was concordant in 59%.

Table 1. Agreement between core laboratory and center-reported assessment of hemodynamic parameters of the native aortic valve.

Parameter	N_{cc}	Centers *Mean ± SD*	ECL *Mean ± SD*	Mean Difference * ± SD	Relative Mean Difference * ± SD	ICC (95% CI)
V_{max}	1055	4.1 ± 0.9	4.1 ± 0.9	0.1 ± 0.4	1% ± 12%	0.89 (0.88,0.91)
MPG	1070	44.1 ± 17.6	42.2 ± 17.0	1.8 ± 6.9	4% ± 16%	0.91 (0.90,0.93)
EOA	942	1.00 ± 0.86	0.90 ± 0.50	0.10 ± 0.41	7% ± 26%	0.74 (0.70,0.78)
EOAi	942	0.51 ± 0.44	0.45 ± 0.25	0.05 ± 0.20	7% ± 26%	0.75 (0.71,0.79)
DVI	985	0.26 ± 0.14	0.27 ± 0.12	-0.01 ± 0.07	-5% ± 19%	0.83 (0.81,0.85)
$LVOT_d$	1024	2.18 ± 0.29	2.06 ± 0.20	0.13 ± 0.25	6% ± 11%	0.44 (0.27,0.56)
$LVOT_{csa}$	1024	3.80 ± 1.23	3.36 ± 0.68	0.46 ± 1.09	11% ± 21%	0.37 (0.25,0.46)
VTI_{LVOT}	1006	24 ± 9	24 ± 5	-0 ± 8	-4% ± 19%	0.42 (0.37,0.47)
VTI_{AV}	1026	99 ± 26	97 ± 26	1 ± 11	1% ± 13%	0.90 (0.89,0.91)
SV	958	88 ± 43	79 ± 21	9 ± 37	8% ± 25%	0.32 (0.25,0.38)

** The (relative) mean difference was calculated by subtracting the ECL values from the center values. CI, confidence interval; DVI, Doppler velocity index; ECL, echocardiographic core laboratory; EOA, effective orifice area; EOAi, EOA index; ICC, intraclass correlation coefficient; LVOTcsa, left ventricular outflow tract cross-sectional area; LVOTd, LVOT diameter; MPG, mean pressure gradient; Ncc, number of complete cases; SD, standard deviation; SV, stroke volume; Vmax, peak aortic jet velocity; VTIAV, velocity-time integral across the aortic valve; VTILVOT, VTI across the LVOT.*

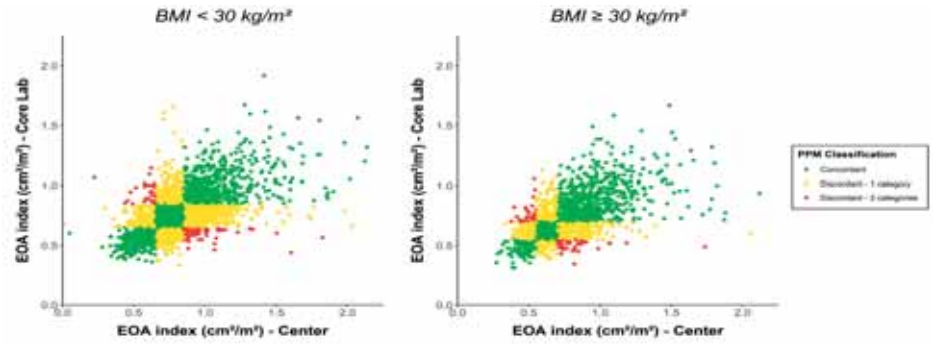
Figure 1. Agreement between core laboratory and center-reported assessment of native aortic regurgitation (AR).



Prosthetic valves

The agreement for investigations of the bioprosthetic aortic valve is reported in Table 2. Again, relative mean differences were largest for $LVOT_{csa}$ and SV, and ICCs were highest for V_{max}, MPG, and VTI_{AV}. At discharge, relative mean differences were comparable to the differences at other follow-up visits, but in general the ICCs were numerically lower (Table S3). An overview of paravalvular leak (PVL) at discharge by assessor is provided in Figure S2. The Cohen's kappa coefficient for agreement on PVL was 0.28 (95% CI 0.18, 0.37). Figure 2 illustrates the postoperative EOAi values and corresponding PPM classification as determined by the centers and the ECL. PPM classification was concordant in 57%. The corresponding Cohen's kappa coefficient was 0.42 (95% CI 0.40, 0.44), while this coefficient was 0.65 (95% CI 0.60, 0.70) for MPG ≥20 mmHg. Figure 3 illustrates differences in assessment on center level. The standardized mean differences for V_{max} were between 0 and 0.5 for all centers, while there was more heterogeneity between centers for other hemodynamic parameters. For example, the standardized mean differences in DVI ranged between -0.8 and 0.3, and those in $LVOT_d$, between -0.2 and 1.3. Differences on the individual patient level are demonstrated in Bland-Altman panels in Figure 4. The difference in V_{max}, MPG, and DVI were close to 0, while there was an average difference in EOA of 0.10 cm^2 (95% limits of agreement -0.68, 0.88). Table 3 presents the differences in longitudinal variability expressed as mean residual. The mean residual in EOA was smaller for the ECL as compared to the centers, while the residuals for V_{max}, MPG, and DVI were more comparable.

Figure 2. Agreement between core laboratory and center-reported effective orifice area index of bioprosthetic aortic valves.



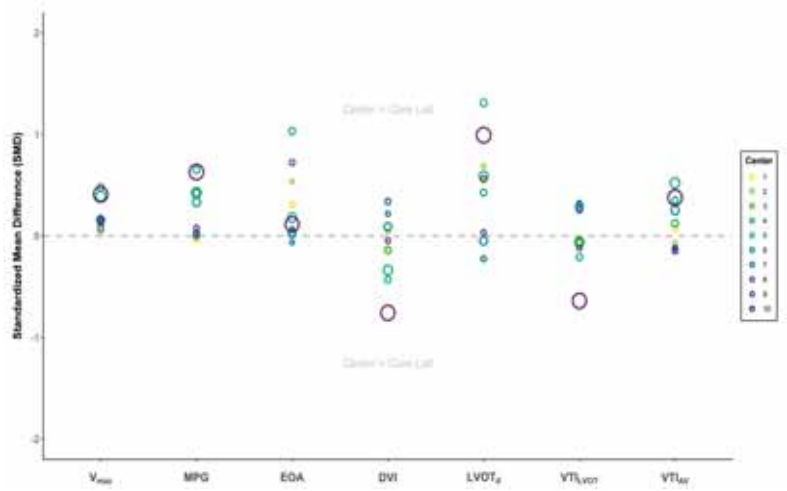
PPM was defined according to the Valve Academic Research Consortium 3 definition (14). Please note that all echocardiographic assessments during follow-up were stacked for this analysis except for the discharge echocardiograms. BMI, body mass index; EOA, effective orifice area; PPM, prosthesis-patient mismatch.

Table 2. Agreement between core laboratory and center-reported assessment of the hemodynamic parameters of the bioprosthetic aortic valve.

Parameter	N_{cc}	Mean Centers (SD)	Mean ECL (SD)	Mean Difference * (SD)	Relative Mean Difference * (SD)	ICC (95% CI)
V_{max}	4995	2.4 ± 0.5	2.4 ± 0.4	0.1 ± 0.2	2% ± 10%	0.84 (0.82,0.87)
MPG	5031	13.4 ± 5.0	12.6 ± 4.7	0.8 ± 2.5	6% ± 19%	0.86 (0.82,0.89)
EOA	4536	1.61 ± 0.51	1.50 ± 0.38	0.10 ± 0.40	5% ± 23%	0.56 (0.51,0.61)
EOAi	4536	0.81 ± 0.25	0.76 ± 0.19	0.05 ± 0.20	5% ± 23%	0.55 (0.50,0.60)
DVI	4728	0.44 ± 0.11	0.45 ± 0.10	-0.01 ± 0.08	-3% ± 17%	0.69 (0.67,0.71)
$LVOT_d$	4873	2.15 ± 0.23	2.06 ± 0.16	0.09 ± 0.20	4% ± 10%	0.44 (0.30,0.55)
$LVOT_{csa}$	4873	3.68 ± 0.82	3.35 ± 0.52	0.33 ± 0.71	8% ± 19%	0.42 (0.28,0.53)
VTI_{LVOT}	4806	22 ± 6	22 ± 5	0 ± 3	0% ± 15%	0.76 (0.75,0.78)
VTI_{AV}	4982	52 ± 11	51 ± 11	1 ± 6	3% ± 13%	0.84 (0.82,0.86)
SV	4595	81 ± 23	74 ± 17	7 ± 18	8% ± 22%	0.54 (0.44,0.63)

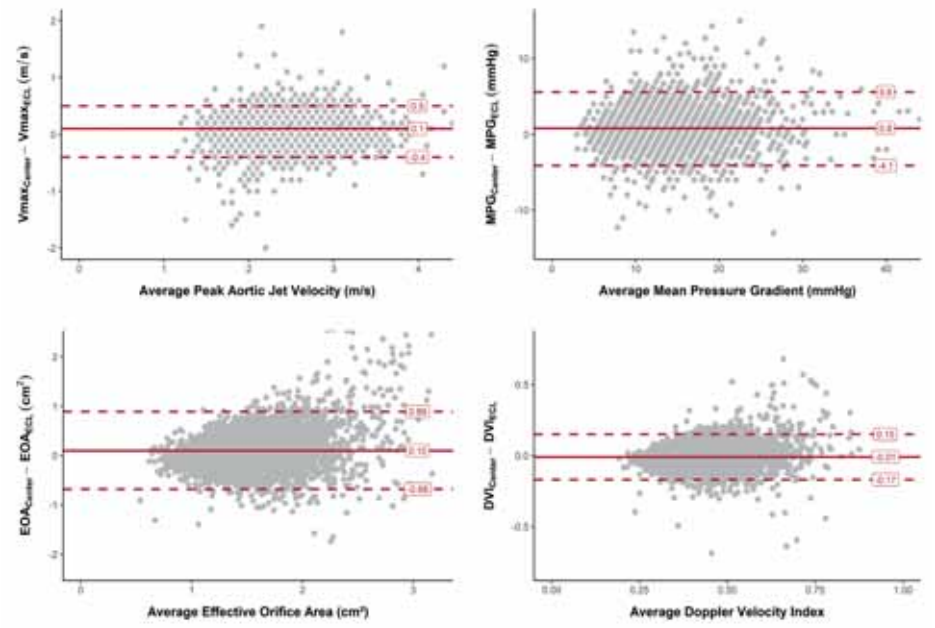
** The (relative) mean difference was calculated by subtracting the ECL values from the center values. Please note that all echocardiographic assessments during follow-up are stacked for this analysis except for the discharge echocardiograms. CI, confidence interval; DVI, Doppler velocity index; ECL, echocardiographic core laboratory; EOA, effective orifice area; EOAi, EOA index; ICC, intraclass correlation coefficient; LVOTcsa, left ventricular outflow tract cross-sectional area; LVOTd, LVOT diameter; MPG, mean pressure gradient; Ncc, number of complete cases; SD, standard deviation; SV, stroke volume; Vmax, peak aortic jet velocity; VTIAV, velocity-time integral across the aortic valve; VTILVOT, VTI across the LVOT.*

Figure 3. Standardized mean differences between core laboratory and 10 largest clinical centers for hemodynamic parameters for bioprosthetic valve performance.



The size of the pictograms corresponds to the number of patients implanted at the particular center. Please note that all echocardiographic assessments during follow-up were stacked for this analysis except for the discharge echocardiograms. DVI, Doppler velocity index; EOA, effective orifice area; LVOTd, left ventricular outflow tract diameter; MPG, mean pressure gradient; Vmax, peak aortic jet velocity; VTIAV, velocity-time integral across the aortic valve; VTILVOT, VTI across the LVOT.

Figure 4. Agreement between core laboratory and center-reported assessment of hemodynamic obstruction for individual patients.



The solid lines represent the mean difference between the value of the center and the ECL, and the dashed lines represent the 95% limits of agreement. Please note that all echocardiographic assessments during follow-up were stacked for this analysis except for the discharge echocardiograms. DVI, Doppler velocity index; ECL, echocardiographic core laboratory; EOA, effective orifice area; MPG, mean pressure gradient; Vmax, peak aortic jet velocity.

Table 3. Longitudinal differences in core laboratory and center-reported echocardiographic assessment of the bioprosthetic valve.

Parameter	N*	Mean Residual ECL (SD)	Mean Residual Centers (SD)
Peak aortic jet velocity (m/s)	893	0.2 ± 0.1	0.2 ± 0.4
Mean pressure gradient (mmHg)	912	1.8 ± 1.1	2.0 ± 1.8
Effective orifice area (cm^2)	585	0.16 ± 0.09	0.24 ± 0.22
Doppler velocity index	699	0.04 ± 0.03	± 0.04

** The number of patients available for longitudinal analysis. The residuals are determined under the assumption of a linear progression of echocardiographic parameters throughout follow-up (see supplementary Figure S1). ECL, echocardiographic core laboratory; SD, standard deviation.*

DISCUSSION

In over 1000 echocardiographic assessments of the native aortic valve and around 5000 evaluations of the bioprosthetic aortic valve, quantitative differences between the ECL and clinical centers were explored. To summarize our findings, agreement was high on the continuous-wave Doppler-related measurements, such as V_{max}, MPG, and the VTI_{AV}, and low on parameters that involved measurement of the $LVOT_d$.

Differences between the ECL and the clinical centers in parameters involving the $LVOT_d$ might be related to the measurement location or to the measurement technique. Measurements obtained closer to the aortic valve will yield larger LVOT diameters and areas (17). For the bioprosthetic valve, the measurement location of the $LVOT_d$ is more clearly defined than for the native aortic valve, which could explain smaller mean differences for the bioprosthetic situation. The measurement technique is also crucial. For the $LVOT_d$, inner edge to inner edge measurement in mid-systole is advised (1). The analysis on center-level differences (Figure 3) showed that there is large heterogeneity between centers in measuring the $LVOT_d$ despite standardization of image acquisition through a study-specific protocol. Small errors have a big impact on any parameter involving the $LVOT_{csa}$ since the LVOT radius is squared and multiplied by π to obtain $LVOT_{csa}$. Clinically important concepts that rely on the $LVOT_d$ include the flow-gradient classification of native severe AS, through SV, and PPM, through EOAi (15, 18, 19). The ICCs for SV was only 0.32, and the Cohen's kappa coefficient for PPM classification was 0.42 with concordant classification by the ECL and the centers in 57%. Such disagreements indicate that parameters beyond the flow-gradient and PPM classification should also be considered to reliably assess severe native AS and hemodynamic obstruction after SAVR.

In the current analysis, the ICCs of V_{max} and MPG were superior to other measures of hemodynamic obstruction for both the native and the bioprosthetic aortic valve. A potential explanation for this could be that V_{max} and MPG are relatively easy to determine as compared to other parameters, which is supported by relatively low intra- and interobserver variability in previous literature (4). This could imply that these parameters may be most trustworthy in studies that lack ECL assessment. However, V_{max} and MPG are highly flow dependent, which makes their use inappropriate in case of reduced LVEF or low-flow states (1). In such instances, EOA(i) or DVI are better alternatives (1, 3). Of these, the DVI values of the clinical centers were found to be more comparable to the ECL and showed higher ICCs in our analysis. It is important to realize, though, that the analyses on the center and individual patient levels showed considerable heterogeneity. Figure 3 reveals between-center differences in various parameters. Moreover, the limits of agreement for EOA in Figure 4 depict substantial variation on patient-level differences, namely ranging between -0.68 and 0.89 cm^2.

Next to our findings on parameters for hemodynamic obstruction, there are also interesting results on the assessment of AR. Agreement on native AR was substantially higher than on PVL (Cohen's kappa coefficient 0.59 vs. 0.28). A previous study on intra-core laboratory variability also showed substantial disagreement in PVL grading (20) and advised a multiparametric approach and further research to improve uniform echocardiographic PVL classification.

In addition, insights into longitudinal differences were provided. The mean residual for ECL assessments was smaller for EOA, while for the other parameters the residuals were more comparable. It is hard to make clinical inferences on precision of longitudinal echo assessments because within-patient variability could be either a result of measurement variation or of physiological factors such as flow. The mean residual that was calculated in this study could not distinguish these causes. If one assumes a true linear progression of hemodynamic parameters over time and negligible impact of physiological fluctuations, a smaller residual indicates more precise measurements.

Details on missing data are also informative. The ECL does not provide values if echocardiographic exams do not meet a minimum quality threshold to measure parameters adequately. For example, EOA and EOAi data at discharge were missing in 55 more cases for the ECL than for the centers. For other parameters, differences in the amount of missing data were generally smaller and could give an impression of the adequacy of the echocardiographic recordings to make each measurement.

Previous studies that compared core laboratory with center-reported assessments have focused on other areas than the aortic valve. The LV function and dimensions as determined by a core laboratory were found to have higher prognostic value for predicting clinical endpoints than the measurements of local centers (6, 7). Other studies showed moderate agreement on ischemia classification of the LV after stress echocardiography (8) and high agreement on echocardiographic measurement of ascending aorta dimensions (9).

Some misconceptions about core laboratories exist. The use of an ECL does not guarantee that echocardiographic values are closer to the true values but does guarantee that echocardiographic examinations and measurements are performed in a standardized and consistent way (21, 22), providing a more homogeneous database. ECLs undergo comprehensive quality control, including reproducibility assessments such as intra- and interobserver variability (5). Because the prognostic value of any parameter depends on measurement variability (23), central analysis in an ECL may potentially enhance the statistical efficiency of a study, which may lower the required sample size or follow-up length (21). ECLs could also provide value to studies beyond just the measurements. They contribute to protocol design, specification of operating procedures, training of study site personnel, and (blinded) interpretation of hemodynamic results (21, 22). The downsides comprise the related costs and complexity of implementation, though the latter is mitigated by improvements in online infrastructure. The added value of an ECL is proportional to the variability and

reproducibility of the measurement under study and to the amount of different assessors or centers involved in clinical trials (21, 22). A central core lab reading decreases heterogeneity. The current analysis provides comprehensive quantitative insights into differences between the ECL and clinical centers, which could enhance the interpretation of aortic valve performance in studies that lack central assessment.

Limitations

All centers participating in the PERIGON trial received training by the ECL and were instructed to follow a prespecified imaging protocol. Measurements in routine clinical practice are likely less standardized and prone to higher variation in studies without ECL involvement or outside the prospective trial setting. By restricting the analysis to complete cases, we primarily excluded information from the clinical centers. ECL data were more often missing because the ECL only returns values if measurements of sufficient quality can be provided. This limits generalizability to all center-reported measurements. Nonetheless, this was the first study to report on differences in measurements of aortic valve performance, and it provided detailed cross-sectional analyses on the group, center, and individual patient level as well as longitudinal analyses. All patients received the same stented bioprosthesis, which eliminated any influence of prosthesis type or model on the observed differences. However, this reduces generalizability to other bioprosthetic valves, especially transcatheter, sutureless, and stentless valves. Moreover, we stacked data from many follow-up visits for the bioprosthetic valve analysis. Data from the same patient were likely correlated, but we did not correct the estimation of the standard errors. Hence, these standard errors could be slightly underestimated. Lastly, we compared all center measurements to those of a single ECL. Other ECLs could have different protocols, which might yield distinct numerical differences or differences in other parameters. Therefore, our results should be interpreted as exploratory and further studies on this topic would be of interest.

CONCLUSIONS

For echocardiographic assessment of the native and bioprosthetic aortic valve, agreement between the ECL and the clinical centers varies per parameter and per center. There is high agreement on continuous-wave Doppler-related measurements. Conversely, agreement is low for parameters that involve measurement of the LVOT diameter. These results provide important context for the interpretation of aortic valve performance in studies that lack central ECL evaluation.

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SUPPLEMENTARY FILES

Available at https://doi.org/10.1111/echo.70047.

PART II

PERIOPERATIVE MANAGEMENT

6

MINIMALLY INVASIVE AORTIC VALVE REPLACEMENT IN CONTEMPORARY PRACTICE: CLINICAL AND HEMODYNAMIC PERFORMANCE FROM A PROSPECTIVE MULTICENTER TRIAL

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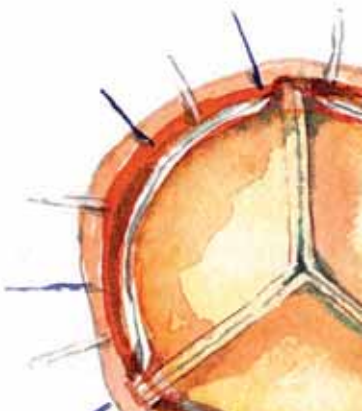
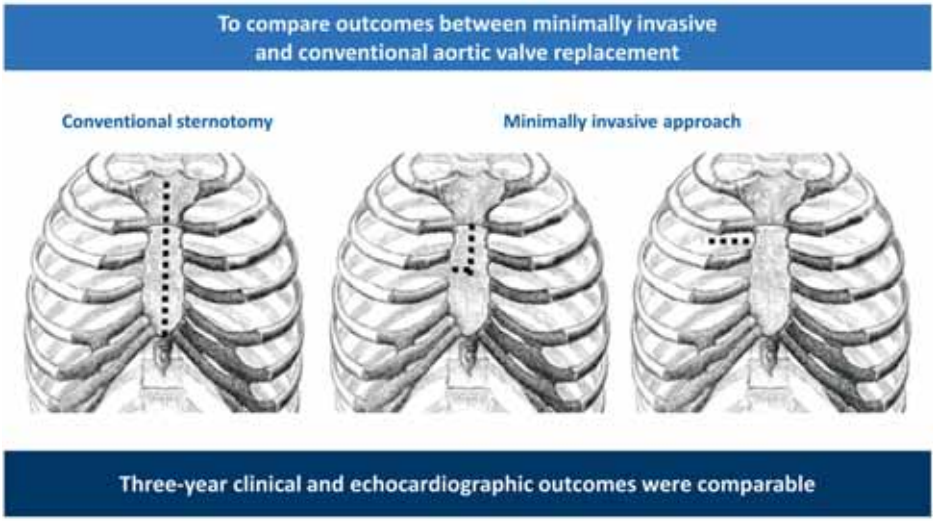
The Thoracic and Cardiovascular Surgeon 2022



GRAPHICAL ABSTRACT



Illustrations of surgical approaches reproduced and adapted from Elattar MA, van Kesteren F, Wiegerinck EM, et al. Automated CTA based measurements for planning support of minimally invasive aortic valve replacement surgery. Med Eng Phys. 2017 Jan;39:123-128. doi: 10.1016/j.medengphy.2016.11.002, with permission.

ABSTRACT

Background: The advent of transcatheter aortic valve replacement has led to an increased emphasis on reducing the invasiveness of surgical procedures. The aim of this study was to evaluate clinical outcomes and hemodynamic performance achieved with minimally invasive aortic valve replacement (MI-AVR) as compared with conventional AVR.

Methods: Patients who underwent surgical AVR with the Avalus bioprosthesis, as part of a prospective multicenter non-randomized trial, were included in this analysis. Surgical approach was left to the discretion of the surgeons. Patient characteristics and clinical outcomes were compared between MI-AVR and conventional AVR groups in the entire cohort (n=1077) and in an isolated AVR subcohort (n=528). Propensity score adjustment was performed to estimate the effect of MI-AVR on adverse events.

Results: Patients treated with MI-AVR were younger, had lower STS scores, and underwent concomitant procedures less often. Valve size implanted was comparable between the groups. MI-AVR was associated with longer procedural times in the isolated AVR subcohort. Post-procedural hemodynamic performance was comparable. There were no significant differences between MI-AVR and conventional AVR in early and 3-year all-cause mortality, thromboembolism, reintervention, or a composite of those endpoints within either the entire cohort or the isolated AVR subcohort. After propensity score adjustment, there remained no association between MI-AVR and the composite endpoint (HR: 0.86, 95% CI 0.47-1.55, p=0.61).

Conclusions: Three-year outcomes after MI-AVR with the Avalus bioprosthetic valve were comparable to conventional AVR. These results provide important insights into the overall ability to reduce the invasiveness of AVR without compromising outcomes.

INTRODUCTION

Surgical aortic valve replacement (AVR) remains the gold standard in young, low-risk patients, while the long-term durability of transcatheter aortic valve replacement (TAVR) has yet to be established in this population (1). However, the advent of TAVR has led to an increased emphasis on reducing the invasiveness of surgical procedures.

While minimally invasive aortic valve replacement (MI-AVR) has been around for more than two decades (2,3), only a minority of isolated AVR patients are treated in this manner (4). The perceived limitation of MI-AVR is that it is technically more challenging and hence may lead to inferior outcomes compared to a full sternotomy, which provides more space to operate and resolve procedural complications. Moreover, it is important to provide insights into the feasibility, safety, and performance of new bioprostheses in the setting of MI-AVR, as the design of the prosthesis may impact the ease of implantation. To compare the risks and benefits of MI-AVR versus conventional AVR in contemporary practice with the Avalus bioprosthesis, we stratified the safety and hemodynamic performance results from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial accordingly.

PATIENTS AND METHODS

Study design

The PERIGON Pivotal Trial (www.clinicaltrials.gov, NCT02088554) is a prospective, single-arm study of the Avalus bioprosthesis (Medtronic, Minneapolis, Minnesota, USA), a stented bovine pericardial aortic valve. The trial is being conducted at 38 sites in Europe, Canada, and the United States. The study design was previously described in detail (5,6). Patients with moderate or severe symptomatic aortic stenosis or chronic severe regurgitation and a clinical indication for surgical AVR, with or without a concomitant procedure, were enrolled. The concomitant procedures were limited to coronary artery bypass grafting, left atrial appendage ligation, patent foramen ovale closure, ascending aortic aneurysm or dissection repair not requiring circulatory arrest, and subaortic membrane resection not requiring myectomy.

The study was designed and conducted in accordance with the Declaration of Helsinki and good clinical practice. Institutional review board or ethics committee approval was obtained at each site, and all patients provided written informed consent. An independent clinical events committee adjudicated all deaths and valve-related adverse events. The original study protocol did not include adjudication of deep sternal/thoracic wound infections by this committee. Therefore, potential infections were screened from adverse event data and subsequently adjudicated by two of the authors (BJJV, MDV) using the definition of The Centers for Disease Control and Prevention (CDC) (7). An independent data and safety monitoring board provided study oversight. An independent core laboratory (MedStar, Washington, DC) evaluated echocardiograms.

In the current study, patients were compared according to the surgical approach performed, specifically MI-AVR (ie, hemisternotomy or right thoracotomy) vs conventional AVR (full sternotomy). Patients who had had a prior open-heart surgery were excluded. The full cohort included both patients who underwent AVR with a concomitant procedure and those who underwent isolated AVR. The isolated AVR subcohort included only patients who received no concomitant procedures.

Follow-up and endpoints

Clinical and echocardiographic (transthoracic) evaluations were performed annually after the first year of follow-up. The current study compared patient and procedural characteristics, early outcomes (ie, within 30 days postimplant), and 3-year outcomes between the MI-AVR and conventional AVR groups. Early outcomes included death and valve-related thromboembolism, major haemorrhage, major paravalvular leak, reintervention, deep sternal/thoracic wound infections, and permanent pacemaker implantation. The 3-year outcomes analysis included all-cause, cardiac, and valve-related mortality, thromboembolism, valve thrombosis, all hemorrhage, major hemorrhage, all paravalvular leak, endocarditis, non-structural valve dysfunction, reintervention, and explant. In addition, a composite outcome of all-cause death, thromboembolism, or reintervention at 3 years was evaluated.

Echocardiographic outcomes included mean aortic gradient, calculated with the simplified Bernoulli equation using the mean velocities measured across the bioprosthesis, and effective orifice area (EOA), which was calculated with the continuity equation.

Statistical analyses

Categorical patient and procedural characteristics are reported as frequencies and percentages, and continuous characteristics are reported as mean ± standard deviation (SD). p values were calculated using the t test (continuous variables) or the chi-square or Fisher exact test (categorical variables). Early and 3-year outcome event rates (and 95% confidence intervals [CIs]) were calculated using the Kaplan-Meier method, and p values were calculated with the log-rank test. Cox proportional hazards models, adjusted for propensity score to account for baseline differences, were fit to examine differences in safety between the MI-AVR and conventional AVR groups in each cohort. Propensity scores were estimated for the isolated AVR cohort using multivariable logistic regression models adjusted for the following potential confounders: age, male sex, body surface area, New York Heart Association (NYHA) class III/IV, Society of Thoracic Surgeons (STS) mortality risk, diabetes, hypertension, peripheral vascular disease, renal dysfunction, stroke/cerebrovascular accident (CVA), coronary artery disease, left ventricular hypertrophy, atrial fibrillation, and isolated/mixed aortic stenosis. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). $p < 0.05$ was considered statistically significant.

RESULTS

Entire cohort

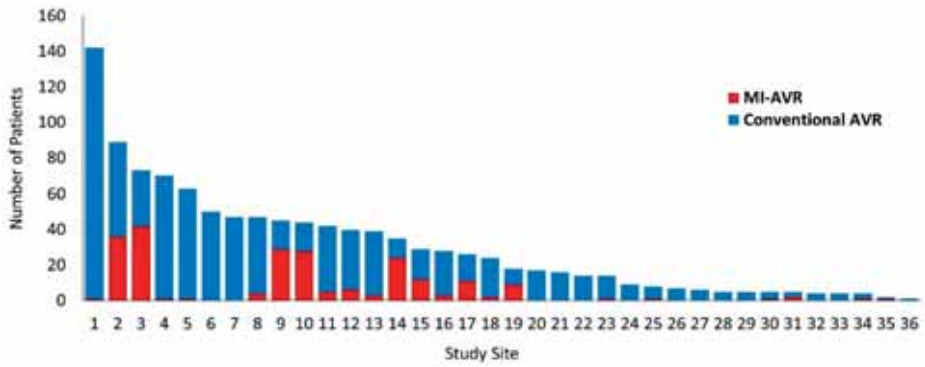
In the present study, 224 (20.8%) patients underwent MI-AVR, and 853 (79.2%) patients underwent conventional AVR. Among 36 participating trial sites, 6 centers reported a minimally invasive approach in 50% or more of their enrolled subjects. These centers enrolled 59% of all minimally invasive patients in this study (Figure 1). The baseline characteristics of the two groups are listed and compared in Table 1. Patients treated with MI-AVR had a lower age, STS score, and prevalence of coronary artery disease, and a higher prevalence of left ventricular hypertrophy. The procedural characteristics of the two groups are listed in Table 2. In the overall cohort, the primary indication for AVR was pure aortic stenosis in the majority of patients. The prevalence of aortic regurgitation and mixed aortic disease was higher in the MI-AVR group. Moreover, patients in the MI-AVR group had shorter cardiopulmonary bypass (98.0 ± 30.1 vs. 106.1 ± 42.6 minutes, $p = 0.001$) and aortic cross-clamp (71.8 ± 21.7 vs. 81.3 ± 33.5 minutes, $p < 0.001$) times, and the Cor-Knot device (LSI Solutions, Victor, New York, USA) was more often used (28.6% vs. 10.2%, $p < 0.001$). The proportion of concomitant procedures was higher in the conventional AVR group (57.3% vs. 26.8%, $p<0.001$), including the proportion of concomitant CABG procedures (41.0% vs. 0.9%, $p < 0.001$). The distribution of valve sizes was similar between both groups. Within the MI-AVR group, 156 (69.6%) patients underwent hemisternotomy, and 68 (30.4%) patients underwent right anterior thoracotomy.

Table 1: Baseline characteristics according to surgical approach.

	Entire cohort (n = 1077)			**Isolated SAVR (n = 528)**		
	MI-AVR	**Conventional SAVR**	**p value**	**MI-AVR**	**Conventional SAVR**	**p value**
	(N = 224)	**(N = 853)**		**(N = 164)**	**(N = 364)**	
Age (years)	67.6 ± 10.2	70.8 ± 8.4	<0.001	67.7 ± 9.7	70.3 ± 8.9	0.003
Male	159 (71.0%)	646 (75.7%)	0.15	121 (73.8%)	253 (69.5%)	0.32
Body surface area (m^2)	2.0 ± 0.2	2.0 ± 0.2	0.17	2.0 ± 0.2	2.0 ± 0.2	0.16
Body mass index (kg/m^2)	29.3 ± 5.2	29.5 ± 5.5	0.66	29.3 ± 5.3	29.6 ± 5.8	0.64
NYHA class III/IV	84 (37.5%)	366 (42.9%)	0.14	59 (36.0%)	145 (39.8%)	0.40
STS risk of mortality (%)	1.5 ± 1.1	2.0 ± 1.3	<0.001	1.4 ± 1.1	1.7 ± 1.2	0.008
Diabetes	55 (24.6%)	232 (27.2%)	0.43	38 (23.2%)	92 (25.3%)	0.60
Hypertension	168 (75.0%)	650 (76.2%)	0.71	117 (71.3%)	253 (69.5%)	0.67
Peripheral vascular disease	14 (6.3%)	65 (7.6%)	0.48	6 (3.7%)	23 (6.3%)	0.21
Renal dysfunction/ insufficiency	29 (12.9%)	85 (10.0%)	0.20	19 (11.6%)	23 (6.3%)	0.039
Stroke/CVA	4 (1.8%)	40 (4.7%)	0.06	1 (0.6%)	22 (6.0%)	0.002

Chronic obstructive lung disease	25 (11.2%)	102 (12.0%)	0.74	19 (11.6%)	50 (13.7%)	0.50
Coronary artery disease	49 (21.9%)	413 (48.4%)	<0.001	38 (23.2%)	86 (23.6%)	0.91
Left ventricular hypertrophy	123 (54.9%)	321 (37.6%)	<0.001	84 (51.2%)	140 (38.5%)	0.006
Percutaneous coronary intervention	22 (9.8%)	121 (14.2%)	0.09	14 (8.5%)	40 (11.0%)	0.39
Atrial fibrillation	19 (8.5%)	90 (10.6%)	0.36	12 (7.3%)	33 (9.1%)	0.51

Figure 1. Distribution of surgical approach across the participating centers of the PERIGON Pivotal Trial.



All-cause mortality was not significantly different between the MI-AVR and conventional AVR groups at 30 days (1.3% [0.4-3.6%] vs.0.8% [0.4-1.6%], respectively; p = 0.47) and at 3-year follow-up (6.0% [3.3-9.7%] vs. 6.9% [5.3-8.8%], p = 0.69). This difference remained nonsignificant for cardiac and valve-related mortality. As reported in Tables 2 and 3, all valve-related adverse events were also not significantly different between the surgical approaches at early and 3-year follow-up, except for all hemorrhage, which was more frequently present in the MI-AVR group (13.1% [8.9-18.1%] vs. 7.6% [5.9-9.6], p = 0.018). This difference was not statistically significant for major hemorrhage (7.2% [4.2-11.2%]) vs. 4.6% [3.3-6.2%], p = 0.14).

Deep sternal/thoracic wound infections occurred in 6 patients after conventional AVR and in 1 patients after MI-AVR (0.70% vs. 0.45%, p =1.00). In addition, two patients who underwent RAT developed an inguinal wound infection.

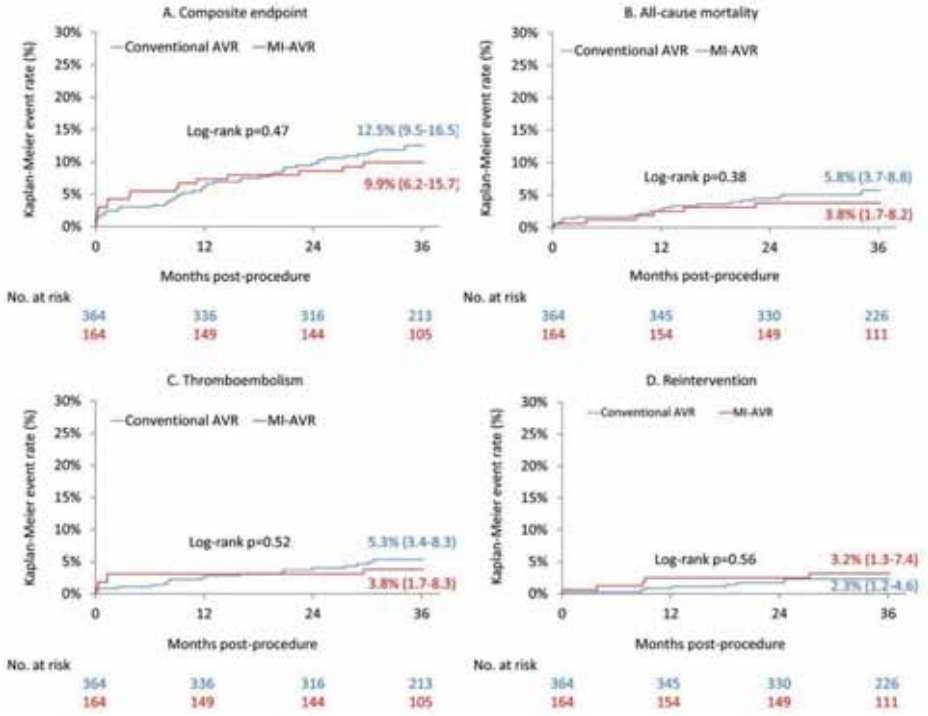
Isolated AVR

The baseline characteristics of the isolated AVR cases are also reported in Table 1. One hundred sixty-four (31.1%) patients underwent MI-AVR, and 364 (68.9%) patients underwent conventional AVR. The prevalence of coronary artery disease was not significantly different between groups in this subcohort, but the conventional AVR group had a higher prevalence of previous cerebrovascular accidents (CVA) and a lower prevalence of renal dysfunction. In accordance with the entire cohort, the MI-AVR group was younger, had a lower STS risk of

mortality, and had a higher prevalence of left ventricular hypertrophy. For the isolated cases, cardiopulmonary bypass (96.8 ± 29.1 vs. 85.1 ± 29.1 minutes, $p < 0.001$) and aortic cross-clamp (70.8 ± 21.5 vs. 63.8 ± 22.8 minutes, $p = 0.001$) times were shorter in the conventional AVR group (Table 2). Differences in the primary indication of AVR, the use of Cor-Knot sutures, and distribution of valve size in the isolated AVR cohort were similar to those observed in the overall cohort. Within the MI-AVR group, 105 (64.0%) patients underwent hemisternotomy, and 59 (36.0%) patients underwent right anterior thoracotomy (RAT).

In accordance with the results of the overall cohort, the unadjusted post-operative mortality and morbidity were not significantly different between the surgical approaches at early and late follow-up (Tables 2 and 3, Figure 2). After propensity score adjustment, there was no association between MI-AVR with the composite endpoint of all-cause mortality, thromboembolism, or reintervention through 3 years (HR: 0.86, 95% CI 0.47-1.55, $p = 0.61$). The adjusted effect of MI-AVR on mortality (HR: 0.89, 95% CI 0.34-2.30, $p = 0.80$) and other valve-related adverse events separately was also not significant (Figure 3), again, except for all hemorrhage (11.9% [7.4-17.7%] vs. 6.1% [3.9-9.0%], $p = 0.039$). Similar to the findings in the entire cohort, there was no significant difference in major hemorrhage ($p = 0.40$). Furthermore, there was no significant difference in EOA and mean gradient between the MI-AVR and conventional AVR groups at discharge up to 3 years (Figure 4).

Figure 2. Three-year outcomes according to surgical approach in the isolated surgical aortic valve replacement (AVR) cohort.



Shown are unadjusted Kaplan-Meier event rates with 95% confidence intervals (CIs) for (A) the composite outcome of all-cause mortality, thromboembolic events, and reintervention; (B) all-cause mortality; (C) thromboembolism; and (D) reintervention. MI-AVR, minimally invasive AVR.

Table 2: Procedural characteristics and early outcomes.

	Entire cohort (n = 1077)			**Isolated SAVR (n = 528)**		
	MI-AVR (N = 224)	**Conventional SAVR (N = 853)**	**p value**	**MI-AVR (N = 164)**	**Conventional SAVR (N = 364)**	**p value**
Total cardiopulmonary bypass time, min	98.0 ± 30.1	106.1 ± 42.6	0.001	96.8 ± 29.1	85.1 ± 29.1	<0.001
Total aortic cross clamp time, min	71.8 ± 21.7	81.3 ± 33.5	<0.001	70.8 ± 21.5	63.8 ± 22.8	0.001
Use of Cor-Knot	64 (28.6%)	87 (10.2%)	<0.001	49 (29.9%)	18 (4.9%)	<0.001
Primary indication			<0.001			0.002
Aortic stenosis	169 (75.4%)	746 (87.5%)		132 (80.5%)	330 (90.7%)	
Aortic regurgitation	20 (8.9%)	38 (4.5%)		10 (6.1%)	16 (4.4%)	
Mixed	35 (15.6%)	69 (8.1%)		22 (13.4%)	18 (4.9%)	
Minimally invasive approach						
Hemisternotomy	156 (69.6%)	NA		105 (64.0%)	NA	
Right anterior thoracotomy	68 (30.4%)	NA		59 (36.0%)	NA	
Concomitant procedures						
CABG	2 (0.9%)	350 (41.0%)	<0.001	NA	NA	NA
Implantable cardiac device	0 (0.0%)	1 (0.1%)	>0.99	NA	NA	NA
Left atrial appendage closure	20 (8.9%)	65 (7.6%)	0.52	NA	NA	NA
Patent foramen ovale closure	3 (1.3%)	10 (1.2%)	0.74	NA	NA	NA
Subaortic membrane resection not requiring myectomy	10 (4.5%)	11 (1.3%)	0.002	NA	NA	NA
Ascending aorta aneurysm repair not requiring circulatory arrest	10 (4.5%)	71 (8.3%)	0.05	NA	NA	NA
Ascending aorta dissection repair not requiring circulatory arrest	1 (0.4%)	0 (0.0%)	0.21	NA	NA	NA
Other	33 (14.7%)	117 (13.7%)	0.70	NA	NA	NA
Valve size						

Table 2: Continued

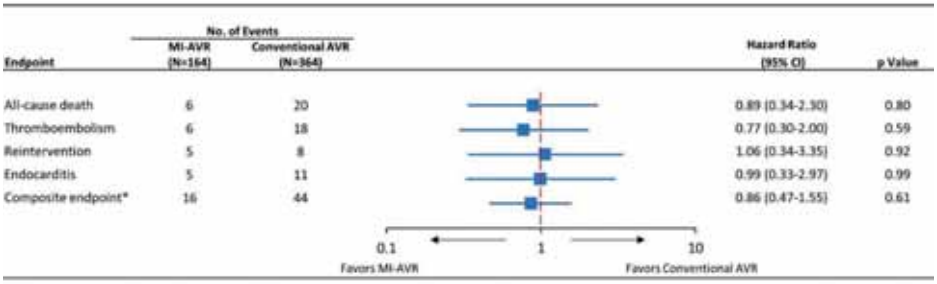
	Entire cohort (n = 1077)			Isolated SAVR (n = 528)		
	MI-AVR (N = 224)	**Conventional SAVR (N = 853)**	**p value**	**MI-AVR (N = 164)**	**Conventional SAVR (N = 364)**	**p value**
Mean valve size (mm)	23.4 ± 2.1	23.5 ± 2.0	0.32	23.3 ± 2.1	23.3 ± 2.1	>0.99
17 mm	0 (0.0%)	1 (0.1%)		0 (0.0%)	1 (0.3%)	
19 mm	10 (4.5%)	31 (3.6%)		8 (4.9%)	18 (4.9%)	
21 mm	48 (21.4%)	156 (18.3%)		37 (22.6%)	73 (20.1%)	
23 mm	78 (34.8%)	310 (36.3%)		61 (37.2%)	144 (39.6%)	
25 mm	65 (29.0%)	270 (31.7%)		40 (24.4%)	97 (26.6%)	
27 mm	23 (10.3%)	75 (8.8%)		18 (11.0%)	27 (7.4%)	
29 mm	0 (0.0%)	10 (1.2%)		0 (0.0%)	4 (1.1%)	
Early outcomes[a,b]						
All-cause mortality	1.3% (0.4-3.6%) (n=3)	0.8% (0.4-1.6%) (n=7)	0.47	0.6% (0.1-3.1%) (n=1)	0.8% (0.2-2.3%) (n=3)	0.80
Thromboembolism	1.8% (0.6-4.3%) (n=4)	1.3% (0.7-2.2%) (n=11)	0.57	1.8% (0.5-4.9%) (n=3)	0.8% (0.2-2.3%) (n=3)	0.31
Major hemorrhage[c]	1.4% (0.4-3.6%) (n=3)	0.7% (0.3-1.5%) (n=6)	0.35	0.6% (0.1-3.1%) (n=1)	0.8% (0.2-2.3%) (n=3)	0.79
Major paravalvular leak	0.0% (NA) (n=0)	0.1% (0.0-0.6%) (n=1)	0.61	0.0% (NA) (n=0)	0.3 (0.0,1.5) (n=1)	0.50
Reintervention	0.4% (0.0-2.3%) (n=1)	0.4% (0.1-1.0%) (n=3)	0.83	0.6% (0.1-3.1%) (n=1)	0.3% (0.0-1.5%) (n=1)	0.56
Implanted cardiac device[d]	3.1% (1.4-6.1%) (n=7)	4.0% (2.8-5.5%) (n=34)	0.56	3.0% (1.1-6.5%) (n=5)	5.0% (3.0-7.5%) (n=18)	0.33

Table 3: Summary of adverse events according to surgical approach at 3 years follow-up[a]

	Entire cohort (n = 1077)			Isolated SAVR (n = 528)		
	MI-AVR (N = 224)	Conventional SAVR (N = 853)	p value[b]	MI-AVR (N = 164)	Conventional SAVR (N = 364)	p value[b]
All-cause mortality	6.0% (3.3-9.7%) (n=13)	6.9% (5.3-8.8%) (n=56)	0.69	3.8% (1.6-7.6%) (n=6)	5.8% (3.6-8.5%) (n=20)	0.38
Cardiac-related mortality	4.1% (2.0-7.3%) (n=9)	3.3% (2.2-4.7%) (n=26)	0.47	3.1% (1.2-6.7%) (n=5)	3.2% (1.7-5.5%) (n=11)	0.99
Valve-related mortality	0.9% (0.2-3.1%) (n=2)	1.1% (0.6-2.1%) (n=9)	0.85	1.3% (0.3-4.2%) (n=2)	0.6% (0.1-2.0%) (n=2)	0.41
Thromboembolism	3.7% (1.8-6.9%) (n=8)	4.8% (3.5-6.5%) (n=39)	0.54	3.8% (1.6-7.6%) (n=6)	5.3% (3.3-8.1%) (n=18)	0.52
Valve thrombosis	0.0% (0.0-0.0%) (n=0)	0.3% (0.1-0.9%) (n=2)	0.47	0.0% (0.0-0.0%) (n=0)	0.6% (0.1-2.0%) (n=2)	0.34
All hemorrhage[c]	13.1% (8.9-18.1%) (n=27)	7.6% (5.9-9.6%) (n=61)	0.018	11.9% (7.4-17.7%) (n=18)	6.1% (3.9-9.0%) (n=21)	0.039
Major hemorrhage[c]	7.2% (4.2-11.2%) (n=15)	4.6% (3.3-6.2%) (n=37)	0.14	5.9% (2.9-10.4%) (n=9)	4.1% (2.3-6.6%) (n=14)	0.40
All paravalvular leak	0.0% (0.0-0.0%) (n=0)	0.7 (0.3-1.5) (n=6)	0.21	0.0% (0.0-0.0%) (n=0)	0.3 (0.0-1.5) (n=1)	0.50
Endocarditis	2.4% (0.9-5.1%) (n=5)	3.2% (2.1-4.6%) (n=25)	0.57	3.2% (1.2-6.8%) (n=5)	3.2% (1.7-5.5%) (n=11)	0.99
Non-structural valve dysfunction	0.0% (0.0-0.0%) (n=0)	0.7% (0.3-1.5%) (n=6)	0.21	0.0% (0.0-0.0%) (n=0)	0.3% (0.0-1.5%) (n=1)	0.50
Reintervention	2.3% (0.9-5.1%) (n=5)	2.0% (1.2-3.2%) (n=16)	0.73	3.2% (1.2-6.8%) (n=5)	2.3% (1.1-4.3%) (n=8)	0.56
Explant	2.3% (0.9-5.1%) (n=5)	2.0% (1.2-3.2%) (n=16)	0.73	3.2% (1.2-6.8%) (n=5)	2.3% (1.1-4.3%) (n=8)	0.56

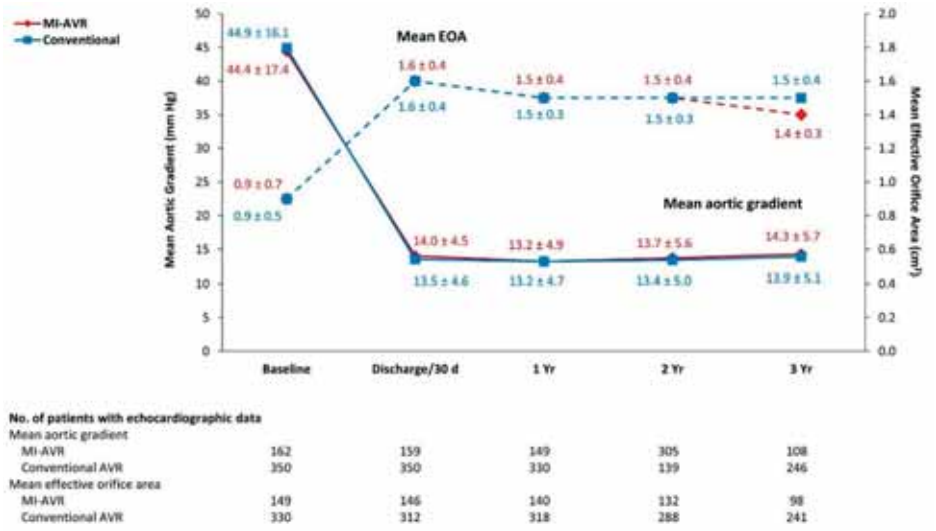
[a] Data are the Kaplan-Meier event rate, 95% confidence interval, and number of patients with an event.bp value from log-rank test through 3 years. cOnly anticoagulant-related hemorrhage events are included.

Figure 3. Factors associated with three-year outcomes in a propensity-score adjusted multivariable model.



*Impact of surgical approach on outcomes at 3 years in the isolated surgical AVR cohort. Propensity-score-adjusted multivariable models were fit to examine differences in outcomes between the minimally invasive aortic valve replacement (MI-AVR) and conventional AVR groups. *The composite outcome comprised all-cause death, thromboembolism, and reintervention.*

Figure 4. Post-procedural hemodynamics according to surgical approach through 3 years of follow-up.



No. of patients with echocardiographic data					
Mean aortic gradient					
MI-AVR	162	159	149	305	108
Conventional AVR	350	350	330	139	246
Mean effective orifice area					
MI-AVR	149	146	140	132	98
Conventional AVR	330	312	318	288	241

Shown are the mean gradient (solid lines) and the effective orifice area (EOA; dashed lines) for the MI-AVR group and conventional AVR group during follow-up.

Subanalysis isolated MI-AVR cohort

The RAT group was significantly younger, had lower STS scores, and less left ventricular hypertrophy compared to the hemisternotomy group. The Cor-Knot was more frequently used in the RAT group (61% vs 11%, p<0.0001). Early and late safety endpoints, valve-related event rates, and hemodynamic performance did not differ between the groups (see supplementary Tables 1-3).

Within the MI-AVR group, the Cor-Knot was used in 49 patients (30%), and manually tied sutures ("No Cor-Knot") were used in 115 patients (70%). The baseline characteristics were comparable apart from a higher frequency of NYHA class III/IV in the No Cor-Knot group. Cardiopulmonary bypass and aortic cross-clamp times were not significantly different between the Cor-Knot group and the No Cor-Knot group (97.0 ± 23.5 vs 96.7 ± 31.2 [p = 0.94] and 70.2 ± 17.9 vs 71.1 ± 23.0 minutes [p = 0.80], respectively) (see supplementary Tables 4-5). There were no significant differences in the early and late safety endpoints, including all-cause mortality, thromboembolism, paravalvular leak, endocarditis, and reintervention, as shown in Table 4.

Table 4: Summary of adverse events according to the use of Cor-Knot at 3 years follow-up[a]

	Cor-Knot (N=49)	**No Cor-Knot (N=115)**	**P-value[b]**
All-cause mortality	4.2% (1.1-15.7%) (n=2)	3.6% (1.4-9.2%) (n=4)	0.8
Cardiac-related mortality	2.0% (0.3-13.6%) (n=1)	3.6% (1.4-9.2%) (n=4)	0.61
Valve-related mortality	2.0% (0.3-13.6%) (n=1)	0.9% (0.1-6.4%) (n=1)	0.56
Thromboembolism	6.6% (2.2-19.2%) (n=3)	2.6% (0.9-8.0%) (n=3)	0.27
Valve thrombosis	0.0% (0.0-0.0%) (n=0)	0.0% (0.0-0.0%) (n=0)	NA
All hemorrhage[c]	11.6% (4.9-25.9%) (n=5)	12.2% (7.2-20.1%) (n=13)	0.86
Major hemorrhage[c]	4.1% (1.0-15.3%) (n=2)	6.6% (3.2-13.4%) (n=7)	0.61
All paravalvular leak	0.0% (0.0-0.0%) (n=0)	0.0% (0.0-0.0%) (n=0)	NA
Endocarditis	6.2% (2.0-18.0%) (n=3)	1.8% (0.5-7.1%) (n=2)	0.15
Non-structural valve dysfunction	0.0% (0.0-0.0%) (n=0)	0.0 (0.0-0.0%) (n=0)	NA
Reintervention	6.3% (2.1-18.3%) (n=3)	1.8% (0.4-6.8%) (n=2)	0.15
Explant	6.3% (2.1-18.3%) (n=3)	1.8% (0.4-6.8%) (n=2)	0.15

NA, not available. aData are the Kaplan-Meier event rate, 95% confidence interval, and number of patients with an event. bP-value from log-rank test through 3 years. cOnly anticoagulant-related hemorrhage events are included.

DISCUSSION

In a cohort of 1077 patients who underwent AVR with the Avalus bioprosthesis, we found that the incidence of postoperative mortality and morbidity were comparable between the MI-AVR and conventional AVR groups up to 3 years of follow-up.

While minimally invasive techniques for AVR were first described in the 1990s (2,3), there remains a lack of consensus about their application in clinical practice (8). Previous attempts to explore the safety of MI-AVR have been hampered by the poor quality of evidence in the literature. In a Cochrane review of randomized controlled trials that compared limited vs. full sternotomy in 2017, only 511 patients were included from 7 clinical trials (9). In addition, a recent meta-analysis by Chang et al. suggested that the comparison of early mortality is subject to publication bias (10). Despite these methodological concerns, neither of these reviews nor the present study found a significant difference in mortality or other major adverse events between MI-AVR and conventional SAVR. The strengths of the present study are its prospective multicenter design, the size of the study population, the robustness of follow-up, adjudication of valve-related safety endpoints by an independent clinical events committee, as well as consistent assessment of hemodynamic performance by an independent core laboratory.

As part of the protocol of the PERIGON Pivotal Trial, surgical approach was left to the discretion of the participating surgeon. This gives insight into the decision-making of experienced surgeons in contemporary practice, and it appears that conventional AVR is still deemed a more appropriate approach for older patients who require concomitant procedures. Because of this evident confounding by indication, a secondary analysis was performed on a narrowed down cohort that included only patients who underwent isolated AVR, although there remained a difference in age, prevalence of left ventricular hypertrophy, and previous stroke. However, both before and after propensity score adjustment, there were no relevant differences in mortality or other valve-related adverse events at 3 years of follow-up, except for all hemorrhage, which was more frequently observed in the MI-AVR group. However, the clinical value of this difference remains unclear since there was no difference in major hemorrhage which was broadly defined in the PERIGON Pivotal Trial as any bleeding episode that resulted in death, hospitalization, reoperation, centesis, or a decrease in hemoglobin to<7 g/dL that required>3 U blood transfusion or that caused>1 L blood loss.

Due to the limited room to manoeuvre with MI-AVR, it can be hypothesized that the optimal valve size may not always be implanted. However, in our study, MI-AVR was not associated with inferior hemodynamic performance in the isolated AVR subcohort, as the average implanted valve size and postoperative echocardiographic parameters (ie, mean gradient and EOA) were not significantly different between the two groups. This corresponds to the work of Furukawa et al, who also found no relevant difference in the prosthesis size implanted (11). In addition, there were no differences in paravalvular leakage and cardiac

device implantation at 30 days between the surgical approaches, demonstrating that the Avalus valve can be safely used in a MI-AVR setting.

As clinical outcomes and hemodynamic performance were comparable in the isolated AVR subcohort, the use of MI-AVR over conventional AVR presents a trade-off between less scarring and longer procedural times. To shorten the MI-AVR procedure and hence make it more attractive for surgeons to adopt these techniques, it has been recommended that sutureless valves be used (10). However, as shown in the PERSIST-AVR trial, the average reduction in cardiopulmonary bypass and aortic cross-clamp times was only 20 minutes with sutureless versus sutured valves (12). This time saved comes at the cost of a three-fold higher risk of permanent pacemaker implantation, which is associated with decreased survival during long-term follow-up (13). In addition, despite the longer procedural times compared to conventional AVR, MI-AVR with a stented bioprosthesis was not associated with a higher rate of postoperative mortality and morbidity. Hence, sutureless valves are not a prerequisite to perform MI-AVR safely.

Another theoretical way of shortening MI-AVR procedures is the use of automated suture fasteners. Literature on automated suture fasteners in MI-AVR is scarce. A recent systematic review and meta-analysis by Sazzad and colleagues (14) included three retrospective cohort studies and one small randomized controlled trial. Short-term outcomes showed reduced cardiopulmonary bypass and aortic cross-clamp times and similar early mortality rates. Mid- and long-term outcomes are lacking, leaving a gap of knowledge about potential complications related to extra foreign material, such as thromboembolism, endocarditis, and reintervention. We did not find a difference in bypass or cross-clamp times in the present study, and all safety endpoints were similar at 30 days and 3 years of follow-up.

While the present study suggests that MI-AVR is as safe as conventional AVR in patients who require isolated AVR, it does not support MI-AVR through hemisternotomy or RAT unequivocally. To prove the benefit of these techniques, future studies should focus on time to recovery and quality-of-life outcomes. These "soft" outcomes may help to align patient preferences with the selection of the most appropriate treatment strategy (8). Furthermore, surgeons should be aware that there is a learning curve associated with the adoption of MI-AVR techniques. Approximately 50 cases are required to achieve a stable operative time (15,16), although cumulative institutional experience could likely benefit the individual learning curve.

Limitations

Although data were prospectively collected, patients were not randomized to the respective treatment strategies, as reflected in differences in baseline characteristics between the groups. Nevertheless, narrowing inclusion criteria and applying propensity score adjustment did not change the results. In addition, follow-up was relatively short as the average duration was 3 years after the procedure. While hemodynamic performance was consistent between the two groups, the PERIGON trial will continue to follow a subset of patients for up to 12 years of follow-up, and those long-term results will provide further insights into the relative safety and hemodynamic performance of the Avalus valve in a MI-AVR setting.

CONCLUSIONS

Three-year outcomes after MI-AVR with the Avalus bioprosthetic valve were comparable to outcomes achieved with a conventional AVR. These results provide important insights into the overall ability to reduce the invasiveness of AVR without compromising outcomes.

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7

PLEDGETED VERSUS NON-PLEDGETED SUTURES IN AORTIC VALVE REPLACEMENT: INSIGHTS FROM A PROSPECTIVE MULTICENTER TRIAL

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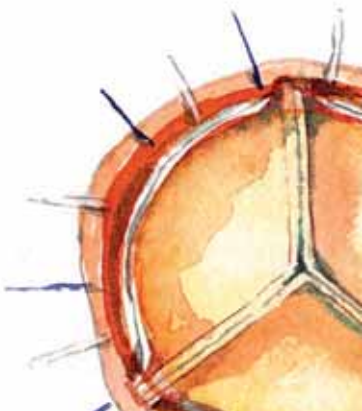
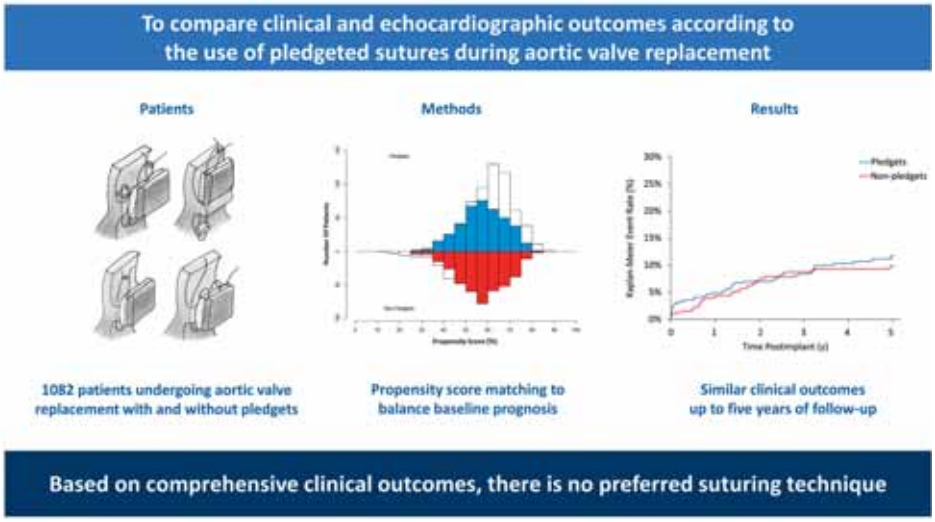
JTCVS Techniques 2023

Presented at the 2022 annual meeting of the Western Thoracic Surgical Association, Koloa, Hawaii, United States of America



GRAPHICAL ABSTRACT



ABSTRACT

Objective: To compare short- and mid-term clinical and echocardiographic outcomes according to the use of pledgeted sutures during aortic valve replacement.

Methods: Patients with aortic stenosis or regurgitation requiring aortic valve replacement were enrolled in a prospective cohort study to evaluate the safety of a new stented bioprosthesis. Outcomes were analyzed according to the use of pledgets (*pledgeted group*) or no pledgets (*non-pledgeted group*). The primary outcome was a composite of thromboembolism, endocarditis, and major paravalvular leak at 5 years of follow-up. Secondary outcomes included multiple clinical endpoints and hemodynamic outcomes. Propensity score matching was performed to adjust for prognostic factors, and subanalyses with small valve sizes (<23 mm) and suturing techniques were performed.

Results: The pledgeted group comprised 640 patients (59%), and the non-pledgeted group 442 (41%), with baseline discrepancies in demography, co-morbidities, and stenosis severity. No significant differences were observed in any outcome. After propensity score matching, the primary outcome occurred in 41 (11.7%) patients in the pledgeted and 36 (9.8%) in the non-pledgeted group ($p = 0.51$). The EOA was smaller in the pledgeted group ($p = 0.045$), while no difference was observed for the mean or peak pressure gradient between groups. Separate subanalyses with small valve sizes and suturing techniques did not demonstrate relevant differences.

Conclusions: In this large propensity-score-matched cohort, comprehensive clinical outcomes were comparable between patients undergoing aortic valve replacement with pledgeted and non-pledgeted sutures up to 5 years of follow-up, but pledgets might lead to a slightly smaller EOA in the long run.

INTRODUCTION

Aortic valve replacement (AVR) is the second-most commonly performed type of cardiac surgery, and rates are increasing due to an aging population (2). Although AVR has been performed and improved over several decades, there is still debate between surgeons about the optimal implantation technique. An interesting topic that lacks consensus is whether to use pledgeted sutures to secure the prosthetic valve, as the literature shows conflicting results (3-7) (Table 1).

Some argue that the use of pledgeted sutures allow for more even distribution of mechanical forces and a tighter connection between the prosthesis and the aortic annulus/root, thereby decreasing the incidence of paravalvular leak (PVL) (3). However, others believe that pledgets create an additional level of obstruction in the left ventricular outflow tract (LVOT), leading to a higher transvalvular gradient, a smaller effective orifice area (EOA) (4, 5), and subsequently more frequent prosthesis-patient mismatch (PPM) (7). Theoretically, the use of pledgets could also induce higher rates of thromboembolism or endocarditis due to extra foreign material.

Within the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial of the Avalus bioprosthesis, the technical details for implantation were left to the discretion of the surgeon. We aimed to provide insight into the effect of pledgeted sutures during AVR on multiple clinical and hemodynamic outcomes. The primary outcome of interest was a composite of thromboembolism, endocarditis, and major PVL at 5-year follow-up.

Table 1. Overview of previous studies regarding the use of pledgets in aortic valve replacement.

Study characteristics					Hemodynamic performance			Clinical outcomes		
Author/year	**Design**	**Valve**	**N**	**FU length (months)**	**MPG (mmHg)**	**EOA (cm^2)**	**PVL**	**Operative mortality**	**TE**	**IE**
Englberger et al. 2005 (3)	RCT secondary analysis	Mechanical (aortic/mitral)	807	60	-	-	1.7% PS vs. 5.8% NPS. HR 0.3 for PS ($p < 0.01$)	-	-	-
LaPar et al. 2011 (6)	Retrospective cohort	Biological, mechanical, homograft	802	82	-	-	PS 1.2% vs. NPS 0.5% (p=0.38)	PS 2.3% vs. NPS 1.9% (p=0.79)	-	-
Tabata et al. 2014 (4)	Retrospective cohort	Biological (19-21 mm)	152	12	-	Post-implant: PS 1.30 ± 0.28 vs. NPS 1.42 ± 0.32 (p=0.03). 1 year: No difference (p=0.13)	No difference (p>0.99)	-	-	-
Ugur et al. 2014 (5)	Prospective cohort	Biological (19-21 mm)	346	12	PS 8.9 ± 3.9 vs. NPS 9.6 ± 4.1 (p=0.16)	1 year: PS 1.53 ± 0.3 vs. NPS 1.42 ± 0.3 (p=0.04)	No difference (p=NA)	-	-	-
Kim et al. 2019 (7)	Retrospective cohort	Biological, mechanical	439	12	-	1 year: PS 1.74 ± 1.38 vs. NPS 1.70 ± 0.34 vs. figure-of-eight 1.7 ± 0.42 (p=0.97)	PS 0.5% vs. NPS 0% vs. figure-of-eight 1% (p=0.99)	PS 2.4% vs. NPS 2.5% vs. figure-of-eight 5.7% (p=0.28)	PS 0.5% vs. NPS 0.8% vs. figure-of-eight 0% (p=0.44)	-

RCT, randomized controlled trial; EOA, effective orifice area; FU, follow-up; IE, infective endocarditis; MPG, mean pressure gradient; NA, not available; NPS, non-pledgeted sutures; PS, pledgeted sutures; PVL, paravalvular leak; TE, thromboembolism.

PATIENTS AND METHODS

Study design

The PERIGON Pivotal Trial (www.clinicaltrials.gov, NCT02088554) is a prospective multicenter trial that is conducted at 38 sites across the United States, Canada, and Europe. In this single-armed trial, clinical and hemodynamic outcomes of the Avalus bioprosthesis (Medtronic, Minneapolis, Minnesota, USA), a stented bovine pericardial aortic valve, are evaluated. The study design was previously described in detail (8, 9). In short, symptomatic patients with moderate or severe aortic stenosis or chronic, severe aortic regurgitation who were admitted for surgical AVR according to clinical indication were enrolled. Patients with and without concomitant procedures, limited to coronary artery bypass grafting (CABG), left atrial appendage ligation, patent foramen ovale closure, ascending aortic aneurysm or dissection repair not requiring circulatory arrest, and subaortic membrane resection not requiring myectomy, were included. In the PERIGON Pivotal Trial protocol, surgical technical details were left to the surgeon's own consideration.

The trial was conducted according to the Declaration of Helsinki and good clinical practice. At each site, approval of the protocol was obtained from the institutional review board or ethics committee (supplementary files, Table S1), and written informed consent was provided by all patients. All deaths and valve-related adverse events were adjudicated by an independent clinical events committee, and study oversight was provided by an independent data and safety monitoring board (Baim Institute for Clinical Research, Boston, Massachusetts, USA). All echocardiographic data were evaluated by an independent core laboratory (MedStar, Washington, DC, USA).

In the present study, patients were stratified to non-everted or everted mattress sutures with pledgets (pledgeted group), and non-everted or everted mattress, continuous, or simple interrupted sutures without pledgets (non-pledgeted group). Patients with previous aortic valve implantation (n=10), figure-of-eight sutures (n=3), or non-categorized sutures (n=23) were excluded.

Follow-up and endpoints

Annual clinical and (transthoracic) echocardiographic evaluations were performed after the first year of follow-up. Patient and procedural characteristics, early outcomes (within 30 days post-implantation), and 5-year outcomes were compared between the pledgeted and non-pledgeted groups. The primary outcome was a composite of thromboembolism, endocarditis, and major PVL at 5-year follow-up. Other clinical parameters included in the early- and mid-term outcome analysis consisted of mortality, thromboembolism, endocarditis, all and major hemorrhage, all and major paravalvular leak, explant, reintervention, and permanent pacemaker implantation.

Echocardiographic outcomes consisted of mean and peak pressure gradients calculated using the simplified Bernoulli formula, and EOA, which was determined by the continuity equation. EOA indexed (EOAi) by body surface area (BSA) was used to classify PPM. PPM was defined according to the Valve Academic Research Consortium 3 criteria as insignificant (EOAi >0.85 cm^2/m^2 or >0.70 cm^2/m^2), moderate (EOAi between 0.85 and 0.66 cm^2/m^2 or 0.70 and 0.56 cm^2/m^2), or severe (EOAi ≤0.65 cm^2/m^2 or ≤0.55 cm^2/m^2) for patients with a body mass index (BMI) <30 kg/m^2 or ≥30 kg/m^2, respectively (10).

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as number and percentage. The independent sample t-test or Mann-Whitney U test was used to compare continuous variables, and the Chi-square- or Fisher exact test was used for categorical variables. Early and 5-year clinical event rates (including 95% confidence interval [CIs]) were summarized using the Kaplan-Meier method, and the log-rank test was used to calculate p values. An additional evaluation of hemodynamic performance post-implantation and at 5-year follow-up in valve sizes smaller than 23 mm was performed. Furthermore, hemodynamic performance according to suturing techniques within the non-pledgeted group was compared between the "mattress" (non-everted and everted mattress sutures) and "non-mattress" (continuous and simple interrupted sutures) groups to investigate differences not related to the use of pledgets.

Propensity score matching was performed to account for potential bias arising from the decision to use pledgets. Propensity scores were calculated based on the following variables: age, male sex, BSA, Society of Thoracic Surgeons (STS) risk of mortality, New York Heart Association (NYHA) class III/IV, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), hypertension, previous myocardial infarction, renal dysfunction/insufficiency, diabetes mellitus (DM), atrial fibrillation, peripheral vascular disease, previous stroke/cerebrovascular accident (CVA), left ventricular ejection fraction (LVEF) at baseline, mean pressure gradient at baseline, isolated/mixed aortic stenosis, and less invasive approach (hemisternotomy or right anterior thoracotomy). Baseline LVEF and baseline mean pressure gradient were missing for 225 (20.8%) and 26 (2.4%) patients, respectively. To avoid losing patients in the post-matched analysis, the missing values were imputed with the median before entering propensity score matching. A 5-to-1 digits greedy 1:1 matching algorithm was used to form a propensity-score-matched cohort for analysis.

A 2-sided alpha level of 0.05 was used in all tests. The balance in baseline characteristics before and after propensity score matching was expressed in standardized mean differences. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

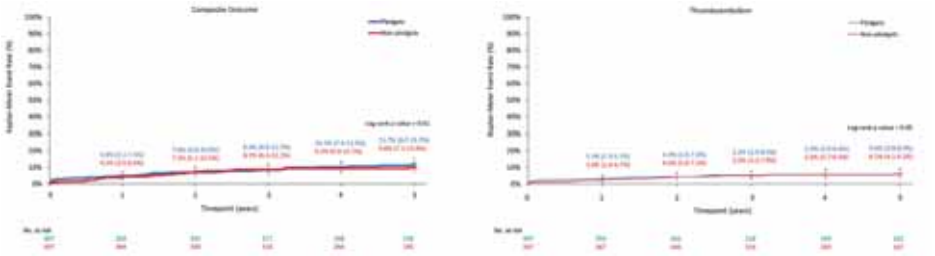
RESULTS

Entire cohort

640 (59%) patients underwent AVR with pledgeted sutures, and 442 (41%) underwent AVR with non-pledgeted sutures. The baseline characteristics are summarized in Table 2. Significant baseline differences existed in age, BSA, BMI, STS risk of mortality, hypertension, left ventricular hypertrophy (LVH), atrial fibrillation, isolated or mixed aortic stenosis as the primary indication for AVR, minimally invasive surgical approach, concomitant procedures, and implanted valve sizes. At 30 days, all clinical and hemodynamic endpoints were comparable (Table S2). At 5-years of follow-up, the composite outcome of thromboembolism, endocarditis, and major PVL occurred in 9.2% of the pledgeted group and 10.2% of the non-pledgeted group (p=0.59) (Table S3). Moreover, there were no significant differences in the separate components of the composite outcome, nor in other clinical or hemodynamic outcomes. After propensity-score matching, 794 patients (397 matched pairs) were eligible for the analysis (Figure S1). The groups were similar with regard to comorbidities and hemodynamic parameters, yet differences in concomitant procedures persisted (Table 2). At 30 days, the composite outcome was 2.8% in the pledgeted group and 1.0% in the non-pledgeted group (p=0.07) (Table S4). The hemodynamic parameters were similar between the two groups.

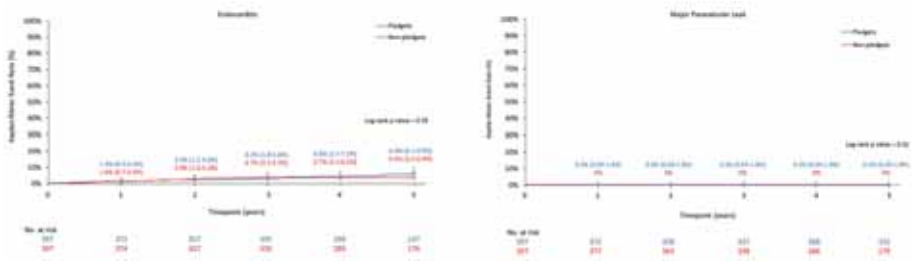
At 5 years of follow-up (Table 3), the composite outcome of thromboembolism, endocarditis, and major PVL occurred in 11.7% of the pledgeted group and in 9.8% of the non-pledgeted group (p=0.51). The separate components were also comparable (Figure 1 and Figure 2). The EOA was smaller in the pledgeted group (p=0.045), but no difference was observed for the mean or peak pressure gradient. The MPG remained stable over time, whereas the EOA decreased especially in the pledgeted group (Figure S2). The degree of PVL was consistent throughout follow-up (Figure 3). The proportion with any PPM at 5-year follow-up was similar between the groups (Table 3).

Figure 1. Kaplan-Meier event rates according to the use of pledgets for patient who underwent aortic valve replacement in the propensity-score-matched cohort.



Displayed are event rates for the composite outcome of thromboembolism, endocarditis, and major paravalvular leak (left), and for thromboembolism (right). The whiskers represent the 95% confidence intervals.

Figure 2. Kaplan-Meier event rates according to the use of pledgets for patient who underwent aortic valve replacement in the propensity-score-matched cohort.



Displayed are event rates for endocarditis (left), and for major paravalvular leak (right). The whiskers represent the 95% confidence intervals.

Table 2. Baseline and procedural characteristics according to the use of pledgets for patient who underwent aortic valve replacement in the entire cohort and the propensity-score-matched cohort.

	Entire cohort (n = 1082)			**Propensity-score-matched cohort (n = 794)**		
	Pledgets (n = 640)	**Non pledgets (n = 442)**	**SMD**	**Pledgets (n = 397)**	**Non pledgets (n = 397)**	**SMD**
Age (years)	69.6 ± 8.5	71.0 ± 9.4	0.148	70.2 ± 8.3	70.3 ± 9.2	0.010
Male	494 (77.2%)	323 (73.1%)	0.095	300 (75.6%)	295 (74.3%)	0.029
Body surface area (m^2)	2.01 ± 0.2	1.96 ± 0.2	0.205	1.98 ± 0.2	1.98 ± 0.2	0.019
Body mass index (kg/m^2)	29.8 ± 5.5	29.0 ± 5.3	0.145	29.4 ± 5.7	29.2 ± 5.4	0.026
NYHA III/IV	272 (42.5%)	189 (42.8%)	0.005	158 (39.8%)	166 (41.8%)	0.041
STS risk of mortality (%)	1.9 ± 1.2	2.1 ± 1.6	0.211	1.90 ± 1.20	1.90 ± 1.24	0.004
Diabetes	179 (28.0%)	114 (25.8%)	0.049	108 (27.2%)	99 (24.9%)	0.052
Hypertension	510 (79.7%)	318 (71.9%)	0.182	293 (73.8%)	291 (73.3%)	0.011
Peripheral vascular disease	40 (6.3%)	39 (8.8%)	0.098	26 (6.5%)	31 (7.8%)	0.049
Renal dysfunction/ insufficiency	65 (10.2%)	50 (11.3%)	0.037	48 (12.1%)	40 (10.1%)	0.064
Stroke/CVA	28 (4.4%)	16 (3.6%)	0.039	10 (2.5%)	13 (3.3%)	0.045
COPD	79 (12.3%)	48 (10.9%)	0.046	45 (11.3%)	42 (10.6%)	0.024
Left ventricular ejection fraction (%)	59.8 ± 9.0	58.6 ± 10.1	0.126	58.67 ± 9.5	59.71 ± 9.0	0.112
Coronary artery disease	288 (45.0%)	183 (41.4%)	0.073	167 (42.1%)	168 (42.3%)	0.005
Left ventricular hypertrophy	284 (44.4%)	161 (36.4%)	0.163	160 (40.3%)	146 (36.8%)	0.073
Atrial fibrillation	52 (8.1%)	59 (13.3%)	0.169	45 (11.3%)	41 (10.3%)	0.032
Isolated/mixed aortic stenosis	597 (93.3%)	425 (96.2%)	0.129	380 (95.7%)	382 (96.2%)	0.026

Table 2. Continued

	Entire cohort (n = 1082)			**Propensity-score-matched cohort (n = 794)**		
	Pledgets (n = 640)	**Non pledgets (n = 442)**	**SMD**	**Pledgets (n = 397)**	**Non pledgets (n = 397)**	**SMD**
Minimally invasive surgical approach	150 (24.3%)	70 (16.5%)	0.200	76 (19.1%)	70 (17.6%)	0.010
Concomitant procedures						
None	288 (45.0%)	242 (54.8%)	0.196	175 (44.1%)	218 (54.9%)	0.218
CABG	223 (34.8%)	128 (29.0%)	0.127	145 (36.5%)	115 (29.0%)	0.162
Ascending aortic aneurysm not requiring circulatory arrest	48 (7.5%)	35 (7.9%)	0.016	30 (7.6%)	32 (8.1%)	0.019
Other[1]	161 (25.2%)	68 (15.4%)	0.245	92 (23.2%)	58 (14.6%)	0.220
Annular calcification	516 (80.6%)	371 (83.9%)	0.16	320 (80.6%)	331 (83.4%)	0.072
Total bypass time (min)	104.2 ± 40.6	105.6 ± 41.0	0.035	101.7 ± 38.4	105.8 ± 41.2	0.103
Aortic cross-clamp time (min)	79.2 ± 31.2	79.5 ± 32.3	0.012	78.2 ± 30.0	79.9 ± 32.4	0.052
Annular diameter[2]	23.7 ± 2.05	23.7 ± 2.17	0.021	23.7 ± 2.13	23.7 ± 2.19	0.019
Valve size implanted						
17 mm	0 (0.0%)	1 (0.2%)	0.067	0 (0.0%)	0 (0.0%)	0.000
19 mm	16 (2.5%)	23 (5.2%)	0.141	8 (2.0%)	20 (5.0%)	0.164
21 mm	115 (18.0%)	88 (19.9%)	0.050	79 (19.9%)	75 (18.9%)	0.025
23 mm	226 (35.3%)	161 (36.4%)	0.023	145 (36.5%)	147 (37.0%)	0.010
25 mm	216 (33.8%)	126 (28.5%)	0.113	125 (31.5%)	114 (28.7%)	0.060
27 mm	62 (9.7%)	36 (8.1%)	0.054	38 (9.6%)	34 (8.6%)	0.035
29 mm	5 (0.8%)	7 (1.6%)	0.074	2 (0.5%)	7 (1.8%)	0.119
Mean pressure gradient (mmHg)	41.7 ± 17.0	43.3 ± 16.8	0.096	43.3 ± 16.9	43.3 ± 16.7	0.001
Effective orifice area (cm^2)	0.78 [0.36,4.67]	0.75 [0.35,3.43]	0.164	0.75 [0.36,3.44]	0.76 [0.35,3.43]	0.013
Indexed effective orifice area (cm^2/m^2)	0.39 [0.17,2.52]	0.38 [0.18,1.82]	0.131	0.38 (0.17-1.83)	0.39 (0.18-1.82)	0.013

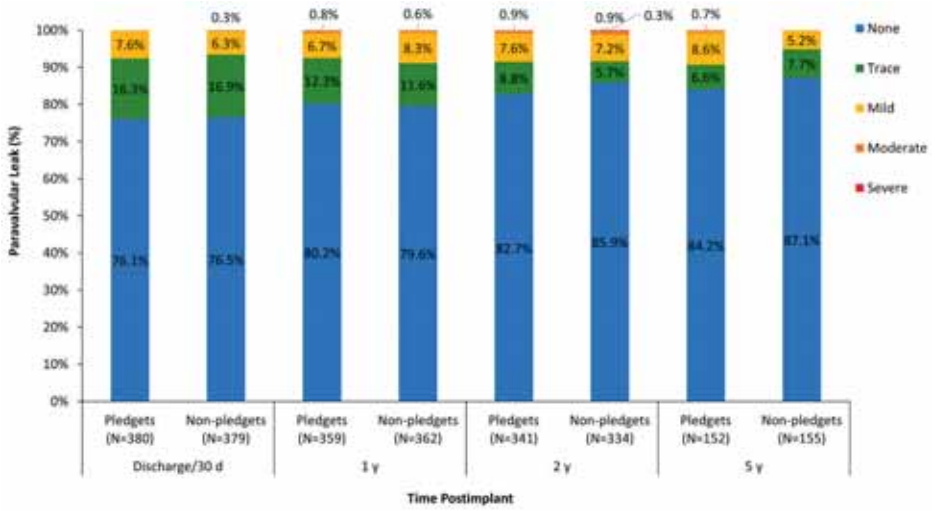
Data are either presented as mean ± standard deviation, median [interquartile range] or counts (percentages). 1 Includes implantable cardiac device, left atrial appendage closure, patent foramen ovale closure, resection of subaortic membrane not requiring myectomy, and dissection repair not requiring circulatory arrest. 2 The annual diameter was determined intraoperatively and corresponds to the size of the replica end of the valve sizer. CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons

Table 3. Clinical outcomes and hemodynamic performance at 5 years of follow-up for patients who underwent aortic valve replacement in the propensity-score-matched cohort.

	Pledgets (n = 397)	**Non pledgets (n = 397)**	**p-value[1]**
Composite endpoint (thromboembolism, endocarditis, and major PVL)	11.7% (8.7-15.7%) (n=41)	9.8% (7.1-13.4%) (n=36)	0.51
Thromboembolism	5.9% (3.9-8.9%) (n=22)	6.1% (4.1-9.3%) (n=22)	0.95
Endocarditis	6.4% (4.1-9.9%) (n=20)	4.2% (2.5-6.9%) (n=15)	0.35
Major paravalvular leak	0.3% (0.0-1.8%) (n=1)	0.0% (NA) (n=0)	0.32
All paravalvular leak	1.1% (0.4-2.8%) (n=4)	1.5% (0.5-4.0%) (n=4)	0.96
All-cause mortality	13.3% (10.0-17.6%) (n=45)	10.5% (7.7-14.2%) (n=37)	0.30
Cardiac-related mortality	6.8% (4.4-10.3%) (n=22)	4.2% (2.5-7.1%) (n=14)	0.15
Valve-related mortality	2.2% (1.1-4.4%) (n=8)	0.5% (0.1-2.1%) (n=2)	0.06
Reintervention	3.1% (1.7-5.5%) (n=11)	3.9% (2.2-6.7%) (n=13)	0.74
Explant	3.1% (1.7-5.5%) (n=11)	3.2% (1.7-5.7%) (n=11)	0.95
Permanent pacemaker implantation	5.6% (3.7-8.5%) (n=21)	6.9% (4.6-10.1%) (n=25)	0.55
Mean pressure gradient (mmHg)	12.3 ± 4.4	12.3 ± 4.0	0.93
Peak pressure gradient (mmHg)	22.0 ± 7.4	21.9 ± 7.4	0.93
EOA (cm^2)	1.35 [0.72,2.87]	1.44 [0.79,2.58]	0.045
EOAi (cm^2/m^2)	0.69 [0.38,1.31]	0.73 [0.41,1.31]	0.06
Prosthesis-patient mismatch			0.07
None	40 (31.7%)	44 (32.6%)	
Moderate	46 (36.5%)	64 (47.4%)	
Severe	40 (31.7%)	27 (20.0%)	

Clinical outcomes are reported as 5-year Kaplan-Meier event rates, including 95% confidence intervals. Hemodynamic performance is presented either as mean ± standard deviation or median [interquartile range]. 1P-value from log-rank test for all clinical outcomes and from independent samples t-test, Mann-Whitney U test, or Chi-square test for echocardiographic data. EOA, effective orifice area; EOAi, EOA indexed by body surface area; NA, not available; PVL, paravalvular leak.

Figure 3. Paravalvular leak over time according to the use of pledgets for patient who underwent aortic valve replacement in the propensity score-matched-cohort.



The frequencies of paravalvular leak severity categories at different timepoints are displayed as stacked bars.

Subanalysis: valve sizes <23 mm

The baseline and procedural characteristics of patients with implanted valve sizes below 23 mm are presented in Table S5. Pledgets were used in 131 patients, and no pledgets in 112 patients. As observed in the entire cohort, significant differences between the groups existed in baseline age, STS risk of mortality, concomitant procedures, and implanted valve size. Additionally, the aortic cross-clamp time was longer in the pledgeted group than in the non-pledgeted group (78.6 ± 29.4 vs. 69.2 ± 31.3 minutes, p = 0.017). The hemodynamic performance up to 30 days and at 5-year follow-up is demonstrated in Table 4. The mean pressure gradient up to 30 days was lower in the pledgeted group compared to the non-pledgeted group (14.9 ± 4.6 vs. 16.4 ± 5.6, p = 0.027), but this difference was absent at 5-year follow-up. All other parameters were comparable at both follow-up points.

Table 4. Hemodynamic performance at discharge up to 30 days and at 5 years of follow-up in valve sizes <23 mm for patients who underwent aortic valve replacement.

	Pledgets (n = 131)	**Non pledgets (n = 112)**	**p-value**
Mean pressure gradient (mmHg)			
Discharge up to 30 days	14.9 ± 4.6	16.4 ± 5.6	0.027
5 years	15.7 ± 5.6	15.0 ± 4.2	0.50
Peak pressure gradient (mmHg)			
Discharge up to 30 days	27.5 ± 8.7	29.8 ± 9.8	0.07

Table 4. Continued

	Pledgets (n = 131)	**Non pledgets (n = 112)**	**p-value**
5 years	27.6 ± 9.2	26.1 ± 8.0	0.38
Effective orifice area (cm^2)			
Discharge up to 30 days	1.31 [0.78,2.54]	1.29 [0.70,2.24]	0.43
5 years	1.09 [0.72,1.95]	1.10 [0.79,1.70]	0.54
Indexed effective orifice area (cm^2/m^2)			
Discharge up to 30 days	0.72 [0.40,1.33]	0.70 [0.31,1.24]	0.81
5 years	0.61 [0.43,1.05]	0.64 [0.43,1.04]	0.47
Prosthesis-patient mismatch			
Discharge up to 30 days			0.79
None	42 (35.9%)	28 (31.5%)	
Moderate	43 (36.8%)	36 (40.4%)	
Severe	32 (27.4%)	25 (28.1%)	
5 years			0.50
None	3 (7.3%)	6 (12.8%)	
Moderate	16 (39.0%)	21 (44.7%)	
Severe	22 (53.7%)	20 (42.6%)	
Paravalvular leak			
Discharge up to 30 days			0.60
None	76 (59.8%)	70 (66.0%)	
Trace	37 (29.1%)	27 (25.5%)	
Mild	14 (11.0%)	9 (8.5%)	
Moderate	0 (0.0%)	0 (0.0%)	
Severe	0 (0.0%)	0 (0.0%)	
5 years			0.33
None	41 (83.7%)	38 (79.2%)	
Trace	3 (6.1%)	7 (14.6%)	
Mild	5 (10.2%)	3 (6.3%)	
Moderate	0 (0.0%)	0 (0.0%)	
Severe	0 (0.0%)	0 (0.0%)	

Numerical data are presented as mean ± standard deviation or median [interquartile range] according to their distribution, and categorical data are summarized as counts (percentages). Data were compared using the independent samples t-test, Mann-Whitney U test, and Chi-square test/Fisher exact test, respectively.

Subanalysis: non-pledgeted sutures

Stratification of patients within the non-pledgeted group resulted in 180 patients in the mattress subgroup and 205 in the non-mattress subgroup. Their baseline characteristics are summarized in Table S6. Significant differences were observed in BMI, NYHA class III/IV, DM, hypertension, renal dysfunction/insufficiency, stroke/CVA, COPD, CAD, LVH, and concomitant procedures. The hemodynamic performance up to 30 days and at 5-year follow-up is presented in Table S7. At both timepoints, no differences related to suturing technique were found in echocardiographic variables, PPM, or PVL.

DISCUSSION

In a propensity-score-matched analysis of a large international cohort, clinical outcomes at 30 days and 5 years of follow-up were comparable between patients undergoing surgical AVR with and without pledgeted sutures.

Previous literature comparing pledgeted to non-pledgeted sutures in AVR mainly focused on hemodynamic performance (Table 1). Hence, insight into clinical outcomes is scarce. A potential disadvantage of pledgeted sutures is an increased risk of infection, pannus, or thrombus formation due to the presence of extra foreign material. A single study (7) evaluated thromboembolism rates, while endocarditis has never been studied to our knowledge. In our analysis, both adverse events rarely occurred at 30 days of follow-up and were comparable at 5 years. Thus, there was no evidence of higher rates of these events when pledgets were used.

Paravalvular leak is another important variable in the choice whether to use pledgeted sutures. Several studies have investigated this parameter but have reported conflicting results. Englberger et al. (3) found a significant reduction in PVL in the pledgeted sutures group. On the contrary, others reported no differences compared to non-pledgeted or figure-of-eight sutures (4-7). Our findings were in line with the latter studies.

Regarding other hemodynamic performance measures such as the EOA, previous results were ambiguous, too. Tabata and colleagues (4) observed a smaller EOA post-implantation in the pledgeted group that disappeared at 1 year, whereas Ugur et al. (5) described a larger EOA at that timepoint. In the current study, the EOA was equal between the groups at short-term follow-up; however, at 5 years a statistically significant difference appeared as a result of a smaller EOA in the pledgeted group. This phenomenon might be due to subvalvular obstruction caused by the pledgets and tissue (pannus) formation/ingrowth developing over time, which could lead to elevated velocities in the LVOT. Theoretically, such obstruction would be more profound in a small LVOT as pledgets have a fixed size, but in our subanalysis of valve sizes <23 mm, the EOAs were similar between the pledgeted and non-pledgeted group (Table 4). Another explanation could be related to measurement error since the smaller EOA was not reflected by the mean or peak pressure gradient. Measurement of the LVOT diameter is prone to error and has a drastic effect on the EOA value as this diameter is

squared to obtain the LVOT area for the continuity equation. The presence of pledgets might complicate the echocardiographic measurement of the LVOT diameter even more when it is examined in close proximity to the aortic annulus. As the absolute difference in EOA was less than 0.1 cm^2, the difference was absent in small valve sizes, and other hemodynamic parameters were equal between the groups, the clinical relevance of this difference in EOA is questionable. External validation of this finding and longer follow-up could provide valuable insights. A derivative of the indexed EOA is PPM. As previous PERIGON substudies challenged the clinical relevance of this concept by outlining shortcomings regarding correspondence with elevated gradient and disproportional normalization by BSA (11-13), we chose to mainly focus on primary echocardiographic parameters rather than PPM in this study.

Although similar pressure gradients at 5 years were observed, a statistically significant difference with lower values in the pledgeted group was found at 30 days, however, this dissimilarity was less than 1 mmHg. Hence, it was not considered clinically important. To further investigate differences related to suturing technique, a subanalysis was executed within the non-pledgeted group. This analysis did not show any difference between mattress and non-mattress suturing techniques.

Hemodynamic outcomes have received specific attention in smaller valve sizes. Two earlier studies reported similar hemodynamic parameters between pledgeted and non-pledgeted sutures (4, 5). Our results are in agreement with these findings.

Strengths and limitations

A major advantage of the current study was that all 1082 patients received the same bioprosthetic valve, which eliminated any bias due to the type of prosthesis. Furthermore, the prospective design with independent adverse event adjudication and core-laboratory assessment of echocardiograms enabled robust and consistent data gathering up to 5 years of follow-up. Despite these strengths, there were limitations. Even though there was apparent harmony between patient characteristics after propensity score matching, the study design could not guarantee complete comparability as adjustment was possible only for measured confounders. Specifically, we did not adjust for surgeon bias, and it is possible that surgeons who opt for one technique versus another may have differential skills, leading to an inextricable confounding effect. The 1082 AVR procedures in this analysis were performed by 132 surgeons, some of whom solely used pledgeted (54 surgeons) or non-pledgeted sutures (33 surgeons). Hence, we did not incorporate surgeon data in the propensity score matching. To achieve complete comparability, randomized treatment allocation would have been a prerequisite, which was not the case. Furthermore, no correction methods were applied to the subanalyses, in which the statistical power was also decreased due to smaller sample sizes. Therefore, these results should be interpreted in the context of these limitations. An increased length of follow-up might have revealed more profound differences in outcomes. It would be of interest to observe whether the difference in EOA will persist and eventually

lead to differences in clinical outcomes such as reintervention. Important aspects that remain unknown to the discussion of whether to use pledgeted sutures for SAVR are the feasibility of reoperations and future valve-in-valve transcatheter AVR for degenerated bioprostheses. Unfortunately, no quantitative claims can be made based on data of the current study. For future studies on this topic, these issues are highly relevant.

CONCLUSIONS

In a propensity-score-matched analysis, comprehensive clinical outcomes were comparable between patients undergoing AVR with pledgeted and non-pledgeted sutures up to 5 years of follow-up. Nevertheless, pledgets might lead to a slight reduction of the EOA in the long run, but this finding requires external validation.

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SUPPLEMENTARY FILES

Available at https://doi.org/10.1016/j.xjtc.2022.10.016.

8

THE USE OF PLEDGET-REINFORCED SUTURES DURING SURGICAL AORTIC VALVE REPLACEMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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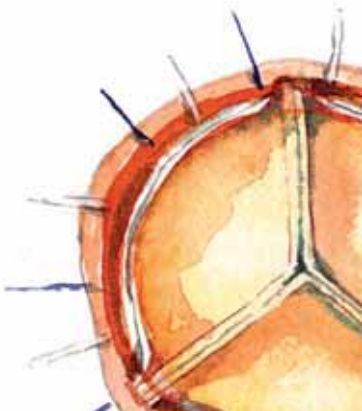
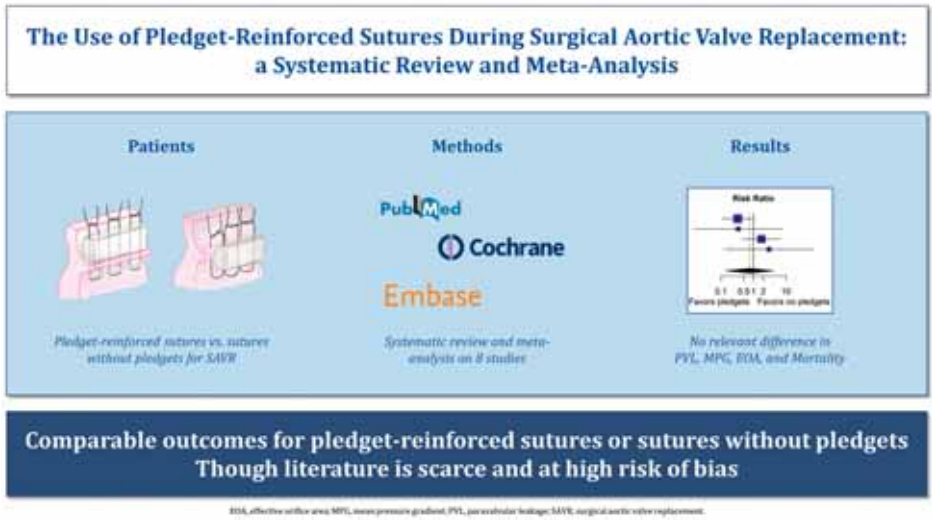
International Journal of Cardiology Heart & Vasculature 2024



GRAPHICAL ABSTRACT



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ABSTRACT

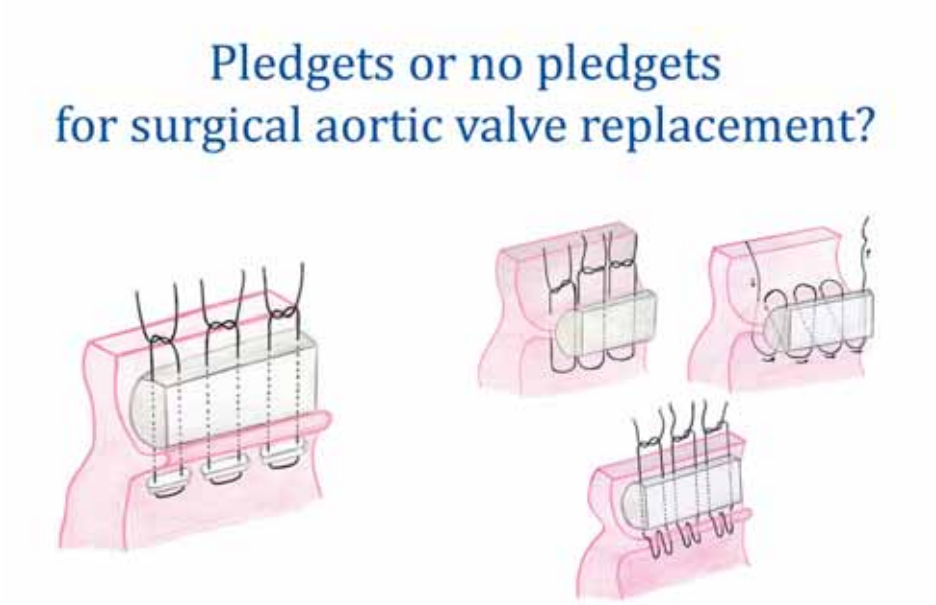
Objective: Literature presents conflicting results on the pros and cons of pledget-reinforced sutures during surgical aortic valve replacement (SAVR). We aimed to investigate the effect of pledget-reinforced sutures versus sutures without pledgets during SAVR on different outcomes in a systematic review and meta-analysis.

Methods: A literature search was performed in PubMed, Cochrane and Embase databases. Studies must include patients undergoing SAVR and must compare any pledget-reinforced with any suturing technique without pledgets. The primary outcome was paravalvular leakage (PVL), and secondary outcomes comprised thromboembolism, endocarditis, mortality, mean pressure gradient (MPG) and effective orifice area (EOA). Results were pooled using a random- and fixed-effects model as risk ratios (RRs) or mean differences (MDs) for which the no pledgets group served as reference.

Results: Nine studies, all observational, met the inclusion criteria. The risk of bias was critical in seven studies, and high and moderate in the other two. The pooled RR for moderate or greater PVL was 0.59 (95% confidence interval [CI] 0.13, 2.73). The pooled RR for mortality at 30-days was 1.02 (95% CI 0.48, 2.18) and during follow-up was 1.13 (95% CI 0.67, 2.00). For MPG and EOA at 1-year follow-up, the pooled MDs were 0.60 mmHg (95% CI -4.92, 6.11) and -0.03 cm^2 (95% CI -0.18, 0.12), respectively.

Conclusions Literature on the use of pledget-reinforced sutures during SAVR is at high risk of bias. Pooled results are inconclusive regarding superiority of either pledget-reinforced sutures or sutures without pledgets. Hence, there is no evidence to support or oppose the use of pledget-reinforced sutures.

CENTRAL PICTURE



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Central Message: Meta-analysis did not reveal differences in outcomes between suturing techniques with or without pledgets during SAVR.

Perspective Statement: Literature on the use of pledget-reinforced sutures during SAVR is scarce and at high risk of bias. Pooled results are inconclusive regarding superiority for either pledgets or no pledgets. These findings suggests that surgeons can stick to their preferred suturing technique until more conclusive evidence is available.

INTRODUCTION

More than 60 years ago the first successful surgical aortic valve replacement (SAVR) took place (2). Since then, numerous advancements have been made to improve the outcomes of individual patients. However, there is still no consensus on some aspects of this surgical procedure including whether pledget-reinforced sutures should be used to implant the prosthetic valve. Experience learns that, even within one center, it strongly depends on the training and preference of the surgeon which suturing technique is applied.

Previous studies have reported conflicting results for outcomes that could be affected by pledgets (3-8). For example, Englberger *et al.* (3) reported lower incidences of paravalvular leak (PVL) when pledgets were used while other studies found similar incidences for suturing techniques with and without pledgets (4-8). Furthermore, it is hypothesized that the use of pledgets might negatively influence the effective orifice area (EOA) as is reported by Lee *et al.* (9), although this difference in EOA is not found in other studies (5, 7, 8). Finally, the introduction of more foreign material into the left ventricle outflow tract might lead to a higher incidence of thrombo-embolic events and endocarditis. To explore the quality of the available literature and examine pooled effects, a systematic review and meta-analysis was performed. Specifically, this study aimed to investigate the effect of any pledget-reinforced suturing technique, as compared to any suturing technique without pledgets, during SAVR on different hemodynamic and clinical outcomes. The goal of this meta-analysis is to provide a clinical recommendation for or against the use of pledgets during SAVR.

METHODS

For this meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (10) and for the development of the protocol, the PRISMA guidelines for protocols (PRISMA-P) (11). The protocol was preregistered prior to the start of the study on PROSPERO with ID number 433066. The primary outcome was moderate or greater PVL post-implantation up to 30 days. Secondary outcomes, measured post-implantation up to 30 days and during mid-term follow-up, included thromboembolism, endocarditis, mortality, mean pressure gradient (MPG), and EOA.

Study selection, data extraction and risk of bias assessment

A literature search was performed in PubMed, Cochrane and Embase on June the 7th 2023. Together with a librarian a search string was developed, which is included in the supplementary files. The main components were based on the population, patients undergoing SAVR, and the intervention, pledget-reinforced sutures. Studies were selected according to the following eligibility criteria: studies must include patients undergoing SAVR and must compare any pledget-reinforced suturing technique with any suturing technique without pledgets. Observational studies and randomized controlled trials published in peer-reviewed journals were included. Systematic reviews, meta-analyses, and conference abstracts were

excluded as well as studies in any language other than English. Two researchers (TB & MC) independently performed title/abstract and full-text screening, using Rayyan software (12), as well as data extraction and risk of bias assessment on study level. Any disagreement was discussed with a third researcher (BV). Data extraction was performed using a prespecified form based on the Cochrane format. If studies included more than one treatment arm with pledget-reinforced sutures or sutures without pledgets, these were grouped to one arm with and without pledgets. If this was not possible, the largest group with pledget-reinforced sutures and the largest group with sutures without pledgets were contrasted. The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) was use (13).

Statistical analysis

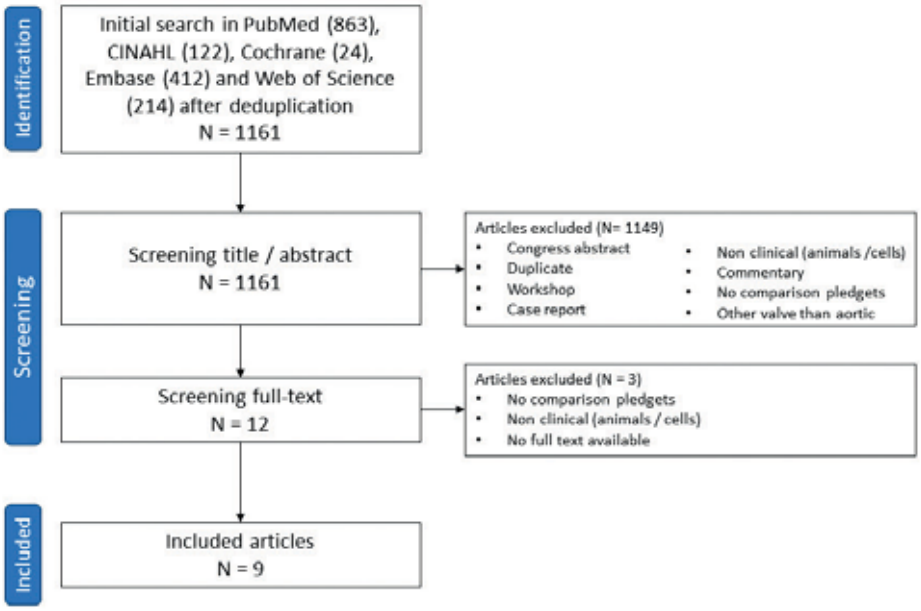
For dichotomous outcomes, risk ratios (RRs) including 95% confidence interval (CI) were extracted or calculated using the cumulative incidences per treatment group. If multiple results on the same outcome were reported, e.g., unadjusted and adjusted for potential confounders, the risk ratio after confounding adjustment was preferred. For continuous outcomes like MPG and EOA, mean differences (MDs) were pooled. Results were pooled using a Hartung-Knapp random-effects model (14) and results were presented using forest plots. As a sensitivity analysis, pooled results of the fixed-effects model were also presented. The Hartung-Knapp model was used because this model provides a realistic estimation of the uncertainty in treatment effect when only limited studies are available (14, 15). To assess heterogeneity, the I^2 was estimated and a 95% prediction interval was calculated around the pooled estimate (16). This prediction interval depicts the expected range of the true treatment effect in a new study (17). Furthermore, the potential of publication bias was evaluated using Egger's test (18) and visualized in funnel plots. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework was used for making clinical practice recommendations about the use of pledget-reinforced sutures during SAVR (19). All statistical analyses were executed using the statistical software R (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org), specifically the R packages *meta* and *robvis*. The data extraction forms, risk of bias assessments, final study data and R script are all available in the supplementary files.

RESULTS

Systematic review

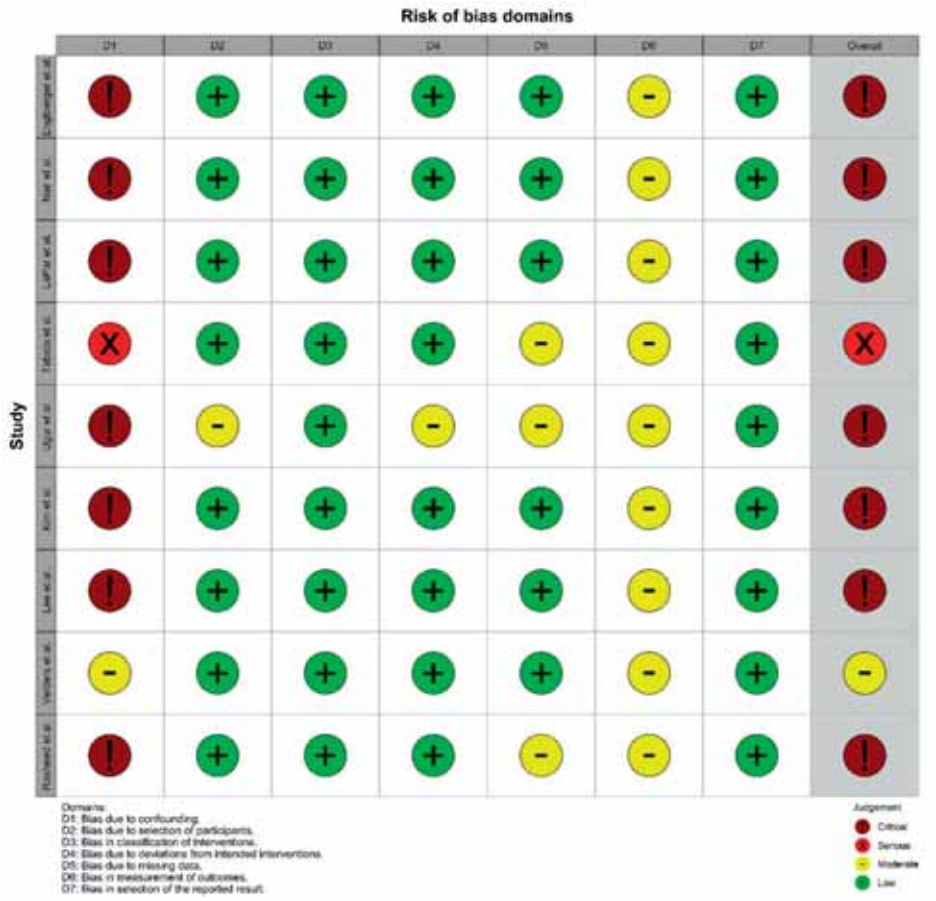
The literature search provided a total of 1161 unique studies. After title and abstract screening, 12 articles were selected for full-text reading. Three studies were excluded because these lacked a comparison of pledget-reinforced sutures and sutures without pledgets, no human subjects were involved or no full-text was available (20-22). Nine studies were eligible for analysis (3-9, 23, 24). Figure 1 illustrates the selection process through a flowchart. The selected studies were all observational studies, of which four with prospective and five with retrospective data collection. Two studies were a secondary analysis of an RCT, however, the patients in this study were not randomized to pledget-reinforced sutures (3, 23). An overview of the study characteristics, patient characteristics, and clinical outcomes is provided in Table 1 and of the risk of bias assessment in Figure 2 and 3.

Figure 1. Flowchart of the selection process of studies on the use of pledget-reinforced sutures during surgical aortic valve replacement.



A schematic presentation of the literature review executed according to the PRISMA guidelines. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Figure 2. Risk of bias assessment for studies on the use of pledget-reinforced sutures during surgical aortic valve replacement.

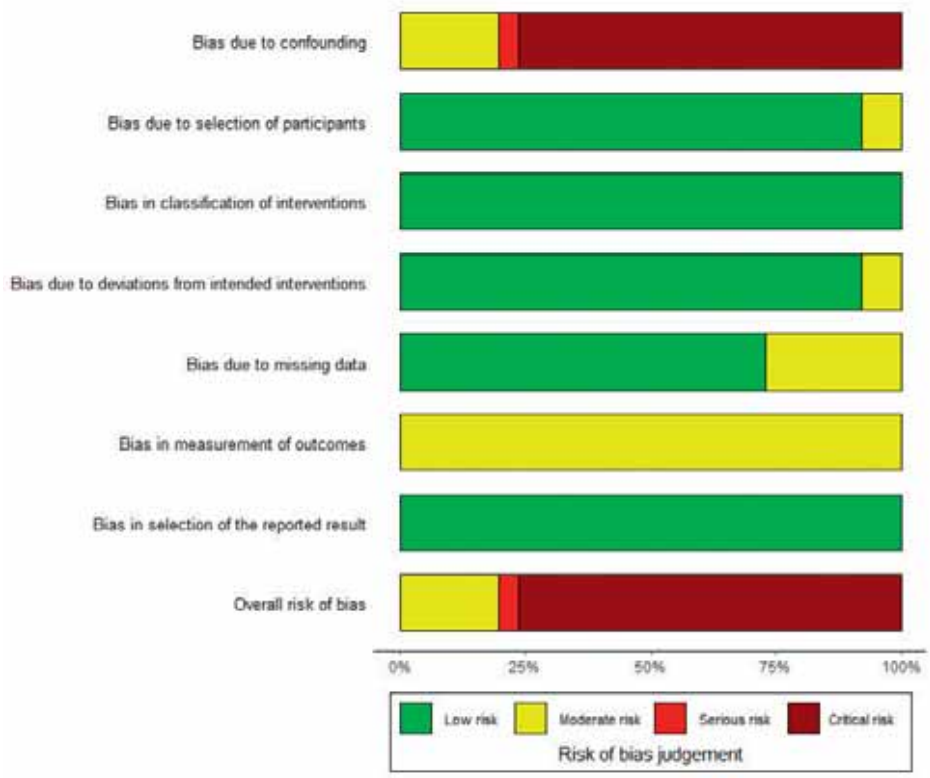


Risk of bias assessment displayed per article according to ROBINS-I. ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions.

Englberger *et al.* (3) performed a retrospective analysis of their AVERT RCT data which included both mechanical SAVR and mitral valve replacement. The analysis comprised a total of 549 aortic valve patients. Englberger *et al.* reported PVL, had a mean follow-up of 30.6 months and risk of bias was critical mainly because no adjustment for confounding was made.

Nair *et al.* (23) retrospectively analyzed data from another RCT. 126 patients received a mechanical aortic valve prosthesis. Follow-up was 10 years, and the primary endpoint was PVL and the risk of bias was critical due to the risk of bias in confounding.

Figure 3. Risk of bias assessment per domain for the included articles on the use of pledget-reinforced sutures during surgical aortic valve replacement.



Risk of bias assessment displayed per domain according to ROBINS-I. ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions.

LaPar *et al.* (4) executed a retrospective cohort study with 802 patients, which included both mechanical and biological SAVRs. The mean follow-up was 82.0 months. Outcome measures included PVL, mortality and thromboembolism and the risk of bias was critical mainly because no adjustment for confounding was made.

Tabata *et al.* (5) included 152 SAVR patients who received a 19- or 21-mm biological valve. In this retrospective cohort study, PVL and EOA were reported up to one-year post-SAVR and risk of bias was serious since multivariable outcome regression was used for a few confounding factors namely sex, body surface area, ejection fraction, annulus size and implantation of 19-mm prosthesis.

Ugur *et al.* (6) included 346 SAVR patients who were implanted with a 19- or 21-mm bioprosthesis. In this prospective cohort study, the mean follow-up was 12 months at which PVL, MPG and EOA were measured. Due to a lack of adjustment methods for confounding, risk of bias was judged as critical.

Kim *et al.* (7) performed a retrospective cohort study including 439 mechanical or biological SAVR patients. The mean follow-up was 16 months. PVL, mortality and EOA were reported, and the risk of bias was critical mainly because the study lacked adjustment methods for confounding.

Lee *et al.* (7) included 215 mechanical or biological SAVR patients in a retrospective cohort study. MPG, EAO and PVL were reported up to a median follow-up of 9.6 months and PVL up to 26 months post-operatively. Mainly because no adjustment method for confounding was used, the risk of bias was judged as critical.

Velders *et al.* (8) performed a prospective cohort study which included 1082 biological SAVR patients. The authors reported on PVL, mortality, endocarditis, thromboembolism, MPG and EOA up to 60 months post-operatively. Propensity score matching was used based on multiple confounding variables and the risk of bias was judged as moderate.

Rasheed *et al.* (24) included 629 mechanical or biological SAVR patients in a retrospective cohort study. The predicted EOA index was reported as the outcome. Risk of bias was critical mainly because no adjustment method for confounding was used.

Table 1. Overview of studies on the use of pledget-reinforced sutures during surgical aortic valve replacement.

Study characteristics									Patient characteristics		Clinical outcomes
Reference	**Year**	**Design**	**N**	**Pledgets / no pledgets**	**Suturing technique, Pledgets / no pledgets**	**FU***	**Primary indication**	**Valve type / size**	**Age (y)**	**Male (%)**	**Endpoints**
Englberger *et al.* (3)	2005	Secondary analysis of RCT	549[a]	414 / 135	P/NP: Simple interrupted, continuous, non-everted and everted mattress, and figure-of-eight	30.6	Stenosis (46.7%), Insufficiency (22.3%), Mixed (30.7%)	Mechanical; all sizes	61.3	58.9	PVL
Nair *et al.* (23)	2010	Secondary analysis of RCT	126	43 / 83	P: interrupted buttressed sutures. NP: Semi-continuous	120	Stenosis (72.2%), Insufficiency (17.8%)	Mechanical; all sizes	62.7	79.4	PVL
LaPar *et al.* (4)	2011	Retrospective cohort	802	291 / 511	P: horizontal mattress. NP: horizontal mattress	82	Stenosis (81.8%), Insufficiency (31.6%),	Mechanical and biological; all sizes	65.2	59.6	PVL, mortality and thromboembolism
Tabata *et al.* (5)	2014	Retrospective cohort	152	102 / 50	P: Non-everting mattress NP: simple interrupted	12	Stenosis (92.1%), Insufficiency unknown	Biological; 19 or 21	76.6	26.3	PVL, EOA
Ugur *et al.* (6)	2014	Prospective cohort	346	269 / 77	P: Non-everting mattress NP: Everting mattrass, simple interrupted or continuous	12	Unknown	Biological; 19 or 21	75.5	29.5	PVL, MPG, EOA
Kim *et al.* (7)	2020	Retrospective cohort	439	212 / 227	P: Interrupted mattress NP: interrupted mattress or figure-of-eight	16	Stenosis (96.8%)[b], Insufficiency (15.5%)[b]	Mechanical and biological; all sizes, sub-analysis <21	64.2	57.4	PVL, mortality, EOA
Lee *et al.* (9)	2020	Retrospective cohort	215	136 / 79	P: Non-everting mattress NP: simple interrupted	9.6	Stenosis (100%)[c]	Mechanical and biological; all sizes, sub-analysis <23	66.9	62.3	PVL, MPG, EOA
Velders *et al.* (8)	2023	Prospective cohort	1082	640 / 442	P: Non-everting or everting mattress NP: Non-everted or everted mattress, and simple interrupted	60	Isolated or mixed stenosis (94.5%)	Biological; all sizes, sub-analysis <23	70.2	75.5	PVL, mortality, endocarditis, Thromboembolism, MPG, EOA
Rasheed *et al.* (24)	2023	Retrospective cohort	629	570 / 59	P: horizontal mattress NP: figure-of-eight	NA	Stenosis (62.2%), Insufficiency (43.4%)[d]	Mechanical and biological; all sizes, sub-analysis <23	64.2	35.2	Predicted EOA index

*a. Only aortic valve replacements of the 807 aortic and mitral valve replacements. b.Only severe aortic valve stenosis or regurgitation. c. Patients were only included with severe aortic stenosis. d. Moderate to severe aortic valve regurgitation. * Follow-up length is expressed in months. EOA, effective orifice area; FU, follow-up; MPG, mean pressure gradient; NA, not available; NP, non-pledget suturing techniques; P, pledget suturing techniques; PVL, paravalvular leak; RCT, randomized controlled trial*

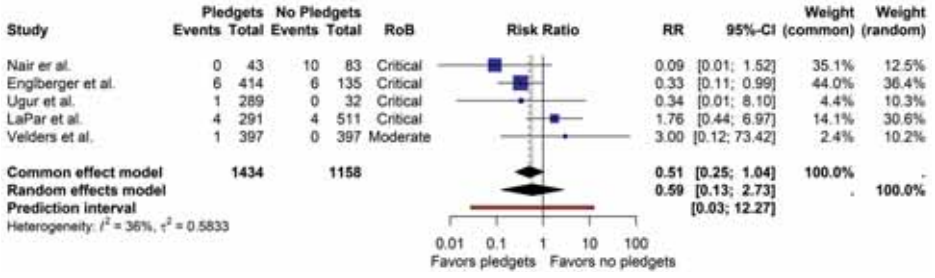
Meta-analysis

Outcomes were pooled if reported by at least three individual studies. An overview of the reported outcomes (including the time of outcome measurement) per study is provided in Supplementary Tables S1 and Table S2.

Moderate or greater PVL post-implantation was reported by five studies at mid-term follow-up. The risk ratio (RR) for pledget-reinforced sutures versus sutures without pledgets was 0.59 (95% CI 0.13, 2.73, Figure 4). The 95% prediction interval ranged from 0.03 to 12.27. Three studies reported on 30-day mortality. The pooled RR was 1.02 (95% CI 0.48, 2.18, Figure 5a). Again, three studies reported on mortality during follow-up, the pooled RR was 1.15 (95% CI 0.67, 2.09, Figure 5b). The MPG and the EOA at 1-year follow-up were reported by three and five studies, respectively. The pooled MDs were 0.60 mmHg (95% CI -4.92, 6.11, Figure 6a) for MPG and -0.03 cm^2 (95% CI -0.18, 0.12, Figure 6b) for EOA, both numerically in favor of sutures without pledgets. The 95% prediction intervals for the MD in MPG and EOA were large: -30.64 to 31.83 mmHg and -0.42 to 0.36 cm^2, respectively. The pooled results of the sensitivity analysis, in which a fixed-effects model was used, were in line with the main analysis using the random-effects model. For the outcomes reported above, funnel plots are presented in Figure S1. Besides mortality during follow-up, these indicated a low suspicion on publication bias which was also reiterated by high p-values for the Egger's test: 0.98 for PVL, 0.36 for 30-day mortality, 0.98 for mortality during follow-up, 0.64 for MPG and 0.77 for EOA, respectively.

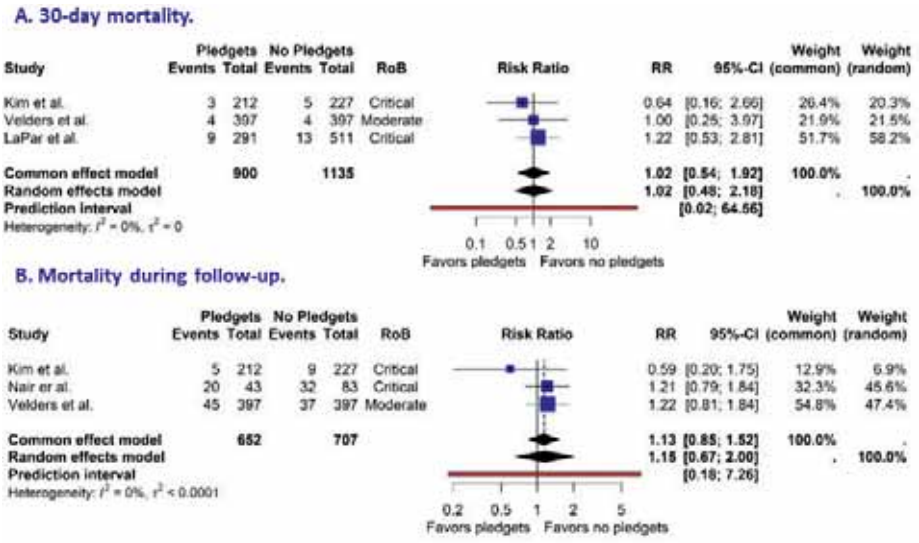
For outcomes which were reported by less than three studies the results are summarized in the supplementary files (Figure S2 - S3). The risks on moderate or greater PVL, mortality, thromboembolism and infective endocarditis at 30-days and during mid-term follow-up were low in both the pledget-reinforced sutures and sutures without pledgets group.

Figure 4. Forest plot on moderate or greater paravalvular leak at mid-term follow-up after surgical aortic valve replacement.



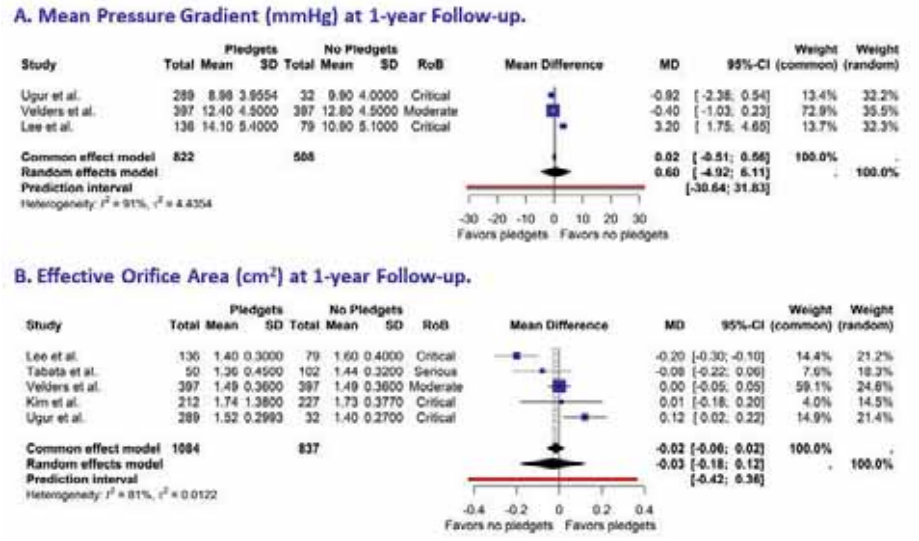
CI, confidence interval; RoB, risk of bias; RR, risk ratio.

Figure 5. Forest plot on 30-day mortality and mortality during follow-up after surgical aortic valve replacement.



CI, confidence interval; RoB, risk of bias; RR, risk ratio.

Figure 6. Forest plot on mean pressure gradient and effective orifice area at 1-year follow-up after surgical aortic valve replacement.



CI, confidence interval; SD, standard deviation; MD, mean difference; RoB, risk of bias

DISCUSSION

This systematic review and meta-analysis provides an overview of the available studies that compared pledget-reinforced sutures to sutures without pledgets for SAVR. Literature on this topic is scarce and at high risk of bias. The pooled results do not demonstrate superiority for any of the two techniques for valve-related outcomes including PVL, mortality, MPG, and EOA.

Numerically, the results for PVL were slightly in favor of pledget-reinforced sutures, while the pooled results for MPG and EOA favored suturing techniques without pledgets. However, the wide confidence and prediction intervals indicate large uncertainty because of the limited amount of included studies and the low number of clinical events. Furthermore, the pooled differences for MPG and EOA were very small (0.60 mmHg and -0.04 cm^2) and therefore unlikely to be clinically relevant. To note, the pooled estimates for MPG and EOA represent the difference at 1-year post-implantation, and these could become larger with longer follow-up. For example, Velders *et al.* (8) reported that the EOA in the pledget-reinforced suture group was about 0.10 cm^2 smaller 5 years after SAVR. This requires further confirmation in future studies.

Patients for which the choice between pledget-reinforced sutures and sutures without pledgets could be extra important are the ones with a small aortic annulus. Several included studies have separately reported their outcomes for labelled valve sizes smaller than 21-mm or 23-mm (7-9, 24) or have specifically selected 19- or 21-mm valves (5, 6). In these analyses, the EOA and MPG were slightly in favor of sutures without pledgets (5, 7, 9, 24), except for one subgroup analysis in which comparable results were found (8). Again, differences were small and unfortunately the reported information was too limited to present in a sub analysis. Current literature is insufficient to draw any firm conclusions for patients with a small aortic annulus and more studies are needed.

The focus of this review was on the difference between any pledget-reinforced suturing technique versus any technique without pledgets. However, there are multiple suturing techniques which can be used for prosthetic valve implantation. Saisho *et al.* tested different suture techniques in an ex vivo study; non-everting mattress sutures with pledgets, and single interrupted, continuous and figure-of-eight sutures without pledgets (1). Figure-of-eight sutures provided the largest EOAs. Two clinical studies included in this review specifically analyzed this suturing technique as a separate treatment group but did not find larger EOAs (7, 24). The limited amount of available data on these differences made analysis on this subject very unreliable and was therefore not performed. Furthermore, Kim *et al.* reported longer cardiopulmonary bypass and aortic cross-clamp times when these techniques were used (7). Further research on the optimal suturing technique for SAVR is of interest to optimize hemodynamic performance and to facilitate the best lifetime management.

With regard to the latter, the suturing technique during the primary SAVR procedure might influence the feasibility and outcomes of future interventions. Redo surgery might be harder when pledget-reinforced sutures have initially been used. For future valve-in-valve procedures, it is essential to create the best possible set-up during the index SAVR. If specific suturing techniques could improve the EOA of the initial surgical valve, these would be preferred to optimize the outcomes of subsequent transcatheter reinterventions.

GRADE recommendations

According to the GRADE framework, the evidence summarized in our meta-analysis is considered to have a low level of certainty (19). The magnitude of the observed effects was small, insignificant and imprecise. In addition, the included studies were at high risk of bias. There is currently no scientific argument to plead for or against the use of pledgets. These findings suggests that surgeons can stick to their preferred suturing technique until more conclusive evidence is available.

Limitations

The limitations of this systematic review and meta-analysis comprise the small number of available studies and their generally low methodological quality. Most included studies reported on few endpoints at varying follow-up times. Furthermore, the prevalence of these endpoints was also low. Moreover, in the included observational studies, the impact of the surgeon on outcomes could be an inextricable source of confounding. If experienced surgeons favor a particular suturing technique, the comparison between pledgets and no pledgets would be intertwined with a comparison in surgical experience. The condition of the native annulus could also have affected the decision to use pledgets and the outcomes after SAVR. However, most studies did not provide any information on the condition of the annulus. Lastly, limited additional details for subgroups like patients with a small annulus or for specific suturing techniques could be provided. On the contrary, this systematic review and meta-analysis generated a comprehensive overview of all available evidence on the use of pledget-reinforced sutures during SAVR. The analysis was executed conform a preregistered protocol and full access is provided to the study data and the statistical code.

CONCLUSIONS

For the choice between pledget-reinforced sutures or sutures without pledgets during SAVR, literature is scarce and at high risk of bias. Pooled results are inconclusive regarding superiority of either pledget-reinforced sutures or sutures without pledgets. There is no evidence to support or oppose the use of pledget-reinforced sutures.

Acknowledgement: we thank A. Malekzadeh, librarian of the Amsterdam University Medical Center, for his help with developing the search strategy.

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SUPPLEMENTARY FILES

Available at https://doi.org/10.1016/j.ijcha.2024.101494.

9

AORTIC ROOT REPLACEMENT WITH THE STENTLESS FREESTYLE BIOPROSTHESIS

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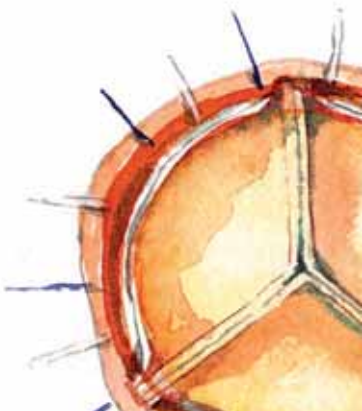
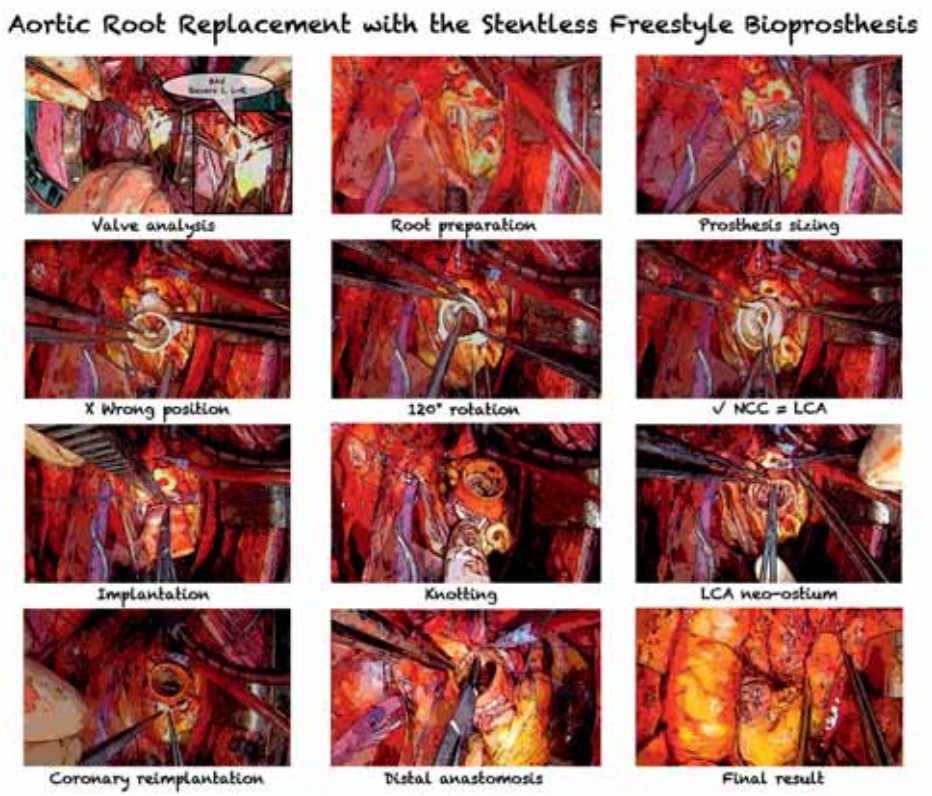
Multimedia manual of cardiothoracic surgery 2023

Video link: **https://mmcts.org/tutorial/1797**



GRAPHICAL ABSTRACT



ABSTRACT

In this video tutorial, the technical details for the implantation of the Freestyle stentless bioprosthesis are outlined based on the case of a 76-year-old male patient with symptomatic stenosis of a bicuspid aortic valve and aortic root dilatation.

INTRODUCTION

The Medtronic Freestyle stentless bioprosthesis (Medtronic Inc., Minneapolis, MN, USA) is a porcine aortic root xenograft. It can be used for various root pathologies, but due to its favourable haemodynamic performance resulting from its stentless design [1,2], it is also a useful prosthesis for the small aortic annulus. Its flexible sewing ring allows for a more versatile implantation compared with composite valved grafts, especially in the setting of infective endocarditis or reoperations. Several follow-up studies of patients with this prosthesis have demonstrated mid- and long-term survival rates that were largely comparable to those of the general population [1,2]. In our institution, we have over 20 years of experience with the Freestyle prosthesis [3]. This video tutorial provides surgical details on the implantation technique for this prosthesis.

Patient Presentation

A 76-year-old male patient with a bicuspid aortic valve was referred to our clinic with symptomatic aortic stenosis and a dilated aortic root. The patient experienced symptoms during minimal exercise. Apart from a single transient ischaemic attack, his medical history contained no relevant cardiovascular diseases. Transthoracic echocardiography showed a heavily calcified aortic valve. Computed tomography revealed a dilated aortic root with a diameter of approximately 48 mm. A coronary angiogram confirmed that there was no coronary artery disease. After shared decision making, the patient opted for a bioprosthesis. Hence, he was scheduled for aortic root replacement with the Freestyle stentless bioprosthesis.

Surgical Technique & Videos

1 - Patient presentation

The preoperative echocardiographic assessment revealed a heavily calcified, stenotic aortic valve. The mean pressure gradient was 40 mmHg, the aortic valve area index was 0.46 cm^2/m^2 and the Doppler velocity index was 0.20. Furthermore, a trace of aortic regurgitation was present. Computed tomography showed a dilated aortic root with a diameter of approximately 48 mm and an elongated ascending aorta.

2 - Exposure and cannulation

After a median sternotomy, the distal ascending aorta was cannulated, and venous drainage was achieved through a two-stage cannula in the right atrium. A left vent was inserted through the upper right pulmonary vein. Finally, the aorta was cross-clamped, and warm blood cardioplegia was administered and repeated every 15–20 minutes.

3 - Aortic root preparation

The aorta was transected just a few centimeters above the sinotubular junction, and the dilated part was removed. To improve exposure, traction sutures were placed in the commissures. The native sinuses were resected, and the coronary arteries were mobilized.

4 - Excision native aortic valve and decalcification

The aortic valve was bicuspid with a raphe between the left and right coronary cusps (Sievers 1, L-R). The valve was excised, and extensive decalcification was performed. Because severe calcifications were also present at the level of the interventricular septum, a bovine pericardial patch was used to reconstruct the annulus at that location. The appropriate valve size was determined to be 29 mm using the manufacturer's sizer.

5 - Freestyle positioning

As can be inferred from the video, the distance between the left and right coronary buttons of the porcine prosthesis did not match the distance between the human ostiae. For that reason, the Freestyle prosthesis was rotated 120 degrees clockwise. In this situation, the left coronary button of the prosthesis corresponded to the right coronary ostium of the patient, whereas the non-coronary cusp of the prosthesis matched the left coronary ostium of the patient.

6 – Implanting the Freestyle prosthesis

The prosthesis can be implanted using a single interrupted or a continuous suturing technique. We demonstrate the continuous suturing technique. It is crucial to implant the Freestyle prosthesis in a flat circular plane; the suture line should not follow the crown-like shape of the native annulus. Three 4-0 polypropylene sutures were placed under the commissures at the height of the nadirs. The manufacturer's sizer was helpful in determining the right distance between the sutures. Using the double green lines on the sewing cuff as a reference, the prosthesis was positioned correctly. After the continuous suture line was completed, the sutures were tightened with a nerve hook before they were tied.

7 – Reimplanting the coronary arteries

A 5-0 polypropylene suture was used to assure total occlusion of the right coronary ostium of the Freestyle prosthesis. Optimal positioning of the coronary buttons is important. When dissecting, coronary buttons should not be mobilized too extensively to maintain an anatomical position. Furthermore, the native ostia of the coronary arteries should not be trimmed too much to enhance the ease of potential reoperations in the future. In the non-coronary sinus of the prosthesis, a neo-ostium was created using a 6-mm punch device. Subsequently, the left coronary artery was reimplanted using a 5-0 running polypropylene suture. One should keep in mind that the tissue of the porcine prosthesis is different from that of the vascular graft that is used during the Bentall procedure. Therefore, more gentle traction on the sutures is required. The right coronary artery button should be positioned under a little traction in the cranial direction to avoid kinking after filling the right ventricle. The optimal position of the button does not always correspond with the button of the prosthesis. Here, a neo-ostium was created just above the native ostium of the prosthesis.

8 - Distal anastomosis

The prosthesis was attached to the ascending aorta without the need for a vascular interposition graft. The distal anastomosis was made with a 4-0 polypropylene suture.

9 - Final result
After de-airing, the aortic cross-clamp was removed while we manually compressed the right coronary artery to prevent any remaining air from entering. Satisfactory performance of the prosthesis was observed on transoesophageal echocardiography. After inspection of all the anastomoses, the chest was closed in a standard fashion.

OUTCOME & DISCUSSION

Outcome
The patient was haemodynamically stable after surgery, and the postoperative course was uneventful. The patient was discharged home on postoperative day 5 after transthoracic echocardiography confirmed good prosthetic performance. The mean and the peak pressure gradients were 5 mmHg and 10 mmHg, respectively. Because the patient was already taking clopidogrel, no additional thromboprophylaxis was prescribed. Normally, we prescribe aspirin for 3 months.

Discussion
As mentioned in the introduction, good clinical and haemodynamic results have been reported for patients treated with the Freestyle stentless bioprosthesis [1-3]. The main reason for reintervention after replacement of the aortic root with this prosthesis is structural valve deterioration, especially in younger patients, followed by endocarditis and non-structural valve deterioration [4]. Apart from root aneurysms, other primary indications for the use of this prosthesis include infective (native and prosthetic valve) endocarditis, type-A aortic dissection or aortic valve replacement in small aortic annuli [2,5]. For the latter, stentless valves may allow superior haemodynamic performance compared to stented valves [1,2], but their use should be weighed against the harm of more extensive surgery.

Aortic root replacement with the Freestyle stentless bioprosthesis is a valuable option for many different pathologies. This video tutorial provides a step-by-step approach outlining essential surgical details for the implantation of this prosthesis.

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10

PERIOPERATIVE CARE DIFFERENCES OF SURGICAL AORTIC VALVE REPLACEMENT BETWEEN NORTH AMERICA AND EUROPE

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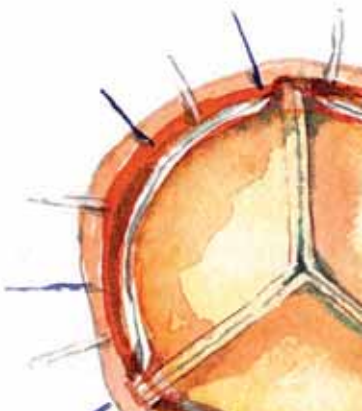
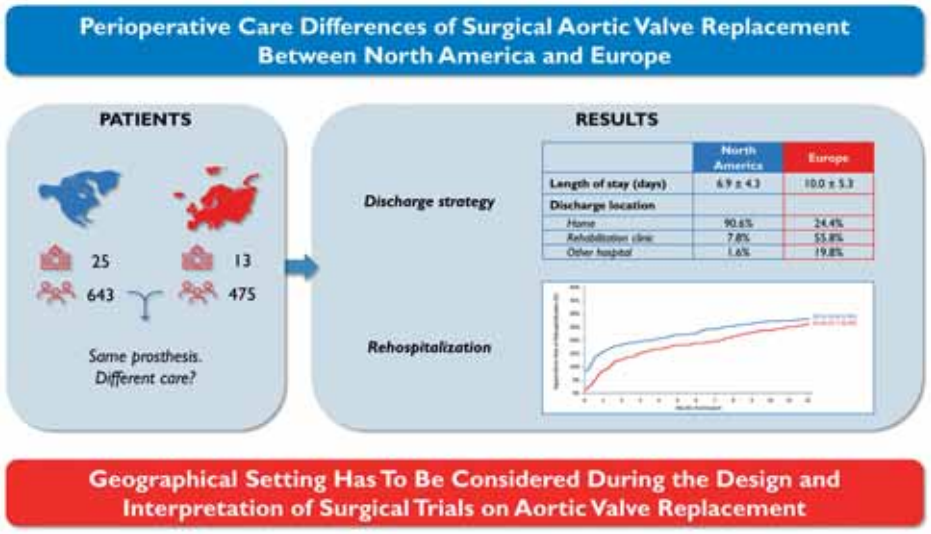
Heart 2023



GRAPHICAL ABSTRACT



ABSTRACT

Objective: To describe differences between North America and Europe in the perioperative management of patients undergoing surgical aortic valve replacement (SAVR).

Methods: Patients with moderate or greater aortic stenosis or regurgitation requiring SAVR were enrolled in a prospective observational cohort evaluating the safety and efficacy of a new stented bioprosthesis at 25 centers in North America (Canada and the United States) and 13 centers in Europe (Germany, the Netherlands, France, the United Kingdom, Switzerland, and Italy). While all patients underwent implantation with the same bioprosthetic model, perioperative management was left to the disvcretion of participating centers. Perioperative care was described in detail including outcomes up to 1-year follow-up.

Results: Among 1118 patients, 643 (58%) were implanted in North America, and 475 (42%) were implanted in Europe. Patients in Europe were older, had a lower body mass index, less bicuspid disease, and worse degree of aortic stenosis at baseline. In Europe, anticoagulant therapy at discharge was more aggressive, whereas length of stay was longer and discharges directly to home were less common. Rehospitalization risk was lower in Europe at 30 days (8.5% vs. 15.9%) but converged at 1-year follow-up (26.5% vs. 28.1%). Within continents, there were major differences between individual countries concerning perioperative management.

Conclusion: Contemporary patients receiving SAVR in North America and Europe were different in baseline characteristics, procedural techniques, antithrombotic regime, and discharge management. Furthermore, rehospitalization differed largely between continents and countries. Hence, geographical setting must be considered during design and interpretation of trials on SAVR.

KEY MESSAGE

What is already known on this topic: North America and Europe have separate guidelines for the perioperative management of patients requiring surgical aortic valve replacement, but the extent of practical differences between these continents is unknown.

What this study adds: This study provides a comprehensive overview of regional differences in perioperative care for these patients.

How this study might affect research, practice or policy: This study outlined that perioperative care differed to a great extent in terms of patient selection, procedural techniques, antithrombotic regime, and discharge management between North America and Europe. These differences must be considered by regional policy makers, especially European guideline committees.

INTRODUCTION

North America and Europe have separate guidelines for the perioperative management of patients requiring surgical aortic valve replacement (SAVR) (1, 2), but the extent of clinical care differences between these continents is unknown. For example, differences in procedural characteristics or antithrombotic regimen affect treatment outcomes; hence, the results of trials executed on different continents could inherently be influenced. As major randomized controlled trials are primarily enrolled in the United States of America (USA) (3, 4), intercontinental differences in perioperative management might challenge the generalizability of results across different regions.

In a large prospective, nonrandomized study evaluating the safety and efficacy of a new stented bioprosthesis, patients were enrolled at 38 centers in North America and Europe. All patients underwent SAVR with the same stented aortic bioprosthesis, while perioperative management was left to the discretion of the participating centers. Our aim was to describe the regional perioperative care in detail to examine comparability and subsequent generalizability of outcomes.

METHODS

The PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial of the Avalus valve (Medtronic, Minneapolis, Minnesota, USA; www.clinicaltrials.gov, NCT02088554) is a single-armed follow-up study executed at 25 centers in North America (Canada and United States) and 13 centers in Europe (Germany, Netherlands, France, United Kingdom, Switzerland, and Italy). In this trial, clinical and hemodynamic outcomes were investigated in patients receiving the Avalus bioprosthesis, a stented bovine pericardial aortic valve. Patients were enrolled between 2014 and 2017 for all valve sizes. Enrollment was reopened in 2019 for size 29 mm and continues through early 2023. Previously, a detailed description of the study design was provided (5, 6). In brief, symptomatic patients with a clinical indication for AVR due to either moderate or severe aortic stenosis (AS) or severe chronic regurgitation were eligible. Several concomitant procedures were allowed, such as coronary artery bypass grafting (CABG). At each center, an ethics committee or institutional review board approved the study (see supplementary files of Klautz et al. (7) for approval number and date for each participating center), and all patients gave written informed consent. An independent clinical events committee was constituted to adjudicate all deaths and valve-related adverse events, while an independent data and safety monitoring board provided study surveillance (Baim Institute for Clinical Research, Boston, Massachusetts, USA). Furthermore, a core laboratory (MedStar, Washington, DC, USA) evaluated all echocardiographic assessments.

Our primary objective was to describe clinical care differences between North America and Europe. Moreover, a per-country subanalysis was performed.

Comprehensive baseline and procedural characteristics were outlined to provide a detailed overview of practical differences. In addition, the antithrombotic regimens and discharge strategies were investigated. Lastly, early clinical endpoints at 30-day and 1-year follow-up were demonstrated. These endpoints included all-cause rehospitalization, all-cause mortality, cardiac mortality, valve-related mortality, thromboembolism, hemorrhage, paravalvular leak, and reintervention.

Statistical analysis

Numerical data were expressed as mean ± standard deviation or median [interquartile range] and compared with the independent samples t-test or Mann-Whitney U test. Categorical data were summarized as counts (frequencies) and compared with the Chi-square/Fisher's exact test. Early clinical event rates up to 1-year of follow-up, including their 95% confidence intervals (CIs), were estimated using the Kaplan-Meier method. Follow-up for this analysis started at the time of surgery and continued until death, withdrawal, or one year after surgery, whichever came first. Clinical outcomes were described but not compared, as the aim of this study was exploring clinical care differences rather than confirming superiority of one continent. At 30-day and 1-year follow-up, data were complete for 99.6% and 93.3%, respectively. A complete case analysis was executed. Statistical tests were executed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). All tests were two-tailed, and a p-value below 0.05 was considered statistically significant. Patients were not involved in the design or analysis of the study. The data underlying this article were provided by the sponsor and will not be shared with third parties for purposes of reproducing the results.

RESULTS

Out of a total of 1118 implanted patients, 643 (58%) were implanted in North America, and 475 (42%) in Europe. 375 patients were implanted in the USA, and 268 in Canada. In Europe, the majority of patients were enrolled in Germany (n=213), followed by the Netherlands (n=114), France (n=86), the United Kingdom (n=45), Switzerland (n=12), and Italy (n=5).

Per continent analysis

Patients who underwent SAVR in North America had on average lower age, higher body surface area (BSA), and higher body mass index (BMI [Table 1]). The STS risk of mortality was also significantly lower. North American patients had more dyslipidemia but less peripheral vascular disease, chronic obstructive pulmonary disease (COPD), congestive heart failure, and left ventricular hypertrophy than European patients. On the other hand, bicuspid aortic valve was more frequent in North America. The primary indication for intervention was significantly different between the continents. Lastly, the mean aortic pressure gradient was lower, and the effective orifice area larger, in North America.

Table 1. Baseline characteristics of patients undergoing surgical aortic valve replacement in North America and Europe.

	North America (n = 643)	**Europe (n = 475)**	**p-value**
Age (years)	68.6 ± 9.7	72.3 ± 7.4	<0.001
Male	494 (76.8%)	345 (72.6%)	0.11
Body surface area (m^2)	2.0 ± 0.2	1.9 ± 0.2	<0.001
Body mass index (kg/m^2)	30.2 ± 5.9	28.3 ± 4.5	<0.001
NYHA class III/IV	276 (42.9%)	196 (41.3%)	0.58
STS Risk of Mortality (%)	1.8 ± 1.2	2.2 ± 1.5	<0.001
Diabetes Mellitus	177 (27.5%)	121 (25.5%)	0.44
Hypertension	489 (76.0%)	363 (76.4%)	0.89
Dyslipidemia	453 (70.5%)	237 (49.9%)	<0.001
Peripheral Vascular Disease	38 (5.9%)	43 (9.1%)	0.045
Renal dysfunction/Insufficiency	59 (9.2%)	60 (12.6%)	0.06
Stroke/CVA	27 (4.2%)	18 (3.8%)	0.73
TIA	31 (4.8%)	29 (6.1%)	0.35
COPD	60 (9.3%)	70 (14.7%)	0.005
Congestive heart failure	102 (15.9%)	120 (25.3%)	<0.001
Coronary artery disease	283 (44.0%)	203 (42.7%)	0.67
Myocardial infarction	58 (9.0%)	41 (8.6%)	0.82
Left ventricular hypertrophy	158 (24.6%)	300 (63.2%)	<0.001
Atrial fibrillation	64 (10.0%)	53 (11.2%)	0.52
Liver disease	15 (2.3%)	9 (1.9%)	0.62
Bicuspid aortic valve	256 (39.8%)	73 (15.4%)	<0.001
Aortic aneurysm	65 (10.1%)	33 (6.9%)	0.06
Primary indication			<0.001
Aortic stenosis	540 (84.0%)	402 (84.6%)	
Aortic regurgitation	49 (7.6%)	15 (3.2%)	
Mixed	49 (7.6%)	57 (12.0%)	
Failed prosthesis	5 (0.8%)	1 (0.2%)	
Smoking	307 (47.7%)	231 (48.6%)	0.77
Substance abuse (drug or alcohol)	17 (2.6%)	6 (1.3%)	0.11
Mean pressure gradient (mm Hg)	40.4 ± 17.9	44.4 ± 15.7	<0.001
Effective orifice area (cm^2)	0.80 [0.65;1.00]	0.74 [0.62;0.89]	<0.001

Data are either presented as mean ± standard deviation, median [interquartile range], or counts (percentages), and compared with the independent samples t-test, Mann-Whitney U test, or Chi-square/Fisher's exact test, respectively. COPD; Chronic obstructive pulmonary disease, CVA; Cerebrovascular accident, NYHA; New York Heart Association, STS; Society of Thoracic Surgeons, TIA; Transient ischemic attack.

The surgical approach was different with a high percentage of conventional median sternotomy in North America (Table 2). The more popular minimally invasive strategy of choice was a hemisternotomy in Europe but a right anterior thoracotomy in North America. Non-everted mattress sutures and pledget use were common in North America, while simple interrupted sutures were more popular in Europe. Concomitant procedures were comparable between continents. While bypass time was also similar, aortic cross-clamp time was somewhat higher in North America.

Table 2. Procedural characteristics of patients undergoing surgical aortic valve replacement in North America and Europe.

	North America (n = 643)	**Europe (n = 475)**	**p-value**
Surgical approach <0.001			
Median sternotomy	547 (85.1%)	343 (72.2%)	
Hemisternotomy	37 (5.8%)	108 (22.7%)	
Right anterior thoracotomy	52 (8.1%)	17 (3.6%)	
Other	7 (1.1%)	7 (1.5%)	
Suturing technique valve implantation			
Simple interrupted	61 (9.5%)	262 (55.2%)	<0.001
Continuous	2 (0.3%)	39 (8.2%)	<0.001
Pledgets	441 (68.6%)	217 (45.7%)	<0.001
Everted mattress	40 (6.2%)	24 (5.1%)	0.41
Non-everted mattress	536 (83.4%)	146 (30.7%)	<0.001
Figure-of-eight	3 (0.5%)	0 (0.0%)	0.27
Cor-knot	144 (22.4%)	24 (5.1%)	<0.001
Other	14 (2.2%)	9 (1.9%)	0.74
Number of sutures	14.3 ± 3.0	15.8 ± 7.9	0.015
Implanted valve size			0.28
17 mm	0 (0.0%)	1 (0.2%)	
19 mm	26 (4.0%)	16 (3.4%)	
21 mm	124 (19.3%)	87 (18.3%)	
23 mm	212 (33.0%)	189 (39.8%)	
25 mm	211 (32.8%)	139 (29.3%)	
27 mm	60 (9.3%)	41 (8.6%)	
29 mm	10 (1.6%)	2 (0.4%)	
Annular enlargement	16 (3.8%)	11 (6.1%)	0.22
Nicks procedure	11 (2.6%)	8 (4.4%)	0.25

Table 2. Continued

	North America (n = 643)	Europe (n = 475)	p-value
Konno procedure	0 (0.0%)	0 (0.0%)	NA
Other	5 (1.2%)	3 (1.7%)	0.70
Aortic Root/STJ enlargement	68 (16.2%)	14 (7.7%)	0.005
Patch closure	39 (9.3%)	13 (7.1%)	0.38
Aortic root replacement	3 (0.7%)	0 (0.0%)	0.56
Other	27 (6.4%)	1 (0.5%)	<0.001
Concomitant procedures			
None	305 (47.4%)	246 (51.8%)	0.15
CABG	216 (33.6%)	146 (30.7%)	0.31
Implantable cardiac device (pacemaker, ICD, CRT, etc.)	0 (0.0%)	1 (0.2%)	0.42
LAA Closure	53 (8.2%)	34 (7.2%)	0.50
PFO Closure	11 (1.7%)	2 (0.4%)	0.05
Resection of Sub-aortic Membrane not Requiring Myectomy	3 (0.5%)	18 (3.8%)	<0.001
Ascending Aortic Aneurysm not Requiring Circulatory Arrest	58 (9.0%)	28 (5.9%)	0.05
Dissection Repair not Requiring Circulatory Arrest	0 (0.0%)	1 (0.2%)	0.42
Other	96 (14.9%)	63 (13.3%)	0.43
Total bypass time (min)	105.8 ± 40.7	104.0 ± 41.7	0.48
Total aortic cross clamp time (min)	81.6 ± 32.0	76.6 ± 30.8	0.010

Data are either presented as mean ± standard deviation, median [interquartile range], or counts (percentages), and compared with the independent samples t-test, Mann-Whitney U test, or Chi-square/Fisher's exact test, respectively. CABG; Coronary artery bypass grafting, CRT; Cardiac resynchronization therapy, ICD; Implantable cardioverter-defibrillator, LAA; Left atrial appendage, NA; Not available, PFO; Patent foramen ovale, STJ; Sinotubular junction.

In North America, more patients received aspirin or other antiplatelet monotherapy (Figure 1). In Europe, oral anticoagulant (OAC) use was more common, both alone and in combination with aspirin and/or and "other" antiplatelet drug. The average length of hospital stay was shorter in North America (6.9 days versus 10.0 days in Europe [Table 3]). In addition, more than 90% of the North American patients went home directly after their initial hospital stay. In Europe, despite their longer stay, most patients were discharged to a rehabilitation clinic (55.8%) or other hospital (19.8%). All-cause rehospitalization risk was higher in North America at 30-days (15.9%, 95% CI 13.3-18.9% vs. Europe 8.5%, 95% CI 6.3-11.4%); however, the risks became more comparable between continents throughout 1-year follow-up (Figure 2). At 30-day and 1-year follow-up, thromboembolism risks were comparable, while all and major hemorrhage risks were different between the continents (Table 4).

Figure 1. Antithrombotic medication at discharge in North America and Europe for patients who underwent surgical aortic valve replacement.

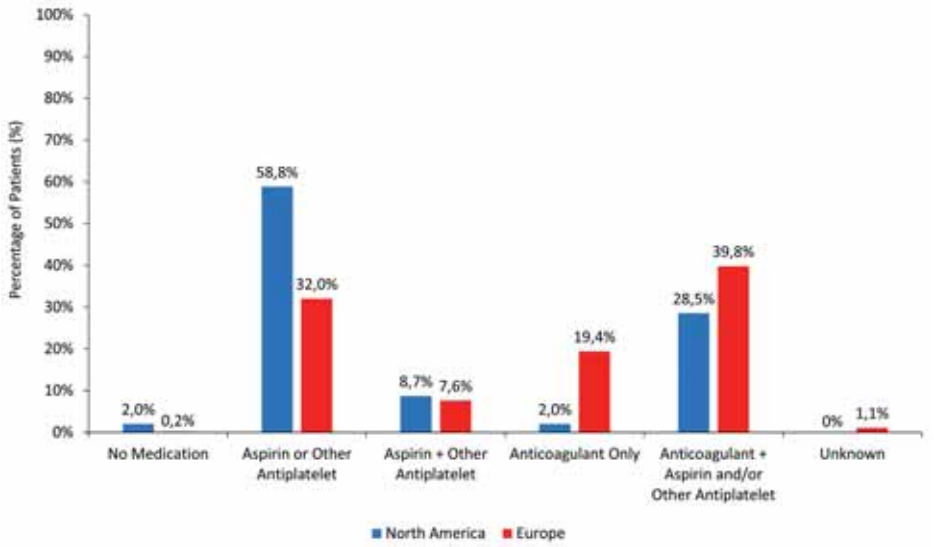


Table 3. Discharge data per continent and per country for patients who underwent surgical aortic valve replacement.

	Per-continent		**Per-country**							
	North America (n = 643)	**Europe (n = 475)**	**USA (n=375)**	**Canada (n=268)**	**Germany (n=213)**	**Netherlands (n=114)**	**France (n=86)**	**UK (n=45)**	**Switzerland (n=12)**	**Italy (n=5)**
Length of stay (days)	6.9 ± 4.3	10.0 ± 5.3	6.8 ± 4.8	7.1 ± 3.5	11.6 ± 5.1	6.8 ± 4.3	11.2 ± 4.5	9.3 ± 6.1	9.3 ± 4.4	5.2 ± 0.8
Discharge location										
Home	568 (90.6%)	110 (24.4%)	328 (91.1%)	240 (89.9%)	20 (10.2%)	47 (42.3%)	1 (1.2%)	41 (93.2%)	0 (0.0%)	1 (20.0%)
Rehabilitation clinic	49 (7.8%)	251 (55.8%)	31 (8.6%)	18 (6.7%)	158 (80.2%)	0 (0.0%)	76 (93.8%)	1 (2.3%)	12 (100.0%)	4 (80.0%)
Other hospital	10 (1.6%)	89 (19.8%)	1 (0.3%)	9 (3.4%)	19 (9.6%)	64 (57.7%)	4 (4.9%)	2 (4.5%)	0 (0.0%)	0 (0.0%)

Data are either presented as mean ± standard deviation, or counts (percentages). UK; United Kingdom, USA; United States of America.

Table 4. Thirty-day and 1-year outcomes for patients who underwent surgical aortic valve replacement in North America and Europe.

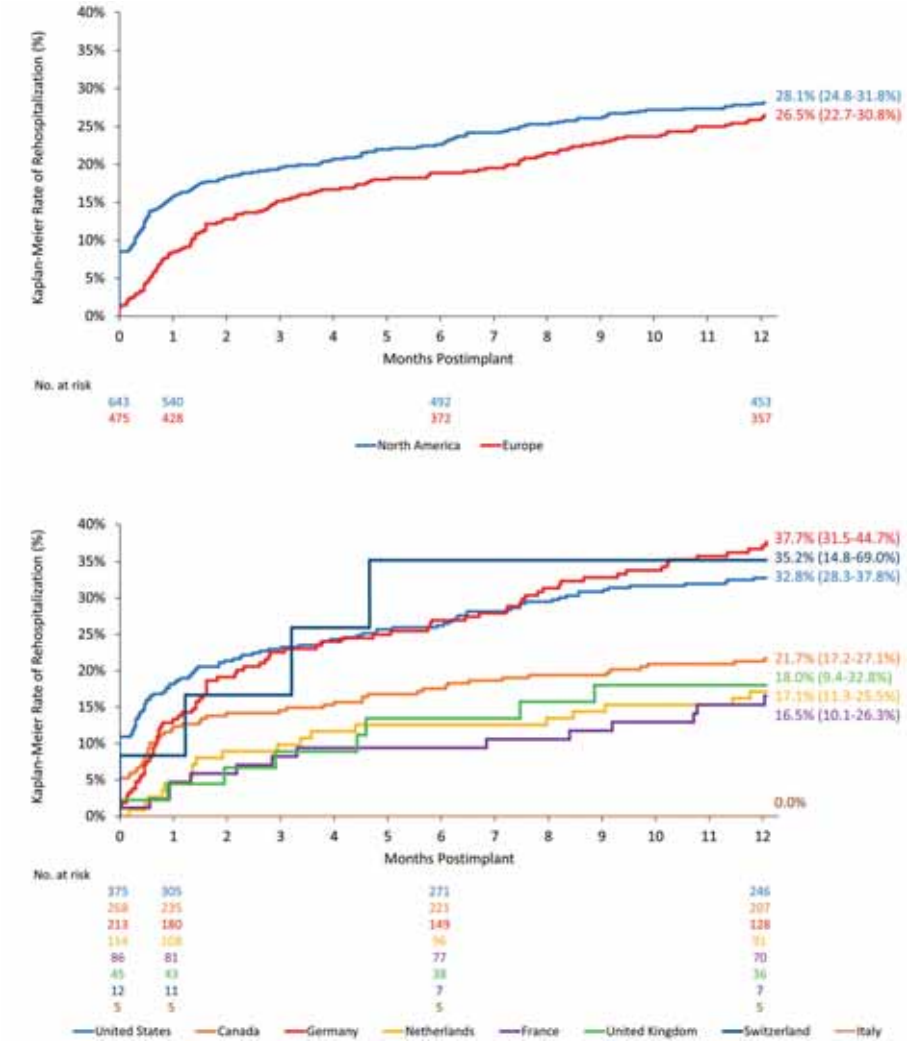
	30-day		*1-year*	
	North America (n = 643)	**Europe (n = 475)**	**North America (n = 643)**	**Europe (n = 475)**
All-cause mortality	0.3% (0.1-1.2%)	1.7% (0.8-3.3%)	2.4% (1.4-3.9%)	4.0% (2.6-6.3%)
Cardiac mortality	0.3% (0.1-1.2%)	0.8% (0.3-2.2%)	0.9% (0.4-2.1%)	2.6% (1.5-4.5%)
Valve-related mortality	0.0% (NA)	0.0% (NA)	0.2% (0.0-1.1%)	0.4% (0.1-1.8%)
Thromboembolism	1.4% (0.7-2.7%)	1.3% (0.6-2.8%)	2.5% (1.5-4.1%)	3.0% (1.8-5.1%)
All hemorrhage*	0.0% (NA)	0.0% (NA)	4.7% (3.3-6.7%)	5.9% (4.1-8.5%)
Major hemorrhage*	2.0% (1.2-3.5%)	0.9% (0.3-2.3%)	4.1% (2.8-6.0%)	2.6% (1.5-4.6%)
All paravalvular leak	1.7% (1.0-3.1%)	0.0% (NA)	1.0% (0.4-2.1%)	0.0% (NA)
Major paravalvular leak	0.3% (0.1-1.2%)	0.0% (NA)	0.3% (0.1-1.3%)	0.0% (NA)
Reintervention	0.3% (0.1-1.2%)	0.4% (0.1-1.7%)	0.8% (0.3-1.9%)	1.1% (0.5-2.6%)

Per country analysis

Patient age in France and the UK was relatively high (Table S1 in the supplementary files). In accordance, the STS risk of mortality score was higher in these countries. In Table S2, the procedural characteristics per country are shown. A surgical approach via hemisternotomy was most commonly used in Germany, while a right anterior thoracotomy was most frequently used in the UK. Within Europe, pledget-reinforced sutures were utilized markedly more often in Germany (87.3%) and in Switzerland (83.3%) compared to the other European countries (13.2% at most). In the USA, application of the Cor-knot (LSI Solutions, Victor, New York, USA), an automated suture fastener, was popular. In Germany, annular enlargement was performed remarkably more in contrast to all other countries, while in Canada 27.5% of patients underwent an aortic root enlargement.

In France, the antithrombotic regimen was most liberal with almost 70% of patients receiving an OAC plus aspirin and/or other antiplatelet therapy (Figure S1). The length of stay per country ranged from a mean of 5 to 12 days (Table 3). In most European countries, the majority of patients were discharged to a rehabilitation clinic; however, in the Netherlands most patients were transferred to another hospital after their initial stay, and most patients in UK were discharged to home. Rehospitalization per country varied widely at both 30-day (Table S3) and 1-year follow-up (Figure 2). Moreover, thromboembolism risks at 30-day and 1-year follow-up differed between the countries with the highest occurrence in the UK (Table S3). The cumulative incidence of all anticoagulant-related hemorrhage was highest in Germany (8.8%, 95% CI 5.7-13.7%) at 1 year, while the major hemorrhage risk was highest in the USA (5.4%, 95% CI 3.5-8.3%).

Figure 2. Kaplan-Meier analysis for rehospitalization up to 1-year follow-up per continent and per country for patients who underwent surgical aortic valve replacement.



The upper panel represents the per-continent analysis, while the lower panel represents the per-country analysis.

DISCUSSION

In a large observational trial executed at 38 centers across North America and Europe, continental and national differences were analyzed. This is the first study that investigated perioperative care for SAVR patients and found differences in patient selection, procedural characteristics, and discharge strategy between continents and countries. As these differences affect trial outcomes, they potentially diminish generalizability of surgical trials performed exclusively or predominantly in a specific region. This form of bias needs to be considered in the interpretation of surgical trials and is of importance for national and international guideline committees.

Generalizability of the effects of surgical interventions, including aortic valve replacement, is not straightforward if intervention effects possibly differ between groups of patients or practice characteristics. In trials, commonly, average treatment effects are estimated and apply to patient groups that are represented in that trial. Generalizing results to patient populations with different characteristics or different clinical practice requires additional assumptions.

Regional differences between North America and Europe have been described before for other cardiovascular diseases. For example, in heart failure patients, major differences were observed in discharge strategies with shorter length of stay in North America (8, 9). Transatlantic variation has to some extent been outlined for transcatheter aortic valve replacement patients (10); however, literature on differences in perioperative care or outcomes for SAVR patients is still lacking.

In the PERIGON Pivotal Trial, European patients were older and had higher STS risk of mortality, more comorbidities (including left ventricular hypertrophy), and worse degree of aortic stenosis. While these parameters relate to each other, European clinicians seem more conservative in their decision for intervention, which could very well explain the differences in valve anatomy and indication between the regions. Minimally invasive approaches were noticeably more popular in Europe, especially in Germany and in the United Kingdom, with national preferences in technique of choice. Those countries might be frontrunners, as in North America a trend for increased minimally invasive surgical AVR has also been observed (11).

Concerning the antithrombotic regimen, the 2020 ACC/AHA guidelines for the management of valvular heart disease (1) make a weak recommendation (class 2a, level of evidence B-NR) for aspirin only for all bioprosthetic SAVR patients in the absence of other indications for OACs and anticoagulation with a vitamin-K antagonist (VKA) for 3-6 months in case bleeding risk is low. The 2021 ESC/EACTS guidelines (2) declare a 2a recommendation for low-dose aspirin or OAC and constrict the use to the first 3 months. Despite these largely similar recommendations and comparable frequencies of atrial fibrillation and LAA closure, the antithrombotic regimens varied widely, even within continents. A potential explanation

for this variation could be that each center acts according to its local protocol as the strength of the evidence is relatively low. A meta-analysis (12) found that the bleeding risk after AVR is affected by the choice of anticoagulation. Hence, regional antithrombotic strategies need to be considered when interpreting thrombosis- and bleeding-related outcomes if adjustment for medication is lacking.

In addition, discharge strategies were very different between continents and countries. Regional insurance policies could play a role in explaining these differences. As a consequence, length of stay, the risk of in-hospital complications, and early rehospitalization, which is, for example, used as component of the primary composite outcome in the PARTNER 3 trial (3), could be affected. Furthermore, rehospitalization has also been integrated into the Valve Academic Research Consortium 3 definitions of primary endpoints in aortic valve research (13). It should be realized that this outcome is extremely variable. Any comparison of the above-mentioned outcome measures between certain treatments could only be reliably interpreted when considering geographical settings.

In this study, there seemed to be an association between the length of stay, the discharge location, and 30-day rehospitalization after SAVR. However, the descriptive design does not allow for causal inferences, and further studies specifically designed to study these relations are of interest to determine the pros and cons of certain discharge strategies.

Limitations

The population of the PERIGON Pivotal Trial is selective due to its eligibility criteria and might therefore be less representative of the entire SAVR population on each continent. However, the permittance of common concomitant procedures like CABG and the multicenter international character of the study enhance generalizability. Of note, only few patients were enrolled in Italy and Switzerland, so the results from these countries are more prone to sampling variability and therefore are less reliable. These small numbers may not represent the wider practice in these countries. Within countries there could also be differences between centers, which were not investigated in this analysis, so center-specific perioperative care and outcomes might not be generalizable to the entire country. In the entire cohort, baseline characteristics will have influenced procedural characteristics and will, in turn, have affected discharge results and antithrombotic regimen. As there were multiple differences in patient and procedural characteristics between continents and between countries, and these are likely accompanied by differences in unmeasured variables, we decided to avoid direct comparisons of clinical outcomes. Hence, although outcomes like mortality, bleeding, and rehospitalization differed per region, no causal inference on the impact of regional perioperative care can be made. Due to our approach of thoroughly comparing continents and countries, multiple statistical tests were executed. As a result, the rate of false-positive findings could be increased. However, since the aim of this study was descriptive rather than confirmative, we choose not to apply correction for multiple testing. All patients received the same prosthesis, so any bias related to prosthetic valve

differences are ruled out. Furthermore, the prospective design of the trial and the presence of an independent clinical events committee enabled robust and accurate data gathering despite widely varying geographical settings. These were major advantages that fitted neatly to the study goal.

CONCLUSION

Current perioperative management of SAVR patients broadly varies between North America and Europe. In a large observational trial, there were major differences in patient selection, procedural techniques, antithrombotic regimen, and discharge strategy. Specifically, the rehospitalization risks differed largely between continents and countries. Hence, these findings stress that geographical setting must be considered during the design and interpretation of surgical trials of aortic valve replacement and in the development of (inter) national guidelines.

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SUPPLEMENTARY FILES

Available at https://doi.org/10.1136/heartjnl-2023-322350.

11

CONFOUNDING ADJUSTMENT IN OBSERVATIONAL STUDIES ON CARDIOTHORACIC INTERVENTIONS: A SYSTEMATIC REVIEW OF METHODOLOGICAL PRACTICE

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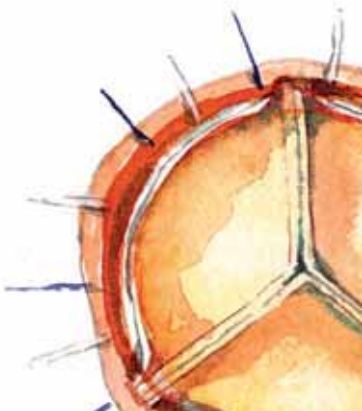
European Journal of Cardio-Thoracic Surgery 2023



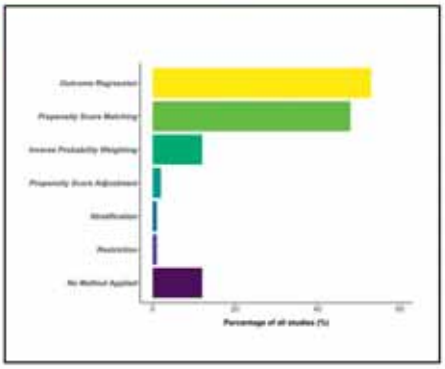
GRAPHICAL ABSTRACT

Confounding Adjustment in Observational Studies on Cardiothoracic Interventions: A Systematic Review of Methodological Practice

Summary

What is the quality of conduct and reporting of confounding adjustment methods in observational studies on cardiothoracic interventions?

Reporting was often insufficient, and quality therefore hard to judge. Appropriate application of these methods is crucial for causal inference on optimal interventions. Reporting is an important aspect of this which can be improved.



Legend: the figure presents the frequency of specific confounding adjustment methods.

ABSTRACT

Objectives: It is unknown which confounding adjustment methods are currently used in the field of cardiothoracic surgery and whether these are appropriately applied. The aim of this study was to systematically evaluate the quality of conduct and reporting of confounding adjustment methods in observational studies on cardiothoracic interventions.

Methods: A systematic review was performed which included all observational studies that compared different interventions and were published between January 1 and July 1, 2022, in three European and American cardiothoracic surgery journals. Detailed information on confounding adjustment methods was extracted and subsequently described.

Results: Ninety-two articles were included in the analysis. Outcome regression (N = 49, 53%) and propensity score matching (N = 44, 48%) were most popular (sometimes used in combination), while 11 (12%) studies applied no method at all. The way of selecting confounders was not reported in 42 (46%) of the studies, solely based on previous literature or clinical knowledge in 14 (16%), and (partly) data-driven in 25 (27%). For the studies that applied propensity score matching, the matched cohorts comprised on average 46% of the entire study population (range 9% - 82%).

Conclusions: Current reporting of confounding adjustment methods is insufficient in a large part of observational studies on cardiothoracic interventions, which makes quality judgement difficult. Appropriate application of confounding adjustment methods is crucial for causal inference on optimal treatment strategies for clinical practice. Reporting on these methods is an important aspect of this, which can be improved.

INTRODUCTION

In cardiothoracic research, many studies aim for causal inference by comparing different surgical interventions or strategies. To make valid inferences, the treatment groups under study need to be comparable to control for bias due to confounding [1]. Randomized controlled trials (RCTs) ensure this by design, however, for observational studies, often confounding adjustment is required. Traditional confounding adjustment methods include stratification, restriction, and multivariable outcome regression [2]. Alternatively, propensity score (PS) methods, which reflect the probability of receiving treatment conditional on observed covariates [3], are increasingly utilized [4]. Confounding adjustment methods differ regarding the data modelling assumptions and the interpretation of results.

While it is mostly clear that confounding adjustment methods are required in observational studies on the effects of cardiothoracic interventions, it is unknown which methods are used and whether these are applied appropriately. Hence, the aim of this study was to systematically evaluate the quality of conduct and reporting of confounding adjustment methods in observational studies on cardiothoracic interventions.

MATERIALS AND METHODS

Ethics statement

There are no individual patient data used in this review and informed consent is not applicable.

Systematic review

To investigate the quality of conduct and reporting of confounding adjustment methods, a systematic review was performed. Observational studies were included that were published between January 1 and July 1, 2022, in one of the following three cardiothoracic journals: the European Journal of Cardio-Thoracic Surgery (EJCTS), The Journal of Thoracic and Cardiovascular Surgery (JTCVS), and Annals of Thoracic Surgery (ATS). Furthermore, only observational studies were included that aimed to estimate a causal effect by comparing outcomes between two (or more) interventions or one (or more) intervention(s) versus no intervention for humans. As inclusion criterium, we specified that the interventions under study could hypothetically be randomized (i.e., a 'well-defined intervention'). Therefore, we excluded studies that investigated a causal contrast between different states [5], like male and female sex, or primary surgery versus reoperation. Furthermore, RCTs, systematic reviews or meta-analyses, case reports / series, prediction studies, and research letters were excluded.

PubMed Central was searched on September 21, 2022. The search strategy is available in the supplementary files. All potentially eligible articles were screened independently by title and abstract by two reviewers (BV and TB) using Rayyan software [6]. Any inconsistencies after deblinding were discussed until joint agreement was reached. Full-text review and data retrieval were performed by BV and checked by TB.

The information to extract, was determined a priori based on confounding theory [1, 2], previous literature [4], and expert knowledge. These items included the sample size (per treatment arm), the primary outcome, the number of primary outcome events in case the outcome was binary or a time-to-event outcome, the confounding adjustment method(s) (including [if present] motivation), the selection and the number of confounders, the number of estimated parameters of the regression model in case outcome regression or propensity methods were used, and whether unmeasured confounding was commented on. If the primary outcome was not explicitly stated, the first outcome mentioned in the title or abstract was considered to be the primary outcome. The number of outcome events was extracted from text, tables or figures like Kaplan-Meier analyses. When different regression models were used as part of different confounding adjustment methods, the number of estimated parameters were determined for the method of which the results were the first mentioned in the article.

When PS methods were used, it was investigated whether the PS model was specified, whether positivity / overlap between the treatment groups was checked, and what the estimated treatment effect was. Positivity refers to the assumption that all individuals have a non-zero probability to receive any of the treatments studied. Overlap is related, because this refers to the presence of treated and untreated subjects for each value of the PS [7]. Lastly, when studies used PS matching (PSM), data were collected on the sample size (per arm) of the matched cohort, the matching method, and whether comparability between treatment groups post matching was checked.

Statistical analysis

The above-mentioned information was summarized as frequencies (percentages) for categorical data, and as mean ± standard deviation or median [interquartile range (IQR)] depending on the distribution, checked using visual inspection of histograms, for numerical data. In addition, for the studies that used outcome regression or PS methods, the number events for the dependent variable per estimated parameter in the regression model was calculated. In general, it is recommended that this number should be at least 10 to assure stable regression modelling [8], although recent studies suggested to relax this rule in particular situations [9].

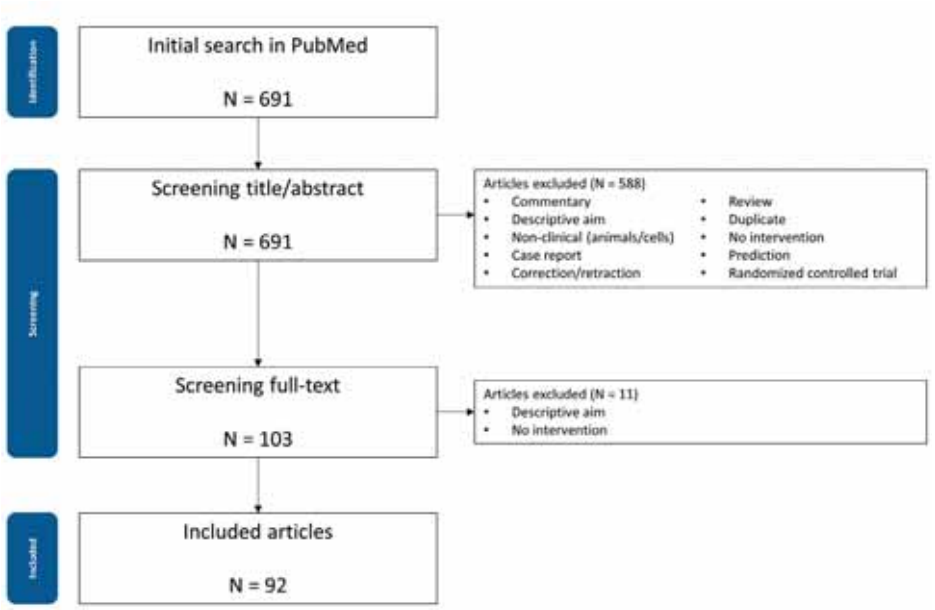
All analyses were executed in R, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org). Reporting was in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [10]. The review was not pre-registered because there is no opportunity for methodological reviews yet. The PRISMA checklist, the R code, and the complete data extraction form are all available in the supplementary files.

RESULTS

Systematic review

The literature search yielded 691 articles. After title and abstract screening, 588 studies were excluded for various reasons reported in the flowchart (Figure 1). Eleven more were excluded based on full-text screening as these studies either did not compare interventions or had a descriptive aim. A total of 92 articles were eligible for the analysis. References to the included articles and the studies that were excluded based on full-text screening are reported in the supplementary files.

Figure 1. Flowchart of review process.



Of the included studies, 50% were published in EJCTS, 28% in JTCVS, and 22% in ATS (Table 1). The median sample size was 799 and the median number of outcome events was 100 for studies with binary or time-to-event primary outcomes. Mortality was the most commonly used primary outcome of interest.

Various (sometimes multiple) confounding adjustment methods were used, among which outcome regression (53%) and PSM (48%) were most popular, while 12% applied no method at all. The motivation for the method of choice was noted in 3 studies (3%). These stated *"As anticipated, the balanced nature of the baseline features in the 2 groups motivates our decision not to perform multivariable adjusted analyses" [11], "Owing to the small sample size and that the 2 groups were later found to be largely similar at baseline, we elected to use weighting rather than matching" [12],* and

"Maximum likelihood binary logistic regression was unable to be used due to low event rates. Therefore, exact logistic regression was used" [13].

Table 1. Details for confounding adjustment methods in observational studies on cardiothoracic interventions.

	All studies, N = 92
STUDY DETAILS	
Journal	
European Journal of Cardio-Thoracic Surgery	46 (50%)
Journal of Thoracic and Cardiovascular Surgery	26 (28%)
Annals of Thoracic Surgery	20 (22%)
Sample size	799 [311,2332]
Outcome events [a]	100 [43,299]
Primary outcome	
Mortality	52 (57%)
Complications	13 (14%)
Recurrence / reoperation	10 (11%)
Adverse events	3 (3%)
Patency / revascularization	5 (5%)
Oncological	2 (2%)
Other	7 (8%)
CONFOUNDING DETAILS	
Numbers of confounders	12 [8,16]
Confounding adjustment method [b]	
Outcome regression	49 (53%)
Stratification	1 (1%)
Restriction	1 (1%)
Propensity score matching	44 (48%)
Propensity score adjustment	2 (2%)
Inverse probability of treatment weighting	11 (12%)
No method applied	11 (12%)
Motivation method described	
Yes	3 (3%)
No	89 (97%)
Selection confounders	
Previous literature	6 (7%)

Table 1. Continued

	All studies, N = 92
Clinical knowledge	8 (9%)
Data-driven	16 (17%)
Clinical knowledge + data-driven	9 (10%)
Not reported	42 (46%)
No confounders selected	11 (12%)
Comment unmeasured confounding	
Yes, presence acknowledged	32 (35%)
Yes, performed quantitative bias analysis	5 (5%)
No comments made	55 (60%)

[a] For studies with binary primary outcomes. [b] The numbers do not add up since some studies used multiple confounding adjustment methods. Categorical data are summarized as counts (percentages) and numerical data as median [interquartile range].

Of the 81 studies that corrected for confounding, 42 (52%) studies did not report on the selection of confounders. In 14 (17%) studies, confounder selection was solely based on previous literature or clinical knowledge and in 25 (31%) this was (partly) data driven. Data-driven approaches included forward or backward stepwise selection (40%), statistically significant associations in univariate outcome regression analysis (36%), statistically significant differences in baseline characteristics between treatment groups (16%), prespecified change in effect measure (4%), and gradient boosted regression (4%). The potential presence of unmeasured confounding was acknowledged in 35%, and a bias analysis in which this potential effect was quantified, for example using the E-value [14], was performed in 5 studies (5%).

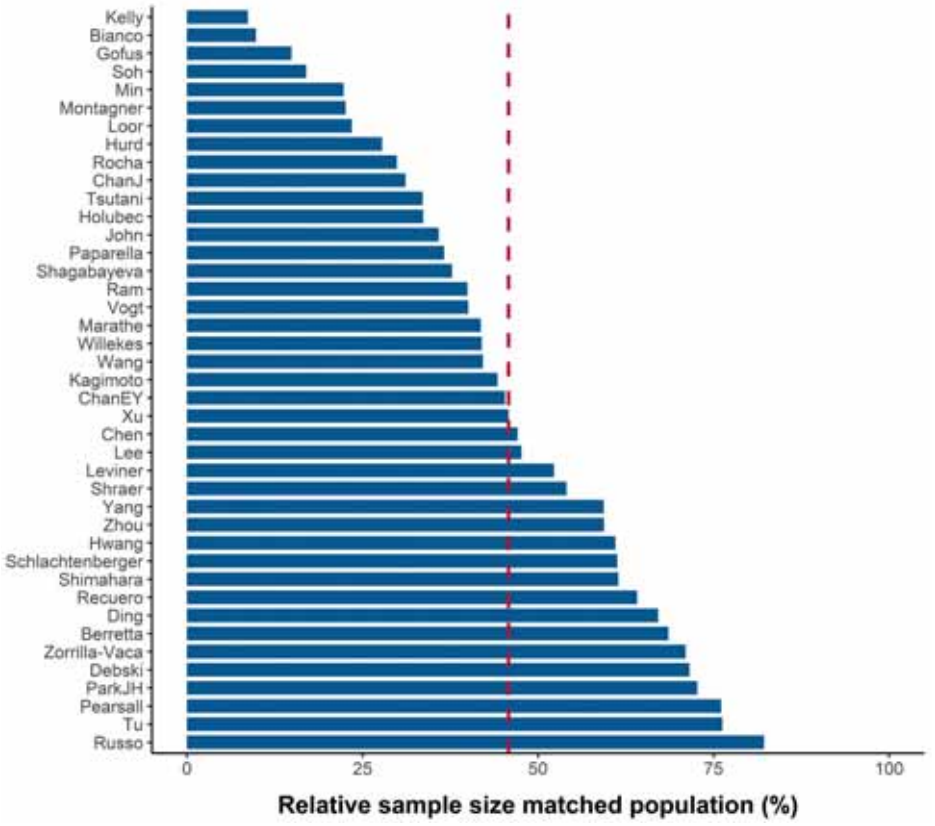
Of the 51 studies that used PS methods, fifty (98%) reported the model/method to calculate the PS (Table 2). Positivity (i.e., overlap of PSs) was checked in 28%. In the studies that applied PSM, matching was mostly based on the distance (on the scale of [the logit of] the PS) between treated and untreated individuals, with 80% using a greedy algorithm or nearest-neighbor matching with or without a caliper. One study (2%) matched on the smallest sum of overall PS distances, whereas 18% of the studies did not report which matching algorithm was used. The matched cohorts comprised on average 46% of the entire study population, and this fraction ranged from a minimum of 9% to a maximum of 82% (Figure 2). In the studies that used matching without replacement, on average 78% of the treated patients and 38% of the untreated remained in the analysis. The two studies that used replacement [15, 16] did not report the number of unique individuals that remained in the analysis.

Table 2. Details for propensity score methods in observational studies on cardiothoracic interventions.

	All PS studies, N = 51
Propensity score calculation specified	50 (98%)
Positivity / overlap checked	14 (28%)
Estimated effect	
Average treatment effect	11 (22%)
Average treatment effect in the treated	2 (4%)
Average treatment effect in the matched	38 (74%)
	All PSM studies, N = 44
Matching method	
Caliper	8 (18%)
Greedy algorithm or nearest-neighbor	6 (14%)
Greedy algorithm or nearest-neighbor + caliper	21 (48%)
Smallest sum of overall PS distances	1 (2%)
Not reported	8 (18%)
Matching with replacement	2 (5%)
Comparability post-matching checked	42 (96%)
Sample size matched / entire population (%) [a]	46 ± 20

[a] *This analysis was executed in PSM studies that matched without replacement, as the studies that used replacement did not report the number of unique individuals that remained in the analysis. Categorical data are summarized as counts (percentages) and numerical data as mean ± standard deviation. PS, propensity score; PSM; PS matching.*

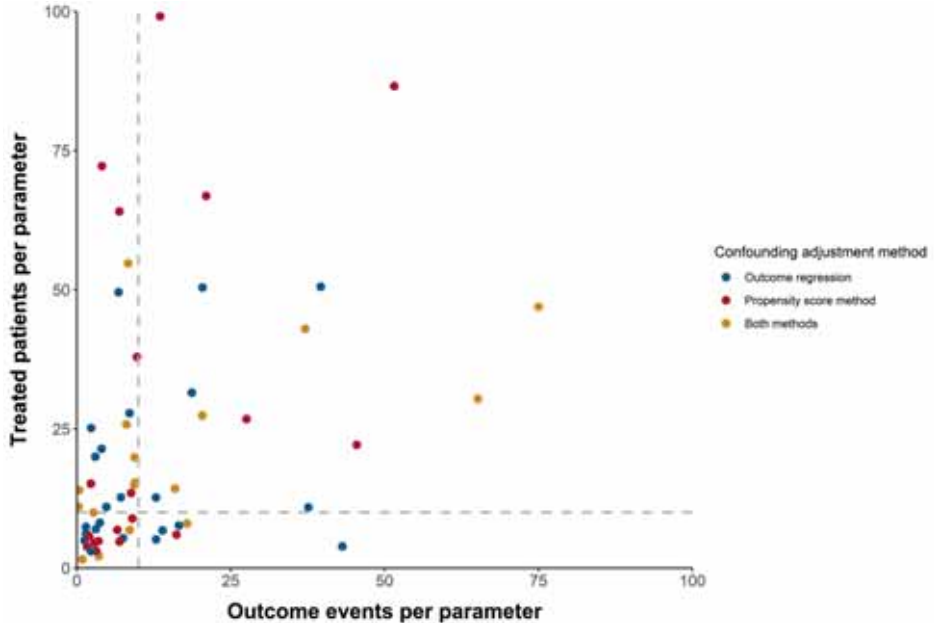
Figure 2. Relative sample size of matched cohort compared to entire population in observational studies on cardiothoracic interventions that used propensity score matching without replacement.



One study that used propensity score matching [33] is not shown as the sample size of the entire population was not reported but only the sample size of the matched cohort. The dashed red line represents the mean of all studies (45.8%).

The number of events of the dependent variable per estimated parameter, for the studies that used binary or survival regression methods in their adjustment is shown in Figure 3, as for the studies that only used outcome regression (N= 28), the median number of outcome events per parameter was 7.4 [IQR 3.2, 18.1]. For the studies that only used PS methods (N= 23), the median number of treated patients per parameter was 22.1 [IQR 6.8, 72.2]. Finally, for the studies that used both outcome regression and PS methods (N= 21), the median number of outcome events per parameter was 9.4 [IQR 6.9, 44.1], while the median number of treated patients per parameter was 15.4 [IQR 10.5, 36.7].

Figure 3. Number of outcome events and treated patients per estimated parameter for regression modelling in studies that used outcome regression and / or propensity score methods.



The interrupted grey lines are placed at 10 events / patients per parameter which is generally considered the minimum for stable regression modelling [8].

DISCUSSION

In this systematic review, we found that reporting on confounding adjustment methods was insufficient in the majority of observational studies on cardiothoracic interventions. This includes no motivation for the choice of the method, not reporting on the selection of confounders, and an incomplete and unclear description of PSM algorithms (if applied).

In 2007, the quality of methodological reporting, specifically for PSM, in cardiovascular surgery was found to be poor and suggestions for improvement were made [17]. Specifically for cardiothoracic researchers, two statistical primers have been published in EJCTS in 2018 and 2019 that elaborated on PS and multivariable regression methods [18, 19]. However, we observed that research practice still falls short on many domains.

Our review focused on reporting of methodological aspects of confounding adjustment in observational studies of cardiothoracic interventions. While our interest also lied in assessment of the quality of conduct, the extent to which this assessment was possible obviously largely depends on the quality of reporting. Hence, for many of the reviewed studies we could only get an indirect impression of the quality of confounding adjustment. We note that this study is not intended to criticize individual studies, but rather meant to

highlight specific points for improvement and to provide methodological guidance. The list of items that we extracted from the included studies highlights key element of observational studies in general and cardiothoracic surgery in particular. Our findings are important for cardiovascular researchers and clinical, methodological and statistical reviewers/editors.

The first thing that needs to be clear is whether a study has a descriptive or causal aim [20]. It was sometimes unclear whether the aim of included studies was just to describe current practice, or to make a comparison between different treatments. For causal inference using observational data, detailed information needs to be available on all confounders that require adjustment. Subsequently, the sample size or number of outcome events needs to be sufficient to apply a particular adjustment method. Of two common data sources, registries might not include detailed information on all confounders, while single center studies might have a limited sample size. Moreover, causal inference requires sufficiently well-defined treatment (strategies) and positivity [1] but these conditions fall outside of the scope of this paper. If either the data are not sufficient or the other conditions cannot be satisfied, one should refrain from causal inference or at least clearly acknowledge the limitations and elaborate on the interpretation of the results.

The selection of a sufficient set of confounders is also a crucial step. Data-driven approaches to select these confounders are discouraged because the risk of omitting important confounders and consequently biased treatment effect estimates [1, 21]. Despite these risks, in this review, we found that data-driven approaches were used in 31%. Instead, confounder selection based on clinical knowledge and previous literature is advised [1]. Ideas about causal relations can be specified and illustrated transparently in causal diagrams like directed acyclic graphs (DAGs). Using these graphs, one can indicate whether residual confounding is expected in an observational study because some confounders might not have been measured. Only one study included in our review [22] used a DAG. While causal diagrams help to select a minimum set of variables to control for all confounding and to prevent selection bias, they do not provide information on the appropriate functional form. For guidance how to model, for example, continuous parameters in regression analysis, other sources such as [21] can be consulted.

Choices regarding a confounding adjustment method need to align with the main interest of the study because different methods may differ regarding the interpretation of results [23]. The latter is explained by the fact that the target quantity of estimation (the "estimand") depends on the analytical approach. For example, the treatment effects estimated by default implementations of inverse probability of treatment weighting (IPTW) and PSM correspond to different causal effects, namely the so-called average treatment effect and the average treatment effect among the treated, respectively. Note that there are many options for these methods, possibly targeting different estimands (some of which are explained here [23]). Another consideration is the appropriateness of the data in relation to the confounding adjustment method, for example the number of events in relation to the number of parameters that needs to be estimated. When the number of outcome events is low, PS methods could be

preferred, because for the latter methods, treatment status (instead of outcome status) is the dependent variable in the regression model and hence the number of (un)treated patients the limiting factor. For example, in Figure 3, it can be observed that for some studies that used outcome regression, PS methods would have been statistically beneficial.

The most popular PS method was PSM. Exact matches between treated and untreated patients limit bias due to confounding but may increase the variance when only a small proportion of patients ends up in the matched cohort. In the end, an optimal balance between bias and variance will result in the smallest overall error. From Figure 2, it can be inferred that on average more than 50% of the initial sample size was discarded with 91% as most extreme finding. For large studies, such as registries, this might be less troubling than for small single center studies. However, the more patients are discarded, the more difficult it becomes to generalize results of the study to a particular group of patients in clinical practice [1]. The effect that is estimated in these situations can be referred to as the average treatment effect in the matched. The second most popular PS method was IPTW. By using this technique, patients are weighted to create a so called "pseudo-population" in which the treatment status is independent of the measured confounders [1]. Details for the use of this technique in practice are described in sources such as [24].

Some confounding adjustment methods were not used in any of the studies included in this review like standardization, instrumental variable analysis and methods like g-estimation that can deal with treatments which can vary over time such as sustained drug use [1,25]. The pros and cons as well as the applicability of various methods are discussed elsewhere [1, 25].

As mentioned above, all confounding adjustment methods can only control for confounders that are measured. Quantitative bias analysis can be performed to provide insights into the effect of unmeasured confounding under different assumptions, for example by calculating the E-value [14] as four studies in our review did [15, 26-29]. Detailed methods on performing quantitative bias analysis are provided elsewhere [30]. As most researchers are unfamiliar with these methods, we suggest consulting an epidemiologist or statistician when applying these.

Confounding is an important threat to causal inference in observational studies of treatment effect; however, it is not the only threat. Methodological initiatives and guidelines like STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) [31] and STRengthening Analytical Thinking for Observational Studies (STRATOS) outline many more crucial aspects. Furthermore, it could be useful to structure the design of an observational study with a hypothetical RCT in mind. A guide to this process called "target trial emulation" is outlined elsewhere [32]. If researchers feel restricted to report on all methodological aspects due to a journal's word count limit, comprehensive details can be described in the supplementary files.

Editors and reviewers share the responsibility to identify the lack of sufficient quality in the reporting of research methodology and statistical analysis in journals, and hopefully these findings should encourage journal editors to strengthen the review process within their publications. Mandatory involvement of a methodological or statistical reviewer/editor could be a way to achieve this.

Limitations

A limitation of our study for investigating the quality of conduct is that the review was based on information reported in published articles. Some information was not reported, while other information was reported ambiguously. Some data elements were therefore difficult to extract. Specifically, these included the primary outcome, the number of outcome events, and the number of estimated parameters for regression analysis. A second limitation is that the review focused on studies published in three major cardiothoracic surgery journals which is a subset of all observational studies of cardiothoracic treatments. The inclusion of more journals and a longer publication period might have led to the identification of more confounding adjustment methods.

CONCLUSION

Current reporting of confounding adjustment methods is insufficient in a large part of observational studies on cardiothoracic interventions, which makes assessment of the quality of confounding adjustment difficult. Appropriate application of confounding adjustment methods is crucial for causal inference on optimal treatment strategies for clinical practice. Reporting on these methods is an important aspect of this, which can be improved.

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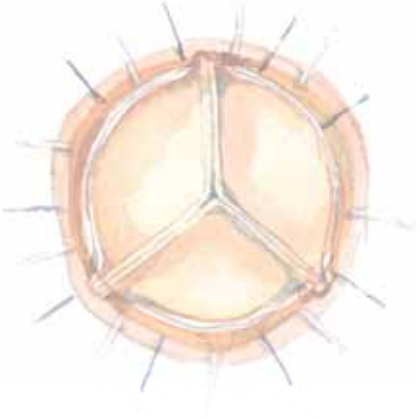
SUPPLEMENTARY FILES

Available at https://doi.org/10.1093/ejcts/ezad271.



PART III

POSTOPERATIVE ASSESSMENT

12

DO POSTOPERATIVE HEMODYNAMIC PARAMETERS ADD PROGNOSTIC VALUE FOR MORTALITY AFTER SURGICAL AORTIC VALVE REPLACEMENT?

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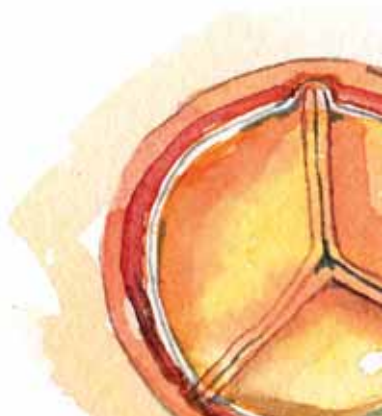
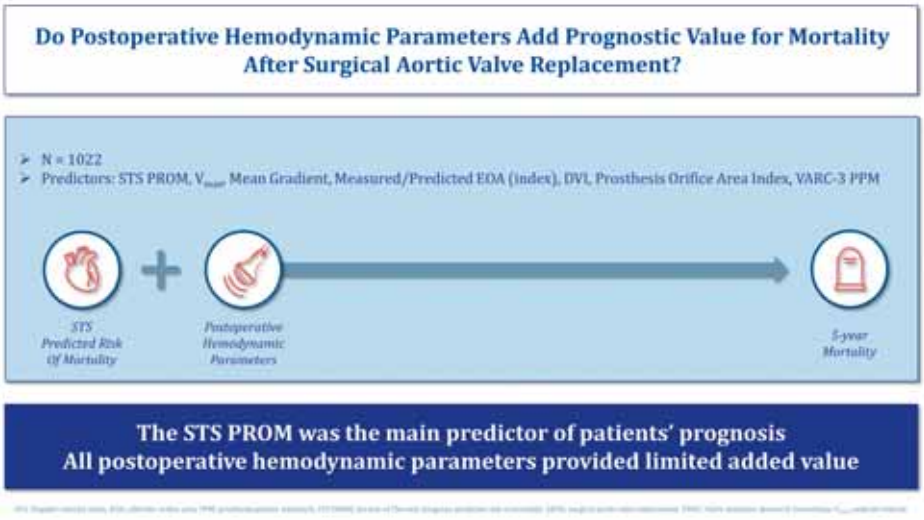
JTCVS Open 2023

Presented at the 2023 European Association of Cardiovascular Imaging, Barcelona, Spain



GRAPHICAL ABSTRACT



ABSTRACT

Background: While various hemodynamic parameters to assess prosthetic performance are available, prosthesis-patient mismatch (PPM) is exclusively defined by effective orifice area (EOA) index thresholds. Adjusting for the Society of Thoracic Surgeons predicted risk of mortality (STS PROM), we aimed to explore the added value of postoperative hemodynamic parameters for the prediction of all-cause mortality 5-year after aortic valve replacement.

Methods: Data were used from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial: a multicenter prospective cohort study regarding the performance of the Avalus bioprosthesis. Candidate predictors were measured at the first follow-up visit; patients who had no echo data, withdrew consent or died before were excluded. Candidate predictors included peak jet velocity, mean pressure gradient, EOA, predicted and measured EOA index, Doppler velocity index, indexed internal prosthesis orifice area, and categories for PPM. Performance of Cox models was investigated using the c-statistic and net reclassification improvement (NRI), among others.

Results: 1118 patients received the study valve, and 1022 were eligible for the current analysis. In univariable analysis, STS PROM was the only significant predictor of all-cause mortality (HR 1.40, 95% CI 1.26-1.55). When extending the STS PROM with single hemodynamic parameters, neither the c-statistics nor the NRI demonstrated added prognostic value compared to a model with STS PROM alone. Similar findings were observed when multiple hemodynamic parameters were added.

Conclusions: The STS PROM was found to be the main predictor of patients' prognosis. The additional prognostic value of postoperative hemodynamic parameters for the prediction of all-cause mortality was limited.

CENTRAL PICTURE

STS; Society of Thoracic Surgeons

Central Message: Postoperative hemodynamic parameters including the VARC 3 criteria for prosthesis-patient mismatch (PPM) added limited prognostic value to the STS PROM for the prediction of mortality after SAVR.

Perspective Statement: These results do not abate the relevance of prosthetic valve size, but rather stress the importance of considering patient characteristics when interpreting hemodynamic parameters for prognostic purposes. Furthermore, these findings challenge the clinical relevance of PPM. Further research on this concept and its relation with adverse events is warranted.

INTRODUCTION

Prosthesis-patient mismatch (PPM) emerges when a prosthetic heart valve is too small for a patient's hemodynamic needs [1]. Several studies, using definitions based on categories of effective orifice area indexed (EOAi) to body surface area (BSA) [2,3], have found that this phenomenon of residual hemodynamic obstruction is associated with increased mortality after aortic valve replacement (AVR) [4-7]. In contrast to EOAi, other postoperative hemodynamic parameters have not been considered to classify PPM; hence, their association with mortality is still unclear.

Since hemodynamic parameters as well as mortality are affected by patient characteristics, e.g., left ventricular ejection fraction, it is important to adjust for those characteristics when investigating their relationship. The Society of Thoracic Surgeons predicted risk of mortality (STS PROM) is a generally recognized risk score based on comprehensive patient characteristics, and, though initially developed to predict 30-day mortality [8], it has also been proven to predict late mortality after AVR through up to 10 years of follow-up [9]. Considering the STS PROM as a reference, we evaluated the added prognostic value of postoperative hemodynamic parameters for the prediction of all-cause mortality 5 years after AVR.

PATIENTS AND METHODS

Patient Data

The study population consisted of patients enrolled in the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial (www.clinicaltrials.gov, NCT02088554): a prospective, multicenter, single-arm trial evaluating the performance of the Avalus bioprosthesis (Medtronic, Minneapolis, Minnesota, USA), a stented bovine pericardial aortic valve. Its study design was formerly outlined in detail [10,11]. In short, the trial included symptomatic patients with moderate or severe aortic stenosis (AS), or chronic severe aortic regurgitation, and a clinical indication for surgical AVR enrolled mainly between 2014 and 2017. All patients received the same stented bioprosthesis. Concomitant procedures were allowed but restricted to coronary artery bypass grafting (CABG) and left atrial appendage ligation, among others. A local institutional review board (IRB) or research ethics committee (REC) provided approval at each site (see supplementary files Klautz *et al.* [12] for IRB/REC approval number and date), and written informed consent was obtained from all participants. All deaths and valve-related events were adjudicated by an independent clinical events committee (Baim Institute for Clinical Research, Boston, Massachusetts, USA), and study oversight was kept by an independent data and safety monitoring board (Baim Institute). Echocardiograms were evaluated by a core laboratory (MedStar Health Research Institute, Washington, DC, USA). The mean pressure gradient was calculated by the simplified Bernoulli formula, the EOA using the continuity equation, and the Doppler velocity index (DVI) by dividing the velocity-time integral (VTI) across the left ventricular outflow tract

(LVOT) by the VTI across the aortic valve. Forward stroke volume (SV) was determined by multiplying the LVOT cross-sectional area by its VTI.

Study design

Since echocardiographic assessment during initial hospital stay was considered of limited quality and subject to physiologic postoperative fluctuations related to recovering cardiac function, the hemodynamic parameters for this analysis were obtained from the first follow-up visit after discharge conducted between 3 and 6 months after implant. Patients who underwent previous cardiac surgery (to focus on primary SAVR procedures), who died or withdrew before their first visit, or had no core laboratory assessed echocardiogram available between 3 and 6 months were excluded. Next to STS PROM, several candidate predictors were selected based on previous literature. These comprised five hemodynamic parameters: peak aortic jet velocity (V_{max}), mean pressure gradient (MPG), EOA, EOAi, DVI, and two additional derivatives (see supplement for calculation): predicted EOAi (pEOAi) and the internal prosthesis orifice area indexed (POAi) to SV. Predicted EOAi has been proposed for determination of the required valve size to avoid PPM in the preoperative setting [13], e.g., constituted in valve charts and Blackstone *et al.* [14] introduced prosthesis-patient sizing based on geometric dimensions and thus POAi. Dichotomous predictors for any, moderate, and severe PPM were added to the analysis to enable interpretation of the results considering the current definition of the Valve Academic Research Consortium 3 (VARC 3) [3].

Statistical analyses

Cox proportional hazards models were used in a nested approach with time-to-death as the dependent variable. Death was defined as all-cause mortality. Suitability of predictors was assessed by evaluating missing data (<20%). The scales of EOA, EOAi, DVI, pEOAi, and POAi were reduced by a factor of 10 in all models to create clinically interpretable hazard ratios (e.g., EOA per 0.1 cm^2 instead of per 1 cm^2). Follow-up started at the first follow-up visit for routine echocardiographic assessment and continued until death or withdrawal from the study, whichever came first. Model performance was investigated using Nagelkerke's R^2, the c-statistic, and the Brier score. The net reclassification improvement (NRI) and the likelihood ratio test (LRT) were used to study improvement of nested models compared to a reference model with STS PROM alone.

The prognostic value of hemodynamic parameters was assessed in different steps. In the first step, univariable analyses of all candidate predictors were carried out. In addition, as STS PROM was initially developed to predict 30-day mortality, its 5-year predictive ability was reassessed in a Kaplan-Meier analysis according to quintiles of STS PROM. Survival according to VARC 3 levels of PPM was demonstrated too. In the second step, the model relating STS PROM to mortality was extended by adding one candidate hemodynamic predictor at a time. In the final step, a "full statistical model" was created to explore the maximal predictive performance of postoperative hemodynamic parameters by adding all continuous hemodynamic predictors except for parameters with excessive missing values

(≥20%) or multicollinearity (Pearson's correlation coefficient >0.8); in these cases, the predictor that performed best in terms of the LRT in the previous steps was chosen.

All analyses were carried out using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org). A p-value below 0.05 was considered significant in two-sided statistical tests. The data underlying this article are owned by the sponsor and will not be shared with third parties for purposes of reproducing the results. More comprehensive information on model building decisions, the outcome measures, and the analytical approach can be found in the supplement.

RESULTS

Of the 1118 who received the study valve, 30 were excluded because they died or withdrew consent before their 3-6 months echo, 30 because no core laboratory assessed echocardiograms was available between 3-6 months post-surgery, and 36 as they underwent previous cardiac surgery (supplementary files, Figure S1). Of the excluded patients, 53% had any PPM at the discharge echo. The remaining 1022 patients were included in the current analysis. The patient characteristics and echocardiographic values of all hemodynamic predictors are presented in Table 1. The mean age was 70.0 ± 8.9 years, and the STS PROM was 1.9 ± 1.3%. Most patients (88%) had a left ventricle ejection fraction of at least 50%. Concomitant procedures are reported in Table S1. Moderate and severe PPM were present in 40% and 15% of the patients, respectively. At 5 years of follow-up, 89 patients had died, and the median follow-up time was 1697 days.

Table 1. Baseline characteristics and echocardiographic parameters at first follow-up visit after surgical aortic valve replacement.

	Total, n = 1022
Patient characteristics	
Age (years)	70.0 ± 8.9
Male	767 (75%)
Body surface area (m^2)	1.99 ± 0.2
Body mass index (kg/m^2)	29.5 ± 5.5
STS PROM (%)	1.9 ± 1.3
Diabetes mellitus	266 (26%)
Hypertension	766 (75%)
Chronic obstructive pulmonary disease	120 (12%)
Left ventricle ejection fraction > 50%	898 (88%)
Coronary artery disease	439 (43%)
NYHA class III/IV	424 (41%)
Previous stroke	39 (4%)

Table 1. Continued

	Total, n = 1022
Peripheral vascular disease	70 (7%)
Renal dysfunction/insufficiency	96 (9%)
Operative characteristics	
Valve size implanted	
17 mm	1 (0.1%)
19 mm	39 (3.8%)
21 mm	194 (19%)
23 mm	364 (36%)
25 mm	320 (31%)
27 mm	93 (9.1%)
29 mm	11 (1.0%)
Echocardiography at first follow-up visit	
Peak aortic jet velocity (ms^{-1})	2.32 ± 0.4
Mean pressure gradient (mm Hg)	12.0 ± 4.1
Effective orifice area (cm^2)	1.56 ± 0.4
Effective orifice area indexed by BSA (cm^2/m^2)	0.79 ± 0.2
Doppler velocity index	0.47 ± 0.1
Predicted effective orifice area indexed by BSA (cm^2/m^2)	0.79 ± 0.1
Internal prosthesis orifice area indexed by SV (cm^2/mL)	0.05 ± 0.0
Any prosthesis-patient mismatch *	528 (55%)
Moderate prosthesis-patient mismatch *	384 (40%)
Severe prosthesis-patient mismatch *	144 (15%)

** According to the Valve Academic Research Consortium 3 definition 3. Numerical data are expressed as mean ± standard deviation, and categorical data as frequency (percentage). BSA; body surface area, NYHA; New York Heart Association, STS PROM; Society of Thoracic Surgeons predicted risk of mortality, SV; stroke volume.*

The largest percentage of missing values per predictor was 5.6%; therefore, none of the candidate predictors exceeded the exclusion threshold of 20% (Table S2). Multicollinearity was observed for V_{max} and MPG, and for EOA and EOAi with Pearson's correlation coefficients of 0.94 and 0.89, respectively (Table S3). The assumptions of proportional hazards and linearity were met for all candidate predictors (Figures S2 and S3).

The results of the univariable analysis of all predictors, are summarized in Table 2. STS PROM was a significant predictor of all-cause mortality (HR 1.40, 95% confidence interval [CI] 1.26-1.55). The HRs of all other predictors were not statistically significant. Moreover, STS PROM performed best in terms of Nagelkerke's R^2 (0.20) and the c-statistic (0.66, 95%

CI 0.60-0.72). Those measures were substantially lower for all other predictors. Nevertheless, the Brier scores were quite similar among all predictors at each time point (Table S4). Survival after the first follow-up visit is stratified by quintiles of STS PROM in Figure 1, and was significantly different between the risk groups (log-rank test p value <0.001). Survival according to VARC 3 levels of PPM was not significantly different (Figure 2, log-rank test p value 0.40).

In the updating step, ten different models were constituted, including STS PROM and one single hemodynamic predictor per model (Table 3). The effect of STS PROM remained significant in all models with HRs around 1.40. After adjustment for STS PROM, none of the hemodynamic predictors was associated with all-cause mortality. Correspondingly, the LRTs indicated no significant improvement, and the c-statistics were similar between the models and comparable to the model with STS PROM as the only predictor variable. Likewise, the NRI did not show improvement for any models.

Table 2. Univariable relations between candidate predictors and mortality in patients who underwent surgical aortic valve replacement.

	HR (95% CI)	**R^2**	**C-Statistic (95% CI)**
STS PROM	1.40 (1.26:1.55)	0.20	0.66 (0.60:0.72)
V_{max}	1.44 (0.86:2.43)	0.01	0.55 (0.49:0.61)
MPG	1.02 (0.98:1.08)	0.01	0.54 (0.48:0.60)
EOA	1.01 (0.95:1.07)	0.00	0.51 (0.44:0.58)
EOAi	1.62 (0.51:5.18)	0.01	0.53 (0.46:0.59)
DVI	1.07 (0.84:1.34)	0.00	0.52 (0.45:0.59)
pEOAi	1.06 (0.83:1.34)	0.00	0.50 (0.44:0.56)
POAi	1.05 (0.28:3.95)	0.00	0.50 (0.44:0.56)
Any PPM	0.75 (0.49:1.15)	0.01	0.54 (0.49:0.59)
Moderate PPM *	0.70 (0.44:1.13)	0.02	0.55 (0.49:0.60)
Severe PPM *	0.88 (0.48:1.63)		

** The reference category for moderate and severe PPM is no PPM. CI; confidence interval, DVI; Doppler velocity index, EOA; effective orifice area, EOAi; EOA indexed by body surface area, HR; hazard ratio, MPG; mean pressure gradient, pEOAi; predicted EOAi, POAi; internal prosthesis orifice area indexed by stroke volume, PPM; prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria 3) , STS PROM; Society of Thoracic Surgeons predicted risk of mortality, Vmax; peak aortic jet velocity.*

Table 3. Prognostic value of single hemodynamic predictors in addition to STS PROM for patients who underwent surgical aortic valve replacement.

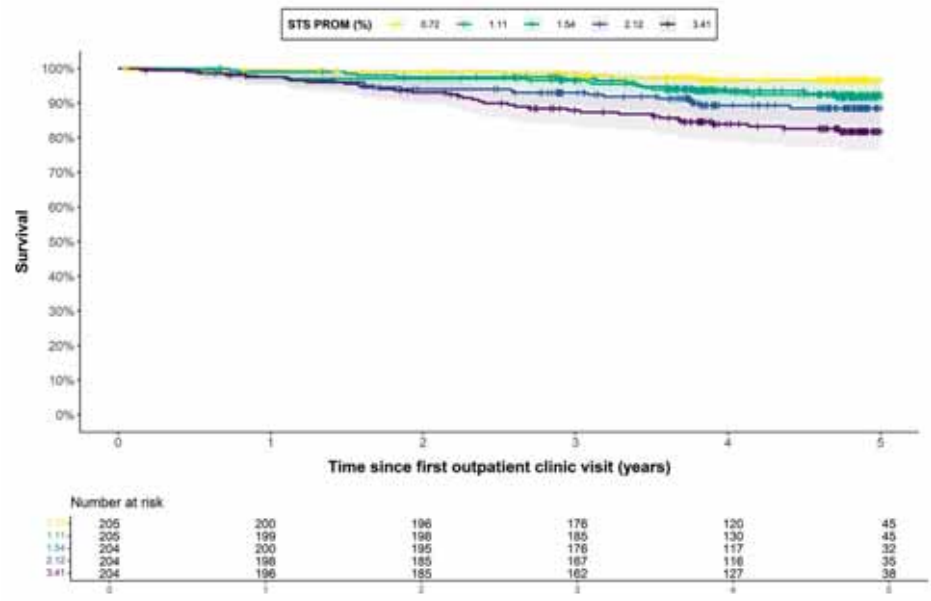
	HR Predictor (95% CI)	**HR STS PROM (95% CI)**	**LRT* p-value**	**C-Statistic (95% CI)**	**NRI* (95% CI)**
STS PROM +					

Table 3. Continued

	HR Predictor (95% CI)	HR STS PROM (95% CI)	LRT* p-value	C-Statistic (95% CI)	NRI* (95% CI)
V_{max}	1.65 (0.97:2.78)	1.41 (1.28:1.56)	0.062	0.68 (0.62:0.73)	0.00 (-0.08:0.08)
MPG	1.03 (0.98:1.08)	1.40 (1.27:1.55)	0.197	0.67 (0.62:0.72)	0.01 (-0.06:0.07)
EOA	1.03 (0.97:1.09)	1.41 (1.27:1.56)	0.359	0.67 (0.61:0.72)	0.02 (-0.06:0.09)
EOAi	1.03 (0.92:1.16)	1.40 (1.26:1.54)	0.584	0.66 (0.61:0.72)	0.02 (-0.07:0.12)
DVI	1.03 (0.81:1.31)	1.40 (1.26:1.55)	0.805	0.66 (0.61:0.72)	0.00 (-0.06:0.06)
pEOAi	0.99 (0.78:1.24)	1.40 (1.26:1.55)	0.899	0.66 (0.61:0.72)	0.00 (-0.08:0.07)
POAi	1.46 (0.39:5.51)	1.40 (1.27:1.55)	0.899	0.65 (0.59:0.71)	0.01 (-0.08:0.09)
Any PPM	0.78 (0.50:1.20)	1.40 (1.26:1.54)	0.221	0.67 (0.61:0.73)	0.03 (-0.07:0.13)
Moderate PPM §	0.73 (0.44:1.18)	1.40 (1.26:1.54)	0.356	0.67 (0.61:0.73)	0.05 (-0.05:0.14)
Severe PPM §	0.91 (0.50:1.68)				

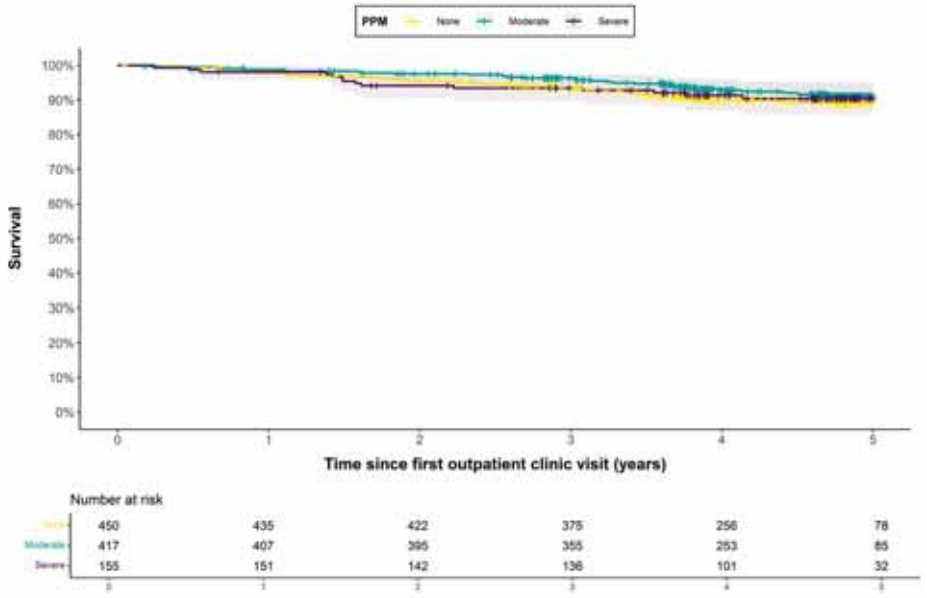
** The LRT and NRI compared a new model with STS PROM + one candidate predictor to a reference model of STS PROM alone. § The reference category for moderate and severe PPM is no PPM. To note, HR Predictor refers to the HR for the predictor specified in each row which is derived from a multivariable model including this predictor and STS PROM. CI; confidence interval, DVI; Doppler velocity index, EOA; effective orifice area, EOAi; EOA indexed by body surface area, HR; hazard ratio, LRT; likelihood ratio test, MPG; mean pressure gradient, NRI; net reclassification improvement, pEOAi; predicted EOAi, POAi; internal prosthesis orifice area indexed by stroke volume, PPM; prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria 1), STS PROM; Society of Thoracic Surgeons predicted risk of mortality, Vmax; peak aortic jet velocity.*

Figure 1. Kaplan-Meier survival curves according to quintiles of STS PROM.



The solid lines represent the survival curves according to quintiles of STS PROM, including the corresponding 95% confidence intervals. The color legend provides the median STS PROM for each quintile. Censoring is indicated by the "+" sign. Note that the follow-up starts at the first outpatient clinic visit, not at the date of surgery. STS PROM, Society of Thoracic Surgeons predicted risk of mortalityz

Figure 2. Kaplan-Meier survival curves according to Valve Academic Research Consortium 3 levels of prosthesis-patient mismatch.



The solid lines represent the survival curves according to the levels of prosthesis-patient mismatch, including the corresponding 95% confidence intervals. Censoring is indicated by the "+" sign. Note that the follow-up starts at the first outpatient clinic visit, not at the date of surgery

In the final step, a full statistical model was fitted, including STS PROM and all the continuous hemodynamic predictors. The LRT showed significant improvement with a p value of 0.003 (Table S5), while this was not supported by the NRI (estimate 0.06, 95% CI -0.06-0.18) or the c-statistic (0.68, 95% CI 0.63-0.74 vs. 0.66, 95% CI 0.60-0.72 for STS PROM alone).

Post-hoc analyses for dichotomized variants of the predictors MPG (≥20 mmHg) or DVI (≤0.35) were executed. In the univariable analysis, the HR for DVI ≤0.35 was 2.23 (95% CI 1.10-4.53), while the c-statistic was comparable to the other models including a single hemodynamic predictor (Table S6). After adjustment for STS PROM, DVI ≤0.35 was a significant predictor of an individual's mortality (HR 2.75 [95% CI 1.35-5.63]), with a significant p-value for the LRT (Table S7). However, the c-statistic of the latter model was similar to a model including STS PROM only, and the NRI did not show significant improvement. The dichotomized variant of MPG (≥20 mmHg) did not provide new insights (Tables S6 and S7).

DISCUSSION

The prognostic value of postoperative hemodynamic parameters for the prediction of all-cause mortality was minimal in addition to the STS PROM, which is available before surgery. The updated models showed limited overall predictive improvement in our data set of over 1000 SAVR patients at 5 years of follow-up.

The predictive effect of STS PROM on long-term mortality has been demonstrated for different types of cardiac surgery. Puskas *et al.* [9] found a significant effect of STS PROM after isolated AVR and AVR + CABG. Our findings are in line with their results, as Figure 1 demonstrates reduced survival with increasing STS PROM. Furthermore, STS PROM was the main determinant of model performance in both the extended models and the optimal statistical model.

On the contrary, little prognostic value of postoperative hemodynamic parameters was observed, even for measured or predicted EOAi. Although any PPM according to the current definition [3] was present in the majority of patients (40% moderate PPM and 15% severe PPM), there was no association with mortality at 5 years. The EOAi thresholds to classify PPM were initially based on its relation with elevated MPG [13]; however, both parameters added no significant prognostic value.

Our findings conflict to some extent with previous meta-analyses [4,5], which concluded that (EOAi-based) PPM negatively impacted survival after surgical AVR. However, many of the individual studies included in the meta-analyses failed to show a negative association between PPM and survival. A potential explanation can be found in differences in study population or different methods to adjust for baseline and procedural characteristics. As the STS PROM is a summarized risk score encompassing a broad range of patient characteristics and preoperative information, other corrections were made in the studies that were included in the meta-analyses [4,5].

Compared to EOAi, the prognostic value of other postoperative hemodynamic parameters is less evident. In an analysis of the National Echo Database Australia, impaired valvular hemodynamic performance after AVR, defined based on combinations of V_{max}, MPG, and EOA, was associated with worse survival [15]. However, this study did not define a standardized measurement moment as "only data from the last recorded echocardiographic examination were used" which troubles interpretation. Hahn and colleagues [16] found no significant effect of DVI (whether treated as a continuous or dichotomized variable) on 2-year mortality in the surgical cohorts of the PARTNER 2 and 3 trials. In our analysis, DVI as a continuous parameter was not associated with mortality, however, DVI ≤0.35 was found to improve the prediction of time-to-death for individuals. Nevertheless, this dichotomized variable did not alter the predictive performance of the model in terms of discriminating between patients with and without the outcome (i.e., the c-statistic). Hence, these conflicting findings within

our analysis and with previous literature challenge the clinical relevance of DVI ≤0.35, and external validation is necessary. For POAi, Blackstone *et al.* [14] observed no significant effect on intermediate- and long-term mortality in a large study comprising 13,258 patients who underwent surgical AVR with different valve types. These results were in line with our findings.

The question remains why the added value of postoperative parameters for the prediction of all-cause mortality 5 years after AVR was so little. First, as demonstrated above, STS PROM was a very strong predictor of mortality on its own. Second, since hemodynamic parameters depend on both the valve and the patient, and the valvular function is drastically improved by surgery, the patient contribution prevailed. This contribution consists of characteristics like LV function, metabolic requirements, and health status, which are represented to a great extent by the STS PROM. After all, a low postoperative gradient can reflect adequate prosthetic valve size, poor LV function, or a combination of both. Third, in our study, residual hemodynamic obstruction after surgery often corresponded to only mild native AS, which is well tolerated. Fourth, the values for hemodynamic parameters were concentrated in a narrow range in the postoperative setting. The smaller between-patient differences become, the larger sample size and number of events are required to generate distinctive predictions. Besides, measurement error might disturb predictions even more as it can induce attenuation as well as amplification of the observed association [17]. As random measurement errors are fixed, the potential consequence is relatively bigger on lower values.

These results do not abate the relevance of prosthetic valve size, but rather stress the importance of considering patient characteristics when interpreting hemodynamic parameters for prognostic purposes.

Limitations

As the current study population mainly consisted of low-risk patients, these findings are less generalizable to intermediate- and high-risk AS patients. However, the study was executed in an international multicenter setting and allowed some common concomitant procedures like CABG, which boost overall representativeness of the population. Moreover, survival in intermediate- and high-risk patients is expected to be even more rigorously affected by patient characteristics like STS PROM. In addition, follow-up beyond 5-years might reveal new associations in this low-risk cohort. While the number of deaths was largely sufficient to study the added value of single hemodynamic parameters to STS PROM, i.e., our main interest, the results from the "full statistical model" were more prone to overfitting and are likely to be affected by collinearity too. Hence, these results should be interpreted with caution, and external validation in larger cohorts with more events is required to test their robustness. To note, the current analysis addresses only the added value of multiple hemodynamic parameters for predicting mortality after SAVR; therefore, it does not provide any information on the etiological question of what the best operative strategy is to optimize hemodynamic performance or clinical outcomes for the patient. Furthermore,

cardiovascular mortality would be a highly interesting secondary outcome; however, there were few CV mortality events in our data, and this would have required the consideration of the competing risk of non-cardiovascular mortality, which further complicates the analysis. An important strength of the current study is that all patients were treated with the same stented bioprosthesis, enabling consistent analysis of hemodynamics unaffected by different valve properties. On the contrary, it reduces generalizability to surgical bioprostheses other than Avalus and to other types of valves such as mechanical, stentless, and TAVR valves and homografts.

CONCLUSION

The STS PROM was found to be the main predictor of patients' prognosis through 5 years of follow-up. In this analysis, the added prognostic value of postoperative hemodynamic parameters for the prediction of all-cause mortality was limited. These results warrant further research on the concept of PPM and its relation with adverse outcomes.

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SUPPLEMENTARY FILES

Available at https://doi.org/10.1016/j.xjon.2023.11.011.

13

BEYOND PROSTHESIS-PATIENT MISMATCH: THE INCREMENTAL PROGNOSTIC VALUE OF ECHOCARDIOGRAPHIC PARAMETERS FOR MORTALITY AFTER BIOPROSTHETIC AVR

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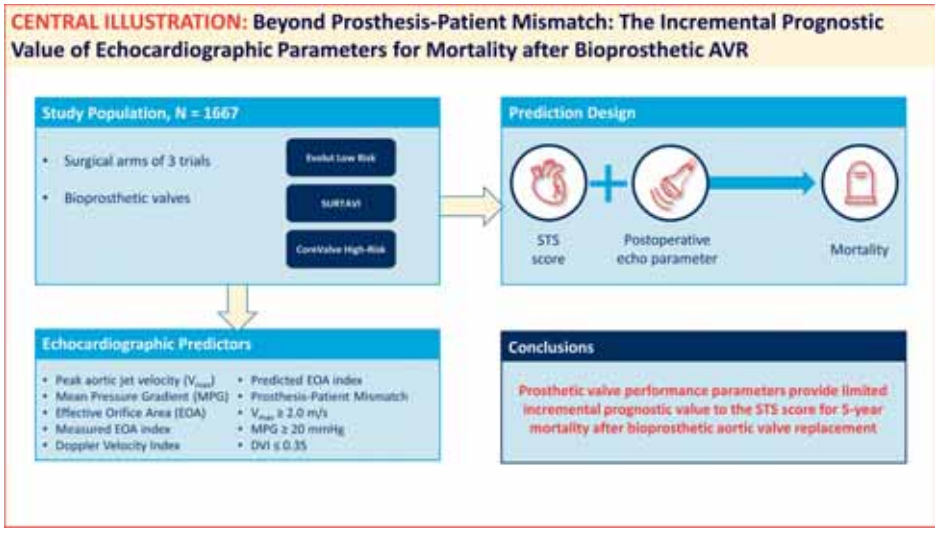
Submitted

GRAPHICAL ABSTRACT



ABSTRACT

Background: While there are many echocardiographic parameters available to assess prosthetic valve performance, prosthesis-patient mismatch (PPM) after surgical aortic valve replacement (SAVR) has only been defined by effective orifice area (EOA) index thresholds.

Objectives: To investigate the incremental prognostic value of various postoperative echocardiographic parameters to the STS score for the prediction of 5-year mortality after bioprosthetic SAVR.

Methods: Patients who received a surgical bioprosthetic valve in the Evolut Low Risk, SURTAVI, or CoreValve US Pivotal High-Risk trial were included. Echocardiographic parameters were measured by a core laboratory. Cox regression models including the STS score were updated by adding one of the following echocardiographic parameters: peak velocity (Vmax), mean pressure gradient (MPG), EOA, EOAi, Doppler velocity index (DVI), predicted EOAi, measured PPM according to the Valve Academic Research Consortium 3, Vmax ≥2.0 m/s, MPG ≥20 mmHg, and DVI ≤0.35. Incremental value was assessed using the likelihood ratio test (LRT) and the change in C-index, among others.

Results: Out of 1829 patients, 1667 were eligible. When added to the STS score, only DVI≤0.35 provided predictive improvement (LRT p-value 0.035). However, the C-indices of all updated models containing both the STS score and one echocardiographic parameters were comparable to the C-index of the STS score alone.

Conclusions: Out of multiple parameters, DVI ≤ 0.35 was the only parameter that provided some predictive improvement to the STS score. However, prosthetic valve performance parameters did not provide incremental value for the discrimination of patient survival to five years after SAVR.

INTRODUCTION

Echocardiography is the primary modality to assess prosthetic valve performance after surgical aortic valve replacement (SAVR) (1). While various hemodynamic parameters for prosthetic valve performance exist (2), prosthesis-patient mismatch (PPM) has exclusively been defined by thresholds of the effective orifice area index (EOAi) (3). Many studies which used these definitions found that PPM was associated with mortality after SAVR but a considerable number did not (4,5). Furthermore, several limitations have been outlined, mainly questioning the validity of body surface area (BSA) indexation (6,7), the appropriateness of the EOAi cut-offs (8), and the usefulness of the valve charts on projected PPM (9). Nevertheless, the association between other postoperative echocardiographic parameters and mortality has been relatively understudied. A comparison of the predictive value in the same population will provide important information which parameter is most strongly related to adverse outcomes.

Echocardiographic parameters are influenced by patient characteristics and comorbidities, such as age, sex, and left ventricular ejection fraction (LVEF). Many of these characteristics are summarized in the Society of Thoracic Surgeons (STS) score; a widely used preoperative risk score which has strong prognostic power for both short and long-term mortality up to 10 years after SAVR (10,11). Because this score is already available prior to surgery, it is of particular interest to investigate whether postoperative hemodynamic parameters for prosthetic valve performance improve the predictions of mortality. Hence, this study aimed to quantify the incremental prognostic value of various postoperative echocardiographic parameters to the STS score for the prediction of 5-year mortality after bioprosthetic SAVR.

PATIENTS AND METHODS

Patient Data

For this analysis, the study population consisted of patients enrolled in the surgical arms of the Evolut Low Risk, Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI), and CoreValve US Pivotal High-Risk randomized controlled trials (RCTs). These RCTs investigated the effect of transcatheter versus surgical AVR in low, intermediate, and high-risk patients, respectively. Throughout this manuscript, the trials are abbreviated as Evolut LR, SURTAVI, and CoreValve HR. The most important design features of the individual RCTs are depicted in Table S1 in the supplementary files. The trial protocols are available in the primary end point analyses (12-14). In these trials, a local institutional review board or research ethics committee provided approval at each participating center and written informed consent was obtained from all patients. The participants allowed to use the collected data for research purposes beyond the scope described in the initial trial protocol. All deaths and valve-related events were adjudicated by an independent clinical events committee (Baim Institute for Clinical Research, Boston, Massachusetts, USA). All echocardiographic parameters were assessed by the same independent core laboratory at

the Mayo Clinic (Rochester, Minnesota, USA). The simplified Bernoulli formula and the continuity equation were used to calculate the mean pressure gradient (MPG) and effective orifice area (EOA). The Doppler velocity index was derived by dividing the velocity-time integral (VTI) across the left ventricular outflow tract (LVOT) by the VTI across the aortic valve. Doppler stroke volume (SV) was determined by taking the product of the LVOT cross-sectional area and the VTI across the LVOT.

Study design

The postoperative hemodynamic parameters that served as predictors of interest were measured 30 days after surgery for patients enrolled in the Evolut LR and CoreValve HR trials. For patients enrolled in the SURTAVI trial, the echocardiographic parameters were measured at a reference echo at discharge because there was no 30-day visit in this study. For this analysis, all patients that were scheduled and underwent SAVR with a bioprosthetic valve were included. Patients who died or withdrew consent before the reference echo, or who had no core laboratory assessed echocardiogram available within the appropriate timeframe around this visit (as specified in the trials' protocols) were excluded. Follow-up started at the day of the reference echo after surgery and continued until death or withdrawal, whichever came first. The primary outcome was all-cause mortality, assessed up to 5-years follow-up. The secondary outcome was cardiovascular mortality (definitions are provided in the trials' protocols) throughout the same follow-up window. The predictors of interest were determined beforehand based on previous literature (1,2,15-17). Apart from the STS score, these comprised the continuous parameters peak aortic jet velocity (V_{max}), MPG, EOA, EOAi, DVI, and projected EOAi (pEOAi). Furthermore, categorical predictors included the Valve Academic Research Consortium (VARC) 3 levels of measured prosthesis-patient mismatch (PPM) and dichotomized variant of $V_{max} \geq 2.0$ m/s, MPG $\geq$ 20 mmHg, and DVI $\leq$ 0.35.

Statistical analyses

To quantify the incremental prognostic value of echocardiographic parameters, Cox regression models were fitted with time-to-death as dependent variable. The suitability of predictors was assessed by evaluating missing data (<20%) and collinearity with the STS score (<0.8). If one of these conditions was violated, the corresponding predictor was omitted from the analysis. Multiple imputations were used to complete missing baseline characteristics and predictor values under the assumption of missing at random. Imputations were based on a trial indicator, all baseline variables, the predictors of interest, and the outcome (18). The imputation method was predictive mean matching for continuous predictors and logistic regression for categorical baseline characteristics with 50 iterations to create 10 imputed datasets. The regression model was separately fitted to each imputed dataset, and estimates pooled conform Rubin's rules (19).

Univariable regression was performed first. Hazard ratios (HRs), Nagelkerke's R^2, and the C-index were calculated (20,21). The scales of EOA, EOAi, DVI, and pEOAi were reduced by a factor of 10 in all analyses to enhance the clinical interpretation of the HRs (e.g., EOA

per 0.1 cm^2 instead of per 1 cm^2 increase). Thereafter, the Cox regression model including the STS score was updated by adding one predictor at a time. Hence, each separate updated model comprised the STS score and a single echocardiographic parameter. The STS score was fitted as a log transformed parameter in all analyses. The predictive performance of the updated models was evaluated using the likelihood ratio test (LRT), the net reclassification improvement (NRI), and (change in) the C-index (20-22). For the LRT and NRI, updated models were compared to a model with the STS score alone. Furthermore, HRs were calculated for each predictor included in the model. For analyses on cardiovascular mortality, non-cardiovascular mortality was handled as competing risk in cause-specific Cox regression models. The cumulative incidence of all-cause mortality according to quintiles of the STS score was illustrated in a Kaplan-Meier analysis. This method was also used to demonstrate survival according to PPM categories and DVI ≤ or > 0.35. Lastly, subgroup analyses were performed in patients with preserved LV ejection fraction (>50%) and SVi > 35 mL/m^2, and in patients with low-flow defined as SVi ≤ 35 mL/m^2.

All analyses were performed using R software, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org). The data underlying this article are owned by the sponsor and will not be shared with third parties for purposes of reproducing the results. Comprehensive details on model building decisions, regression modelling assumptions, the outcome measures, the R packages used, and the analytical approach are reported in the supplementary files.

RESULTS

Out of the 1829 patients who were scheduled for SAVR and actually underwent surgery in the Evolut LR, SURTAVI, and CoreValve HR trial, 1667 met the inclusion criteria. A flowchart is provided in the supplementary files (Figure S1). The average age was 78 years, 59% was male, and the median STS score was 3.4 (interquartile range 2.1, 5.4, Table 1). Stented valves were most frequently implanted (84%, Table S2). At the postoperative reference echo, 30% of the patients was classified with any PPM (22% moderate and 8% severe). At 5-year follow-up, 404 patients had died of which 235 CV deaths. The median follow-up time was 1425 days.

Table 1. Baseline characteristics and postoperative echocardiographic parameters at the reference echo for patients who underwent surgical aortic valve replacement.

	Evolut LR N = 643	**SURTAVI N = 708**	**CoreValve HR N = 316**	**All N = 1667**
Age (years)	74 ± 6	80 ± 6	83 ± 6	78 ± 7
Male	428 (67%)	391 (55%)	165 (52%)	984 (59%)
Body surface area (m^2)	2.00 ± 0.23	1.92 ± 0.24	1.85 ± 0.23	1.94 ± 0.24
Body mass index (kg/m^2)	30.8 ± 5.8	29.3 ± 6	28.5 ± 6.3	29.7 ± 5.9

Table 1. Continued

	Evolut LR N = 643	**SURTAVI N = 708**	**CoreValve HR N = 316**	**All N = 1667**
STS PROM (%)	1.9 [1.4, 2.4]	4.4 [3.4, 5.5]	7.0 [5.3, 9.0]	3.4 [2.1, 5.4]
Diabetes mellitus	196 (31%)	244 (35%)	144 (46%)	584 (35%)
Hypertension	530 (83%)	638 (90%)	304 (96%)	1472 (88%)
Chronic obstructive pulmonary disease	112 (18%)	237 (34%)	138 (44%)	487 (30%)
Left ventricle ejection fraction (%)	63 ± 8	60 ± 11	58 ± 10	61 ± 10
Atrial fibrillation or flutter	90 (14%)	191 (27%)	142 (45%)	423 (25%)
NYHA class III/IV	182 (28%)	415 (59%)	273 (86%)	870 (52%)
Previous stroke / cerebrovascular accident	78 (12%)	50 (7%)	45 (14%)	173 (10%)
Peripheral vascular disease	54 (8%)	209 (30%)	131 (42%)	394 (24%)
Preoperative serum creatinine >2 mg/dl	1 (0%)	14 (2%)	15 (5%)	30 (2%)
Any concomitant procedure	168 (26%)	207 (29%)	31 (10%)	406 (24%)
Concomitant CABG	88 (14%)	166 (23%)	15 (5%)	269 (16%)
Postoperative reference echo				
Peak aortic jet velocity (ms^{-1})	2.2 ± 0.4	2.3 ± 0.5	2.3 ± 0.6	2.3 ± 0.5
Mean pressure gradient (mm Hg)	10.5 ± 4.0	12.5 ± 5.8	11.7 ± 5.7	11.6 ± 5.2
Effective orifice area (cm^2)	2.03 ± 0.58	1.81 ± 0.62	1.60 ± 0.51	1.86 ± 0.61
Effective orifice area index (cm^2/m^2)	1.03 ± 0.29	0.95 ± 0.32	0.87 ± 0.27	0.97 ± 0.31
Doppler velocity index	0.51 ± 0.11	0.51 ± 0.12	0.50 ± 0.12	0.51 ± 0.12
Stroke volume (mL)	82 ± 23	70 ± 22	67 ± 20	74 ± 23
Stroke volume index (mL/m^2)	41 ± 11	37 ± 11	36 ± 11	38 ± 11
Predicted effective orifice area index (cm^2/m^2)	0.86 ± 0.11	0.86 ± 0.13	0.86 ± 0.14	0.86 ± 0.13
Prosthesis-patient mismatch				
Any	108 (20%)	174 (34%)	119 (43%)	401 (30%)
Moderate	90 (17%)	123 (24%)	76 (27%)	289 (22%)
Severe	18 (3%)	51 (10%)	43 (16%)	112 (8%)
Peak aortic jet velocity ≥ 2.0 m/s	433 (68%)	516 (77%)	212 (69%)	1161 (72%)
Mean pressure gradient ≥ 20 mmHg	16 (3%)	68 (10%)	25 (8.1%)	109 (7%)
Doppler velocity index ≤ 0.35	32 (5%)	55 (9%)	30 (10%)	117 (8%)

Numerical data are expressed as mean ± standard deviation or median [interquartile range], and categorical data as count (percentage). BSA, body surface area; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS PROM, Society of Thoracic Surgeons predicted risk of mortality.

Missing data are presented in Table S3, and the correlation between the STS score and all other predictors is presented in Table S4. None of the predictors was missing in >20% of patients or had a correlation >0.8 with the STS score, hence, all were included in the

analysis. Graphical inspections of the linearity and proportional hazards assumptions for all-cause and CV mortality are delineated in Figures S2-5.

In the univariable analysis on 5-year all-cause mortality, various echocardiographic parameters were associated with mortality. The C-index was highest for the STS score (0.67, 95% confidence interval [CI] 0.64, 0.70, Table 2). The results of the multivariable analysis on 5-year all-cause mortality in which the STS score was updated with echocardiographic parameters are summarized in Table 3. The LRT p-values were lowest for DVI ≤ 0.35 and EOAi with values of 0.035 and 0.060, respectively. The corresponding adjusted HRs were 1.45 (95% CI 1.05, 2.02) and 0.97 (95% CI 0.93, 1.00). The C-indices of all updated models were similar to the one with only the STS score (0.67 vs. 0.67) and all NRIs were close to 0.

Table 2. Univariable relations between candidate predictors and 5-year all-cause mortality in patients who underwent surgical aortic valve replacement.

	HR (95% CI)	**R^2**	**C-index (95% CI)**
Log STS PROM	2.61 (2.20, 3.09)	0.19	0.67 (0.64, 0.70)
V_{max}	0.95 (0.77, 1.16)	0.00	0.50 (0.47, 0.53)
MPG	0.99 (0.97, 1.01)	0.00	0.51 (0.48, 0.54)
EOA	0.97 (0.95, 0.99)	0.02	0.57 (0.54, 0.60)
EOAi	0.95 (0.91, 0.98)	0.02	0.56 (0.53, 0.60)
DVI	0.92 (0.84, 1.01)	0.00	0.54 (0.51, 0.57)
pEOAi	1.00 (0.92, 1.08)	0.00	0.50 (0.47, 0.53)
Any PPM	1.41 (1.14, 1.75)	0.02	0.54 (0.52, 0.57)
Moderate PPM §	1.34 (1.04, 1.73)	0.02	0.55 (0.52. 0.57)
Severe PPM §	1.57 (1.13, 2.18)		
V_{max} ≥ 2.0 m/s	0.84 (0.68, 1.04)	0.00	0.51 (0.49, 0.52)
MPG ≥ 20 mmHg	0.92 (0.61, 1.39)	0.00	0.50 (0.48, 0.51)
DVI ≤ 0.35	1.67 (1.20, 2.33)	0.01	0.53 (0.51, 0.54)

** The reference category for moderate and severe PPM is no PPM. CI; confidence interval, DVI; Doppler velocity index, EOA; effective orifice area, EOAi; EOA indexed by body surface area, HR; hazard ratio, MPG; mean pressure gradient, pEOAi; predicted EOAi, POAi; internal prosthesis orifice area indexed by stroke volume, PPM; prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria (3)) , STS PROM; Society of Thoracic Surgeons predicted risk of mortality, SV(i); stroke volume (index), Vmax; peak aortic jet velocity.*

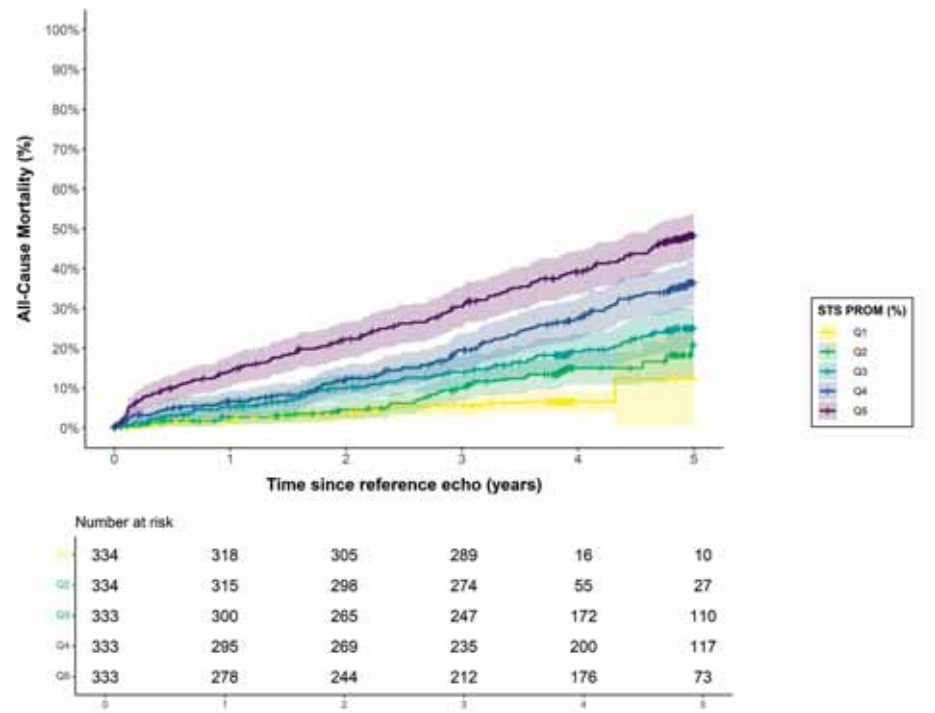
Table 3. Incremental prognostic value of single hemodynamic predictors to the STS PROM for 5-year all-cause mortality after surgical aortic valve replacement.

	HR Predictor (95% CI)	**HR Log STS PROM (95% CI)**	**LRT* p-value**	**C-index (95% CI)**	**NRI* (95% CI)**
Log STS PROM +					
V_{max}	0.95 (0.78, 1.16)	2.60 (2.20, 3.08)	0.615	0.67 (0.64, 0.70)	0.01 (-0.02, 0.04)
MPG	0.99 (0.97, 1.01)	2.60 (2.20, 3.08)	0.319	0.67 (0.64, 0.70)	0.01 (-0.02, 0.04)
EOA	0.99 (0.97, 1.01)	2.55 (2.15, 3.04)	0.273	0.67 (0.64, 0.70)	0.02 (-0.02, 0.07)
EOAi	0.97 (0.93, 1.00)	2.56 (2.16, 3.03)	0.060	0.67 (0.65, 0.70)	0.02 (-0.02, 0.07)
DVI	0.93 (0.86, 1.02)	2.60 (2.19, 3.08)	0.138	0.67 (0.65, 0.70)	0.02 (-0.02, 0.06)
pEOAi	1.00 (0.92, 1.07)	2.61 (2.20, 3.09)	0.904	0.67 (0.64, 0.70)	0.00 (-0.03, 0.04)
Any PPM	1.20 (0.97, 1.50)	2.56 (2.15, 3.03)	0.103	0.67 (0.65, 0.70)	0.01 (-0.03, 0.06)
Moderate PPM §	1.19 (0.92, 1.53)	2.55 (2.15, 3.03)	0.258	0.67 (0.65, 0.70)	0.02 (-0.03, 0.06)
Severe PPM §	1.23 (0.88, 1.72)				
$V_{max} \geq 2.0$ m/s	0.87 (0.70, 1.08)	2.60 (2.19, 3.07)	0.224	0.67 (0.64, 0.70)	-0.01 (-0.05, 0.03)
MPG ≥ 20 mmHg	0.82 (0.54, 1.24)	2.62 (2.21, 3.10)	0.340	0.67 (0.64, 0.70)	0.01 (-0.02, 0.05)
DVI ≤ 0.35	1.45 (1.05, 2.02)	2.57 (2.17, 3.05)	0.035	0.67 (0.65, 0.70)	0.00 (-0.03, 0.04)

** The LRT and NRI compared a new model with STS PROM + one hemodynamic predictor to a reference model of STS PROM alone. § The reference category for moderate and severe PPM is no PPM. CI, confidence interval; DVI, Doppler velocity index; EOA, effective orifice area; EOAi, EOA indexed by body surface area; HR, hazard ratio; LRT, likelihood ratio test; MPG, mean pressure gradient; NRI, net reclassification improvement; pEOAi, predicted EOAi; PPM, prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria (3)); STS PROM, Society of Thoracic Surgeons predicted risk of mortality; SV(i), stroke volume (index); Vmax, peak aortic jet velocity.*

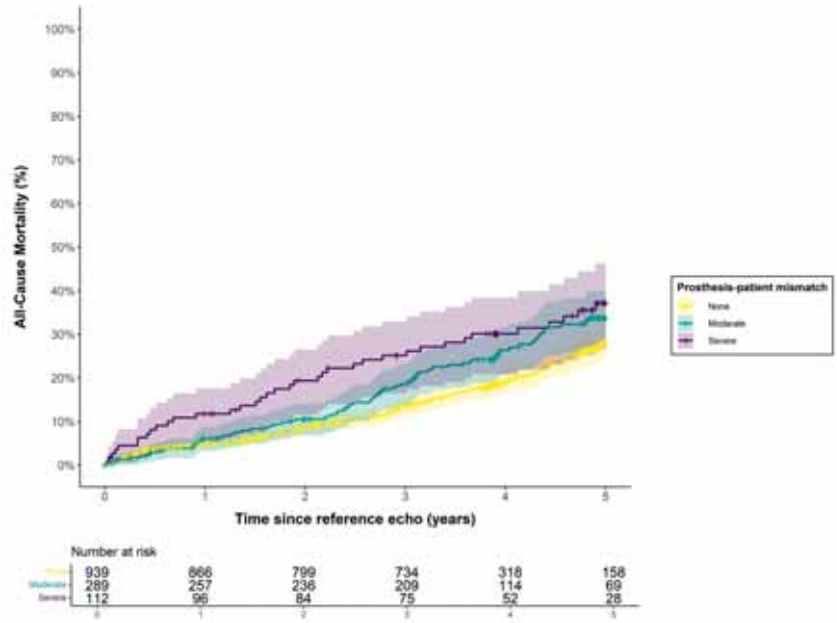
Figure 1 demonstrates the all-cause mortality risk throughout 5-year follow-up stratified to quintiles of the STS score. The median STS score for quintile 1, 2, 3, 4 and 5 were 1.4, 2.3, 3.4, 4.9, and 7.7%. The lowest quintile had the lowest risk of mortality, while the highest had the highest risk of mortality. Figure 2 and 3 demonstrate the Kaplan-Meier analyses according the PPM categories and DVI ≤ or > 0.35.

Figure 1. Kaplan-Meier survival analysis according to quintiles of Society of Thoracic Surgeons score for patients that underwent surgical aortic valve replacement.



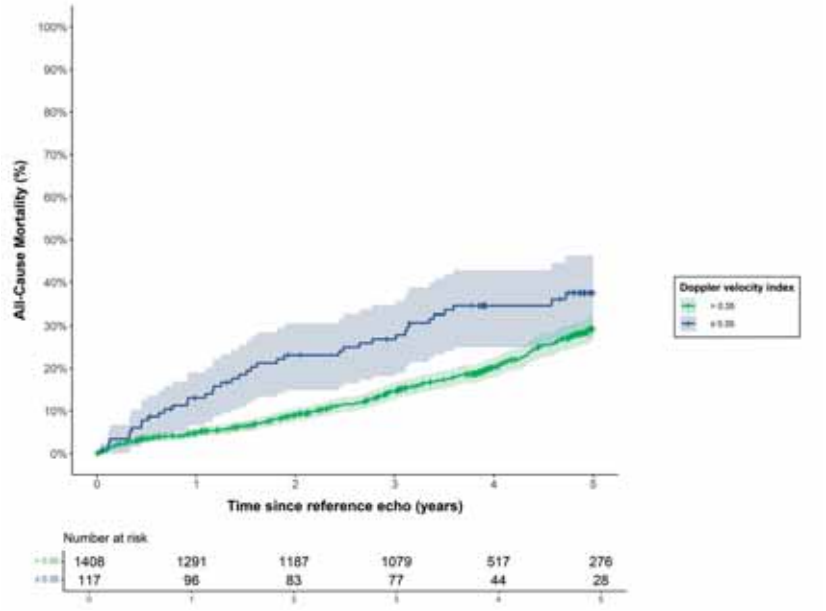
Q1 is the quintile with the lowest STS score, while Q5 is the quintile with the highest STS score. Q, quintile; STS, Society of Thoracic Surgeons.

Figure 2. Kaplan-Meier survival analysis according to categories of prosthesis-patient mismatch for patients that underwent surgical aortic valve replacement.



Prosthesis-patient mismatch was defined based on the Valve Academic Research Consortium 3 criteria (3).

Figure 3. Kaplan-Meier survival analysis according to Doppler velocity index ≤ 0.35 for patients that underwent surgical aortic valve replacement.



For 5-year cardiovascular mortality, the univariable analysis is presented in Table S5 and the multivariable in Table 4. The LRT p-values were lowest for DVI and DVI ≤ 0.35 (0.007 and 0.017, respectively), followed by EOAi and PPM. The C-indices of all updated models hardly improved as compared to the C-index of the STS score alone (0.68 vs. 0.67), and all NRIs were close to 0.

The results of the subanalyses are presented in the supplementary files (Tables S6-9) but not discussed in detail. In the 10 imputed data sets, on average 866 had preserved ejection fraction and SVi > 35 mL/m^2, of which 158 had died at 5-year follow-up. The subgroup of patients with low-flow comprised on average 717 patients, of which 216 had died at 5-year follow-up. In both subgroups, none of the echocardiographic parameters provided incremental prognostic value to the STS score for 5-year mortality after SAVR.

Table 4. Incremental prognostic value of single hemodynamic predictors to the STS PROM for 5-year cardiovascular mortality after surgical aortic valve replacement.

	HR Predictor (95% CI)	**HR Log STS PROM (95% CI)**	**LRT* p-value**	**C-index (95% CI)**	**NRI* (95% CI)**
Log STS PROM +					
V_{max}	0.99 (0.77, 1.27)	2.50 (2.01, 3.11)	0.917	0.68 (0.65, 0.72)	0.00 (-0.04, 0.03)
MPG	1.00 (0.97, 1.02)	2.50 (2.01, 3.11)	0.684	0.68 (0.65, 0.71)	-0.01 (-0.05, 0.03)
EOA	0.98 (0.96,1.00)	2.41 (1.93, 3.01)	0.127	0.68 (0.64, 0.71)	0.00 (-0.05, 0.06)
EOAi	0.95 (0.91, 1.00)	2.43 (1.95, 3.03)	0.035	0.68 (0.65, 0.72)	0.02 (-0.04, 0.08)
DVI	0.86 (0.77, 0.96)	2.47 (1.99, 3.07)	0.007	0.68 (0.65, 0.72)	0.02 (-0.04, 0.07)
pEOAi	0.97 (0.88, 1.07)	2.50 (2.01, 3.11)	0.574	0.68 (0.65, 0.72)	0.00 (-0.04, 0.03)
Any PPM	1.36 (1.03, 1.79)	2.42 (1.94, 3.02)	0.033	0.69 (0.66, 0.72)	0.00 (-0.06, 0.06)
Moderate PPM §	1.24 (0.88, 1.74)	2.39 (1.92, 2.99)	0.042	0.69 (0.65, 0.72)	0.00 (-0.06, 0.07)
Severe PPM §	1.62 (1.10, 2.39)				
V_{max} ≥ 2.0 m/s	0.91 (0.68, 1.21)	2.49 (2.00, 3.10)	0.513	0.68 (0.65, 0.72)	0.00 (-0.05, 0.04)
MPG ≥ 20 mmHg	0.84 (0.49, 1.43)	2.51 (2.02, 3.12)	0.366	0.68 (0.65, 0.71)	-0.01 (-0.05, 0.02)
DVI ≤ 0.35	1.67 (1.13, 2.48)	2.45 (1.97, 3.05)	0.017	0.68 (0.65, 0.72)	0.01 (-0.04, 0.06)

** The LRT and NRI compared a new model with STS PROM + one hemodynamic predictor to a reference model of STS PROM alone. § The reference category for moderate and severe PPM is no PPM. CI, confidence interval; DVI, Doppler velocity index; EOA, effective orifice area; EOAi, EOA indexed by body surface area; HR, hazard ratio; LRT, likelihood ratio test; MPG, mean pressure gradient; NRI, net reclassification improvement; pEOAi, predicted EOAi; PPM, prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria (3)); STS PROM, Society of Thoracic Surgeons predicted risk of mortality; SV(i), stroke volume (index); Vmax, peak aortic jet velocity.*

DISCUSSION

This pooled analysis leveraging core laboratory echo data of three RCTs found that most echocardiographic parameters have no incremental predictive value for 5-year all-cause mortality after SAVR, when considered in addition to the STS score. The only exception was DVI, which – when dichotomized at 0.35 – provided some predictive improvement.

These results are in line with those from a previous study by our group based on 1022 SAVR patients enrolled in the PERIGON Pivotal trial (17). In that analysis, the added prognostic value of postoperative echocardiographic parameters to the STS score was also limited and the discrimination between patients that died or survived also remained unchanged when prosthetic valve performance parameters were added to the STS score.

The hemodynamic parameter that was most strongly related to all-cause mortality independent of the STS score was DVI ≤ 0.35. For patients with the same STS score, those with a postoperative DVI ≤ 0.35 have a mortality risk that is approximately 1.45 times higher than for those with values > 0.35. This association was even stronger than the one of severe PPM, which is currently used to define residual hemodynamic obstruction after SAVR. This finding reinforces the results of our previous study (17). Moreover, Hahn and colleagues also found that DVI ≤ 0.35 was associated with a poor prognosis after SAVR in the PARTNER studies (16). This evidence indicates that DVI ≤ 0.35 seems to be a robust parameter for clinically relevant hemodynamic obstruction after SAVR.

PPM, especially the severe category, is associated with adverse outcomes in many studies, however, in a considerable number it is not (4,5). There could be several potential explanations for this, including some reported limitations of the current EOAi-based definition. The validity of the indexation of EOA to BSA has been questioned, because BSA seems to be a poor proxy for cardiac output (6). As a result, the probability to have PPM after SAVR seems to increase with increasing BSA, while the probability on hemodynamic obstruction as defined by a MPG ≥ 20 mmHg and/or Doppler velocity index < 0.35 remains unchanged. The clinical implication of this indexation fallacy becomes apparent in the following literature example (7); in a study among an Asian and Western population, the Western population with a large BSA had significantly lower velocities and gradients after AVR but a significantly higher incidence of PPM. Another drawback is that there is relatively large variability in EOA, mainly because of the need to measure the LVOT diameter (1). Using the projected EOAi from valve charts or reference studies does not seem to be a solution since it might not correspond well to measured PPM after SAVR (9) and because pEOAi provided the poorest prognostic value out of all parameters tested in the current analysis.

Theoretically, one might expect that any form of residual obstruction after SAVR would especially associate with long-term outcomes. Obstruction at the level of the aortic valve induces an increased afterload which negatively impacts cardiac remodeling and could

provoke heart failure in time. The proportional hazards plots do not show this particular pattern though. The HRs seem to be most extreme at 1 to 2 years after surgery and tend to decline thereafter. A potential explanation could be that echocardiographic values do not fully represent valvular performance, but also reflect the health of the patient. For example, in Table S10 and S11 it can be observed that the patients with DVI ≤ 0.35 or severe PPM are also the ones with the highest STS scores, lowest LVEF, and lowest SV. These patients tend to die relatively quickly after SAVR. The strong link between the health of the patient and the echocardiographic parameters for prosthetic valve performance could also explain the limited incremental prognostic value to the STS score. Moreover, in general, predictors tend to become less powerful when the time between their measurement and the outcome increases. For 5-year mortality and beyond, information on the progression of echocardiographic parameters could yield superior prognostic value to single measurements shortly after surgery.

Limitations

The current study has some limitations. Because data from RCTs were used with specific eligibility criteria, the results might not generalize to the entire SAVR population. Furthermore, only patients who received a bioprosthesis were included in this analysis of which the majority received a stented valve. Moreover, the maximum follow-up time for the Evolut LR trial at the time of analysis was 4 years, so the low-risk patients have been censored at that timepoint and did not contribute follow-up time to the entire 5-year period. Longer follow-up of all patients would lead to more events and might alter the results. On the contrary, this analysis has multiple strengths. All clinical events were adjudicated by the same independent clinical events committee and all echocardiographic data by the Mayo Clinic core laboratory. The pooled cohort comprised many patients with many mortality events which allowed for stable predictions and high statistical power. It also allowed for studying cardiovascular mortality and for performing subanalyses in specific clinical groups.

CONCLUSIONS

Out of multiple parameters, DVI ≤ 0.35 was the only parameter that provided some predictive improvement to the STS score for the prediction of all-cause mortality after SAVR. However, prosthetic valve performance parameters did not provide incremental value for the discrimination of patients that die or survive throughout 5-year follow-up. These results indicate that patient characteristics, summarized in the STS score, are the main predictor of the patient's prognosis after SAVR and that prosthetic valve performance parameters provide limited added value.

Acknowledgements: We would like to thank Shuzhen Li for arranging access to the study data and for performing additional statistical validation.

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SUPPLEMENTARY FILES

Comprehensive methods and statistical analysis

Calculation projected effective orifice area index

The projected effective orifice area index (pEOAi) is the EOAi that is expected for a particular valve size and body surface area and is usually depicted in a valve chart that could be used prior to surgery [1]. To determine the pEOAi for each patient, the expected EOA of the prosthesis type and size that a patient received is divided by its body surface area. The expected EOA per prosthesis type and size were retrieved from reference studies [2-6].

Predictor suitability

Suitability of predictors was assessed by evaluating missing data and collinearity. Predictors of interest were excluded if the percentage of missing data exceeded 20% since those variables would probably be missing frequently in daily clinical practice. The Society of Thoracic Surgeons (STS) score, serving as a reference, was included in the analysis regardless of missing data. Collinearity between the STS score and the predictors of interest was investigated using Pearson's correlation coefficient for continuous predictors (R function *cor()* from R package *stats*), and point biserial correlation for dichotomous predictors (R function *cor.test()* from R package *stats*). If the correlation coefficient exceeded 0.8, the incremental prognostic value of that predictor was not studied.

Cox regression assumptions

For Cox regression modelling, linearity between continuous predictors and the log relative hazard on the outcome of all-cause and cardiovascular mortality was investigated. The assumption of linearity was checked using visual inspection of restricted cubic splines plots with 5 data knots (R function *rcspline.plot()* in R package *Hmisc*). In addition, the assumption of proportional hazards was studied by graphical inspection of Schoenfeld residuals (R function *cox.zph()* in R packages *survival*) but no adjustments were made in case of violations because average hazard ratios (HRs) throughout the prespecified follow-up windows were of interest.

Sample size considerations

In predictive analytics, the required sample size strongly depends on the number of outcome events [7]. The larger this number is in relation to the number of fitted parameters (or degrees of freedom in statistical terms) in the regression analysis, the more stable the prediction become. According to a common rule of thumb to limit overfitting, a minimum of 10 events per fitted parameter is needed. Since the extended models included two parameters, namely the STS score + one echocardiographic parameter, and the largest model in this analysis included three parameters, namely the STS score + moderate and severe prosthesis-patient mismatch, a minimum of 20 and 30 outcome events was considered appropriate, respectively.

Missing data

Multiple imputations were used to complete missing predictor data under the assumption of missing at random (MAR). The MAR assumption was deemed reasonable since missing predictor data were considered to be dependent on information that was measured. For example, echocardiographic variables like peak aortic jet velocity, mean pressure gradient and EOA correlate well and some variables even share the same underlying measurements (such as the velocity-time integral across the aortic valve). Imputations were based on a trial indicator, all baseline variables, the predictors of interest, and the outcome [8]. The imputation method was predictive mean matching for continuous predictors and logistics regression for categorical baseline characteristics with 50 iterations to create 10 imputed datasets (R function *mice()* in the R package *mice*). The regression model was separately fitted to each imputed dataset, and estimates pooled conform Rubin's rules [9].

Performance and improvement measures

Univariable regression was performed first. Hazard ratios (HRs), Nagelkerke's R^2, and the C-index were calculated [10,11]. The HRs depict the relative instantaneous hazard on the outcome per unit increase in the predictor for patients that are alive and did not experience the outcome yet (R function *coxph()* from the R package *survival*). Nagelkerke's R^2 is a measure for explained variation in the outcome (R function *rsq()* in the R package *survMisc*) and is commonly calculated for logistic regression models but can also be used for survival data [10]. The C-index (R function *coxph()* from the R package *survival*) is a measure for discrimination and is an extension to the C-statistic for censored data[10,11]. The C-index calculates the probability that for a pair of two patients, the patient with a higher predicted risk experiences the outcome earlier than a patient with a lower predicted risk (i.e, that this patient experiences the outcome either later or not at all). A value of 0.5 implies that a model perform equally well to using no model or chance, while a value of 1 indicates perfect discrimination.

In multivariable analysis, HRs, the likelihood ratio test (LRT), the C-index, and the net reclassification index (NRI) were estimated. The calculation and interpretation of the HRs and C-index are identical to the univariable analysis. The LRT (R function *D2()* from the R package *mice*) and the NRI (R function *nricens()* from the R package *nricens*) were used to investigate improvement of updated models compared to a reference model with the STS score alone. To estimate valid p-values for the LRT after multiple imputations, the separate Chi-square test statistics were pooled conform the D2 method as proposed by Li *et al.* [12]. Subsequently, the p-values corresponding to the pooled test statistics were derived from the F distribution (R function *pf()* from R package *stats*). The NRI estimates the probabilities for (in)correct reclassification of cases and controls in a new as compared to an old (reference) model, ranging from 2 (all cases and controls correctly reclassified) to -2 (all cases and controls incorrectly reclassified) [10,13]. A more detailed explanation can be found in the article by Pencina *et al.* [13]. For the models investigating 5-year mortality, a three-category NRI is utilized in which the cut-offs were based on the 5-year cumulative incidences in the PARTNER 1 [14], and PARTNER 2 trial [15] which were 62.4% and 42.1%

for all-cause mortality, and 47.6%, and 27.6% for CV mortality. These risks also include the deaths of patients that died before postoperative reference echo at discharge/30-days, while these patients will be excluded from our analysis. To compensate for this overestimation, we attenuated the cumulative incidences from the PARTNER trials by $\frac{deaths\ before\ reference\ echo}{total\ deaths}$ in our study. For example, if we exclude 5% of the total 5-year deaths, the three-category NRI cut-offs will be 0.95 (= 1-0.05) times the corresponding risks in the PARTNER studies. Similar methods were used to determine the cut-offs for 5-year CV mortality.

Data visualization

The cumulative incidence of all-cause mortality per quintile of the STS score throughout five years was plotted using the Kaplan-Meier method (R function *ggsurvplot()* from R package *survminer*).

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Table S1. Study designs of the CoreValve High Risk, SURTAVI, and Evolut Low Risk trials.

	CoreValve High Risk	**SURTAVI**	**Evolut Low Risk**
No. of patients who received a surgical bioprosthetic valve*	354	793	682
Study type	Randomized	Randomized	Randomized
No. of sites	45	87	86
Geographic location(s)	United States	Europe, United States, Canada	Australia, Canada, France, Japan, Netherlands, New Zealand, United States
Echocardiographic core laboratory	Mayo Clinic Rochester, Minnesota, USA	Mayo Clinic Rochester, Minnesota, USA	Mayo Clinic Rochester, Minnesota, USA
Adjudication of deaths, safety-related adverse events	Independent CEC: Baim Institute for Clinical Research, Boston, Massachusetts, USA	Independent CEC: Baim Institute for Clinical Research, Boston, Massachusetts, USA	Independent CEC: Baim Institute for Clinical Research, Boston, Massachusetts, USA
Patient selection	• Severe AS • NYHA class II or greater • Increased risk of surgery (ie, risk of death within 30 d ≥15% and the risk of death or irreversible complications within 30 d after surgery <50%)	• Symptomatic, severe AS • Intermediate surgical risk (ie, estimated risk of 30-d surgical death of 3%-15% using STS-PROM criteria)	• Severe AS with suitable anatomy for TAVR or surgery • Predicted risk of death within 30 d after surgery of no more than 3%
Key exclusion criteria	• AMI ≤30 d before index procedure • Percutaneous/peripheral BMS within 30 d or DES within 6 mo of index procedure • Blood dyscrasias • CAD requiring revascularization • Cardiogenic shock • Severe LV dysfunction with LVEF <20 • CVA or TIA within 6 mo of index procedure	• Refusal of SAVR as a treatment option • Any contraindication for placement of a bioprosthetic valve (eg, need for mechanical valve) • Known hypersensitivity or contraindication to all anticoagulation/antiplatelet • regimens (or inability to be anticoagulated for the index procedure), nitinol, or sensitivity to contrast medium that cannot be adequately pre-medicated • Blood dyscrasias • Ongoing sepsis, including active endocarditis	• Any contraindication to placement of a bioprosthetic valve (eg, need for a mechanical valve) • Known hypersensitivity or contraindication to any of the following that cannot be adequately premedicated: (1) aspirin or heparin (HIT/HITTS) and bivalirudin; (2) ticlopidine and clopidogrel; (3) nitinol (titanium or nickel); or (4) contrast media • Blood dyscrasias • Ongoing sepsis, including active endocarditis

Table S1. Continued

	CoreValve High Risk	SURTAVI	Evolut Low Risk
Concomitant procedures allowed in patients who received a surgical AVR?	No	Yes, limited procedures allowed	Yes, limited procedures allowed
Primary end point(s)	Rate of any death at 1 y	Composite of death from any cause or disabling stroke at 24 mo	All-cause mortality or disabling stroke at 2 y
Planned maximum follow-up, including TTE	5 y	5 y in entire cohort, 10 y in a LTFU cohort	10 y
Current follow-up	5 y	5 y	4 y

Reproduced and adjusted from open access manuscript Vriesendorp MD, et al. Why the categorization of indexed effective orifice area is not justified for the classification of prosthesis-patient mismatch. J Thorac Cardiovasc Surg. 2022 Sep;164(3):822-829.e6. doi: 10.1016/j.jtcvs.2020.10.123. CEC, Clinical events committee; AS, aortic stenosis; AR, aortic regurgitation; AVR, aortic valve replacement; NYHA, New York Heart Association; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR, transcatheter aortic valve replacement; AMI, acute myocardial infarction; BMS, bare metal stent; DES, drug-eluting stent; CAD, coronary artery disease; LV, left ventricle; LVEF, left ventricular ejection fraction; CVA, cerebrovascular accident; TIA, transient ischemic attack; SAVR, surgical aortic valve replacement; HIT/HITTS, heparin-induced thrombocytopenia and heparin-induced thrombocytopenia with thrombosis syndrome; TTE, transthoracic echocardiography; EOAi, indexed effective orifice area; LTFU, long-term follow-up. ∗ The numbers indicate only the SAVR patients included in the current analysis.

Table S2. Overview of implanted bioprostheses for patients who underwent surgical aortic valve replacement.

Bioprosthetic valve type	**N (%)**
Stented	1397 (84%)
Perimount	661
Trifecta	370
Mosaic	218
Hancock II	57
Mitroflow	44
Biocor/Epic	35
Inspiris Resilia	7
Avalus	5
Stentless	64 (4%)
Freestyle	61
Solo	3
Sutureless	206 (12%)
Intuity	109
Perceval	89
3F Enable	8

Table S3. Overview of missing data.

Candidate predictor	**Missing data**
Society of Thoracic Surgeons predicted risk of mortality	0 (0%)
Peak aortic jet velocity	47 (2.8%)
Mean pressure gradient	49 (2.9%)
Effective orifice area	327 (19.6%)
Effective orifice area index	327 (19.6%)
Doppler velocity index	142 (8.5%)
Stroke volume	320 (19.2%)
Stroke volume index	320 (19.2%)
Predicted effective orifice area index	111 (6.7%)
Chronic obstructive pulmonary disease	28 (1.7%)
Peripheral vascular disease	3 (0.2%)
Hypertension	1 (0.1%)
Previous stroke / cerebrovascular accident	1 (0.1%)
Atrial fibrillation or flutter	1 (0.1%)
Implanted labelled valve size	85 (5.1%)

Table S4. Correlation between the Society of Thoracic Surgeons predicted risk of mortality and each candidate predictor.

CANDIDATE PREDICTOR	LOG STS PROM
Peak aortic jet velocity	0.05
Mean pressure gradient	0.06
Effective orifice area	-0.23
Effective orifice area indexed by BSA	-0.13
Doppler velocity index	-0.02
Predicted effective orifice area indexed by BSA	0.02
Any prosthesis-patient mismatch*	0.16
Moderate prosthesis-patient mismatch*	0.08
Severe prosthesis-patient mismatch*	0.14
Peak aortic jet velocity ≥ 2.0 m/s	-0.01
Mean pressure gradient ≥ 20 mmHg	0.07
Doppler velocity index ≤ 0.35	0.08

STS PROM, Society of Thoracic Surgeons predicted risk of mortality.

Table S5. Univariable relations between candidate predictors and 5-year cardiovascular mortality in patients who underwent surgical aortic valve replacement.

	HR (95% CI)	R^2	C-Index (95% CI)
Log STS PROM	2.50 (2.01, 3.11)	0.17	0.67 (0.63, 0.70)
V_{max}	0.99 (0.76, 1.28)	0.00	0.50 (0.45, 0.54)
MPG	1.00 (0.97, 1.02)	0.00	0.50 (0.46, 0.54)
EOA	0.96 (0.94, 0.99)	0.03	0.58 (0.54, 0.62)
EOAi	0.93 (0.89, 0.98)	0.03	0.58 (0.54, 0.63)
DVI	0.84 (0.75, 0.95)	0.02	0.57 (0.53, 0.61)
pEOAi	0.97 (0.88, 1.08)	0.00	0.52 (0.48, 0.55)
Any PPM	1.58 (1.20, 2.07)	0.03	0.56 (0.52, 0.59)
Moderate PPM §	1.39 (0.99, 1.95)	0.04	0.56 (0.53, 0.60)
Severe PPM §	2.03 (1.39, 2.98)		
V_{max} ≥ 2.0 m/s	0.87 (0.66, 1.16)	0.00	0.51 (0.48, 0.54)
MPG ≥ 20 mmHg	0.87 (0.51, 1.50)	0.00	0.50 (0.48, 0.52)
DVI ≤ 0.35	1.91 (1.28, 2.84)	0.02	0.54 (0.51, 0.56)

** The reference category for moderate and severe PPM is no PPM. CI; confidence interval, DVI; Doppler velocity index, EOA; effective orifice area, EOAi; EOA indexed by body surface area, HR; hazard ratio, MPG; mean pressure gradient, pEOAi; predicted EOAi, POAi; internal prosthesis orifice area indexed by stroke volume, PPM; prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria 16) , STS PROM; Society of Thoracic Surgeons predicted risk of mortality, SV(i); stroke volume (index), Vmax; peak aortic jet velocity.*

Table S6. Univariable relations between candidate predictors and 5-year all-cause mortality in patients with preserved ejection fraction and normal-flow who underwent surgical aortic valve replacement.

	HR (95% CI)	R^2	C-Index (95% CI)
Log STS PROM	2.47 (1.89, 3.23)	0.17	0.66 (0.62, 0.71)
V_{max}	1.05 (0.74, 1.47)	0.00	0.51 (0.46, 0.57)
MPG	1.00 (0.96, 1.03)	0.00	0.50 (0.44, 0.55)
EOA	0.99 (0.96, 1.02)	0.00	0.53 (0.47, 0.59)
EOAi	0.99 (0.94, 1.05)	0.00	0.53 (0.46, 0.60)
DVI	1.04 (0.90, 1.21)	0.00	0.50 (0.45, 0.55)
pEOAi	1.03 (0.90, 1.17)	0.00	0.51 (0.46, 0.56)
Any PPM	1.48 (1.00, 2.20)	0.01	0.54 (0.50, 0.57)
Moderate PPM §	1.56 (1.02, 2.38)	0.02	0.54 (0.51, 0.58)
Severe PPM §	0.93 (0.24, 3.63)		
$V_{max} \geq 2.0$ m/s	0.84 (0.58, 1.23)	0.00	0.51 (0.47, 0.54)
MPG ≥ 20 mmHg	0.92 (0.50, 1.71)	0.00	0.50 (0.47, 0.53)
DVI ≤ 0.35	1.27 (0.53, 3.07)	0.00	0.50 (0.49, 0.52)

** The reference category for moderate and severe PPM is no PPM. Normal-flow is defined as stroke volume index >35 mL/m2.CI; confidence interval, DVI; Doppler velocity index, EOA; effective orifice area, EOAi; EOA indexed by body surface area, HR; hazard ratio, MPG; mean pressure gradient, pEOAi; predicted EOAi, POAi; internal prosthesis orifice area indexed by stroke volume, PPM; prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria 16) , STS PROM; Society of Thoracic Surgeons predicted risk of mortality, SV(i); stroke volume (index), Vmax; peak aortic jet velocity.*

Table S7. Incremental prognostic value of single hemodynamic predictors to the STS PROM for 5-year all-cause mortality in patients with preserved ejection fraction and normal-flow who underwent surgical aortic valve replacement.

	HR Predictor (95% CI)	HR Log STS PROM (95% CI)	LRT* p-value	C-Index (95% CI)	NRI* (95% CI)
Log STS PROM +					
V_{max}	0.99 (0.72, 1.37)	2.47 (1.89, 3.23)	0.820	0.66 (0.62, 0.71)	0.00 (-0.04, 0.04)
MPG	0.99 (0.96, 1.02)	2.48 (1.89, 3.24)	0.536	0.66 (0.62, 0.71)	0.01 (-0.04, 0.06)
EOA	1.01 (0.98, 1.04)	2.50 (1.91, 3.27)	0.699	0.66 (0.62, 0.71)	0.01 (-0.04, 0.05)
EOAi	1.00 (0.95, 1.06)	2.47 (1.89,3.23)	0.843	0.66 (0.62, 0.71)	0.00 (-0.04, 0.05)
DVI	1.02 (0.88, 1.18)	2.46 (1.88, 3.23)	0.819	0.66 (0.62, 0.71)	0.00 (-0.04, 0.04)
pEOAi	1.02 (0.90, 1.16)	2.47 (1.89, 3.23)	0.743	0.66 (0.62, 0.71)	0.01 (-0.04, 0.05)
Any PPM	1.19 (0.80, 1.78)	2.42 (1.84, 3.17)	0.413	0.66 (0.62 0.71)	0.00 (-0.05, 0.05)

Table S7. Continued

	HR Predictor (95% CI)	HR Log STS PROM (95% CI)	LRT* p-value	C-Index (95% CI)	NRI* (95% CI)
Moderate PPM §	NA	NA	NA	NA	NA
Severe PPM §	NA				
V_{max} ≥ 2.0 m/s	0.86 (0.59, 1.25)	2.46 (1.88, 3.22)	0.448	0.67 (0.62, 0.71)	0.00 (-0.04, 0.05)
MPG ≥ 20 mmHg	0.80 (0.43, 1.48)	2.49 (1.90, 3.25)	0.478	0.66 (0.62, 0.71)	0.01 (-0.04, 0.05)
DVI ≤ 0.35	1.29 (0.53, 3.16)	2.48 (1.89, 3.24)	0.639	0.66 (0.62, 0.71)	0.00 (-0.03, 0.04)

** The LRT and NRI compared a new model with STS PROM + one candidate predictor to a reference model of STS PROM alone. § The reference category for moderate and severe PPM is no PPM. Normal-flow is defined as stroke volume index >35 mL/m2. CI; confidence interval, DVI; Doppler velocity index, EOA; effective orifice area, EOAi; EOA indexed by body surface area, HR; hazard ratio, LRT; likelihood ratio test, MPG; mean pressure gradient, NRI; net reclassification improvement, pEOAi; predicted EOAi, PPM; prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria 16), STS PROM; Society of Thoracic Surgeons predicted risk of mortality, SV(i); stroke volume (index), Vmax; peak aortic jet velocity.*

Table S8. Univariable relations between candidate predictors and 5-year all-cause mortality in patients with low-flow who underwent surgical aortic valve replacement.

	HR (95% CI)	R^2	C-Index (95% CI)
Log STS PROM	2.68 (2.08, 3.44)	0.19	0.66 (0.63, 0.70)
V_{max}	0.98 (0.74, 1.29)	0.00	0.50 (0.46, 0.54)
MPG	1.00 (0.97, 1.02)	0.00	0.50 (0.46, 0.54)
EOA	0.98 (0.95, 1.01)	0.00	0.53 (0.49, 0.58)
EOAi	0.98 (0.92, 1.04)	0.00	0.52 (0.48, 0.56)
DVI	0.93 (0.81, 1.05)	0.00	0.54 (0.49, 0.58)
pEOAi	1.02 (0.91, 1.15)	0.00	0.51 (0.47, 0.55)
Any PPM	1.03 (0.77, 1.40)	0.01	0.51 (0.47, 0.55)
Moderate PPM §	0.95 (0.67, 1.35)	0.02	0.53 (0.49, 0.57)
Severe PPM §	1.19 (0.82, 1.74)		
V_{max} ≥ 2.0 m/s	0.88 (0.66, 1.18)	0.00	0.51 (0.48, 0.54)
MPG ≥ 20 mmHg	1.08 (0.58, 2.00)	0.00	0.50 (0.48, 0.52)
DVI ≤ 0.35	1.61 (1.09, 2.38)	0.02	0.54 (0.51, 0.56)

** The reference category for moderate and severe PPM is no PPM. Normal-flow is defined as stroke volume index >35 mL/m2.CI; confidence interval, DVI; Doppler velocity index, EOA; effective orifice area, EOAi; EOA indexed by body surface area, HR; hazard ratio, MPG; mean pressure gradient, pEOAi; predicted EOAi, POAi; internal prosthesis orifice area indexed by stroke volume, PPM; prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria 16) , STS PROM; Society of Thoracic Surgeons predicted risk of mortality, SV(i); stroke volume (index), Vmax; peak aortic jet velocity.*

Table S9. Incremental prognostic value of single hemodynamic predictors to the STS PROM for 5-year all-cause mortality in patients with low-flow who underwent surgical aortic valve replacement.

	HR Predictor (95% CI)	**HR Log STS PROM (95% CI)**	**LRT* p-value**	**C-Index (95% CI)**	**NRI* (95% CI)**
Log STS PROM +					
V_{max}	1.05 (0.80, 1.38)	2.69 (2.09, 3.47)	0.752	0.67 (0.63, 0.70)	-0.01 (-0.06, 0.05)
MPG	1.00 (0.98, 1.03)	2.68 (2.08, 3.46)	0.867	0.67 (0.63, 0.70)	0.00 (-0.06, 0.06)
EOA	1.00 (0.98, 1.04)	2.68 (2.08, 3.46)	0.807	0.66 (0.63, 0.70)	0.00 (-0.05, 0.04)
EOAi	0.99 (0.93, 1.05)	2.67 (2.08, 3.44)	0.743	0.67 (0.63, 0.70)	0.00 (-0.05, 0.05)
DVI	0.93 (0.82, 1.05)	2.67 (2.08, 3.43)	0.241	0.67 (0.63, 0.71)	0.00 (-0.04, 0.04)
pEOAi	1.00 (0.90, 1.12)	2.68 (2.08, 3.44)	0.841	0.66 (0.63, 0.70)	0.01 (-0.03, 0.05)
Any PPM	1.00 (0.74, 1.35)	2.68 (2.08, 3.14)	0.771	0.66 (0.63, 0.70)	0.00 (-0.06, 0.07)
Moderate PPM §	0.98 (0.69, 1.39)	2.67 (2.08, 3.43)	0.953	0.67 (0.63, 0.70)	0.00 (-0.07, 0.07)
Severe PPM §	1.02 (0.70, 1.50)				
$V_{max} \geq 2.0$ m/s	0.95 (0.72, 1.27)	2.67 (2.08, 3.43)	0.767	0.66 (0.63, 0.70)	0.00 (-0.05, 0.06)
MPG ≥ 20 mmHg	1.00 (0.53, 1.86)	2.68 (2.09, 3.44)	0.800	0.66 (0.63, 0.70)	0.00 (-0.04, 0.04)
DVI ≤ 0.35	1.39 (0.93, 2.06)	2.62 (2.04, 3.36)	0.123	0.67 (0.63, 0.71)	0.00 (-0.07, 0.07)

** The LRT and NRI compared a new model with STS PROM + one candidate predictor to a reference model of STS PROM alone. § The reference category for moderate and severe PPM is no PPM. Normal-flow is defined as stroke volume index >35 mL/m2. CI; confidence interval, DVI; Doppler velocity index, EOA; effective orifice area, EOAi; EOA indexed by body surface area, HR; hazard ratio, LRT; likelihood ratio test, MPG; mean pressure gradient, NRI; net reclassification improvement, pEOAi; predicted EOAi, PPM; prosthesis-patient mismatch (according to the Valve Academic Research Consortium 3 criteria 16), STS PROM; Society of Thoracic Surgeons predicted risk of mortality, SV(i); stroke volume (index), Vmax; peak aortic jet velocity.*

Table S10. Baseline characteristics and postoperative echocardiographic parameters at the reference echo for patients who underwent surgical aortic valve replacement stratified to DVI > or ≤ 0.35.

	DVI > 0.35 N = 1408	**DVI ≤ 0.35 N = 117**
Age (years)	78 ± 7	78 ± 7.43
Male	838 (60%)	64 (55%)
Body surface area (m^2)	1.93 ± 0.24	1.92 ± 0.26
Body mass index (kg/m^2)	29.7 ± 5.9	29.7 ± 5.7
STS PROM (%)	3.3 [2.0, 5.3]	4.3 [2.5, 6.2]
Diabetes mellitus	486 (35%)	49 (42%)
Hypertension	1241 (88%)	108 (92%)
Chronic obstructive pulmonary disease	406 (29%)	34 (30%)
Left ventricle ejection fraction (%)	61 ± 9	55 ± 13
Atrial fibrillation or flutter	337 (24%)	44 (38%)
NYHA class III/IV	727 (52%)	68 (58%)
Previous stroke / cerebrovascular accident	148 (11%)	15 (13%)
Peripheral vascular disease	344 (25%)	23 (20%)
Preoperative serum creatinine >2 mg/dl	15 (5%)	30 (2%)
Any concomitant procedure	330 (25%)	34 (29%)
Concomitant CABG	214 (15%)	27 (23%)
Postoperative reference echo		
Peak aortic jet velocity (ms^{-1})	2.22 ± 0.46	2.82 ± 0.54
Mean pressure gradient (mm Hg)	11.0 ± 4.6	18.21 ± 7.07
Effective orifice area (cm^2)	1.91 ± 0.59	1.10 ± 0.31
Effective orifice area index (cm^2/m^2)	1.00 ± 0.29	0.58 ± 0.14
Doppler velocity index	0.52 ± 0.10	0.31 ± 0.04
Stroke volume (mL)	75 ± 23	60 ± 22
Stroke volume index (mL/m^2)	39 ± 11	31 ± 10
Predicted effective orifice area index (cm^2/m^2)	0.87 ± 0.12	0.78 ± 0.12
Prosthesis-patient mismatch		
Any	316 (25.4%)	85 (89.5%)
Moderate	257 (20.6%)	32 (33.7%)
Severe	59 (4.7%)	53 (55.8%)
Peak aortic jet velocity ≥ 2.0 m/s	980 (70%)	114 (97%)
Mean pressure gradient ≥ 20 mmHg	62 (4%)	38 (33%)
Stroke volume index ≤ 35 mL/m^2	487 (39%)	68 (72%)

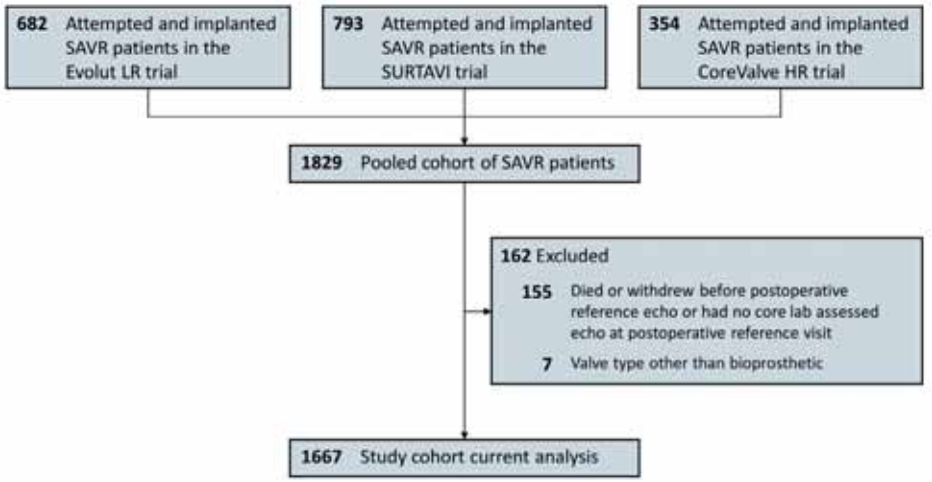
Numerical data are expressed as mean ± standard deviation or median [interquartile range], and categorical data as count (percentage). BSA, body surface area; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS PROM, Society of Thoracic Surgeons predicted risk of mortality.

Table S11. Baseline characteristics and postoperative echocardiographic parameters at the reference echo for patients who underwent surgical aortic valve replacement stratified to categories of prosthesis-patient mismatch.

	No PPM N = 939	**Moderate PPM N = 289**	**Severe PPM N = 112**
Age (years)	78 ± 7	78 ± 7	80 ± 8
Male	597 (64%)	160 (55%)	48 (43%)
Body surface area (m^2)	1.94 ± 0.24	1.93 ± 0.24	1.90 ± 0.25
Body mass index (kg/m^2)	29.8 ± 5.8	29.1 ± 5.8	29.3 ± 6.2
STS PROM (%)	3.0 [1.9, 5.0]	4.0 [2.2, 5.7]	4.9 [3.0, 6.9]
Diabetes mellitus	305 (33%)	121 (42%)	38 (34%)
Hypertension	827 (88%)	264 (91%)	98 (88%)
Chronic obstructive pulmonary disease	246 (27%)	91 (32%)	38 (34%)
Left ventricle ejection fraction (%)	62 ± 9	59 ± 11	58 ± 12
Atrial fibrillation or flutter	212 (23%)	97 (34%)	34 (30%)
NYHA class III/IV	462 (49%)	164 (57%)	71 (63%)
Previous stroke / cerebrovascular accident	99 (11%)	31 (11%)	13 (11%)
Peripheral vascular disease	215 (23%)	77 (27%)	30 (27%)
Preoperative serum creatinine >2 mg/dl	16 (2%)	5 (2%)	3 (3%)
Any concomitant procedure	222 (24%)	67 (23%)	25 (22%)
Concomitant CABG	143 (15%)	39 (14%)	21 (19%)
Postoperative reference echo			
Peak aortic jet velocity (ms^{-1})	2.12 ± 0.42	2.48 ± 0.46	2.82 ± 0.53
Mean pressure gradient (mm Hg)	10.0 ± 4.0	13.8 ± 5.2	17.9 ± 6.8
Effective orifice area (cm^2)	2.12 ± 0.52	1.36 (0.18)	0.96 ± 0.18
Effective orifice area index (cm^2/m^2)	1.10 ± 0.26	0.71 (0.08)	0.51 ± 0.09
Doppler velocity index	0.55 ± 0.10	0.43 (0.07)	0.36 ± 0.07
Stroke volume (mL)	81 ± 23	62 ± 16	51 ± 13
Stroke volume index (mL/m^2)	41.72 ± 11	32 ± 8	27 ± 6
Predicted effective orifice area index (cm^2/m^2)	0.89 ± 0.12	0.82 ± 0.11	0.76 ± 0.11
Peak aortic jet velocity ≥ 2.0 m/s	593 (63%)	256 (89%)	108 (96%)
Mean pressure gradient ≥ 20 mmHg	21 (2%)	31 (11%)	33 (30%)
Doppler velocity index ≤ 0.35	10 (1%)	32 (11%)	53 (47%)
Stroke volume index ≤ 35 mL/m^2	267 (28%)	188 (65%)	100 (89%)

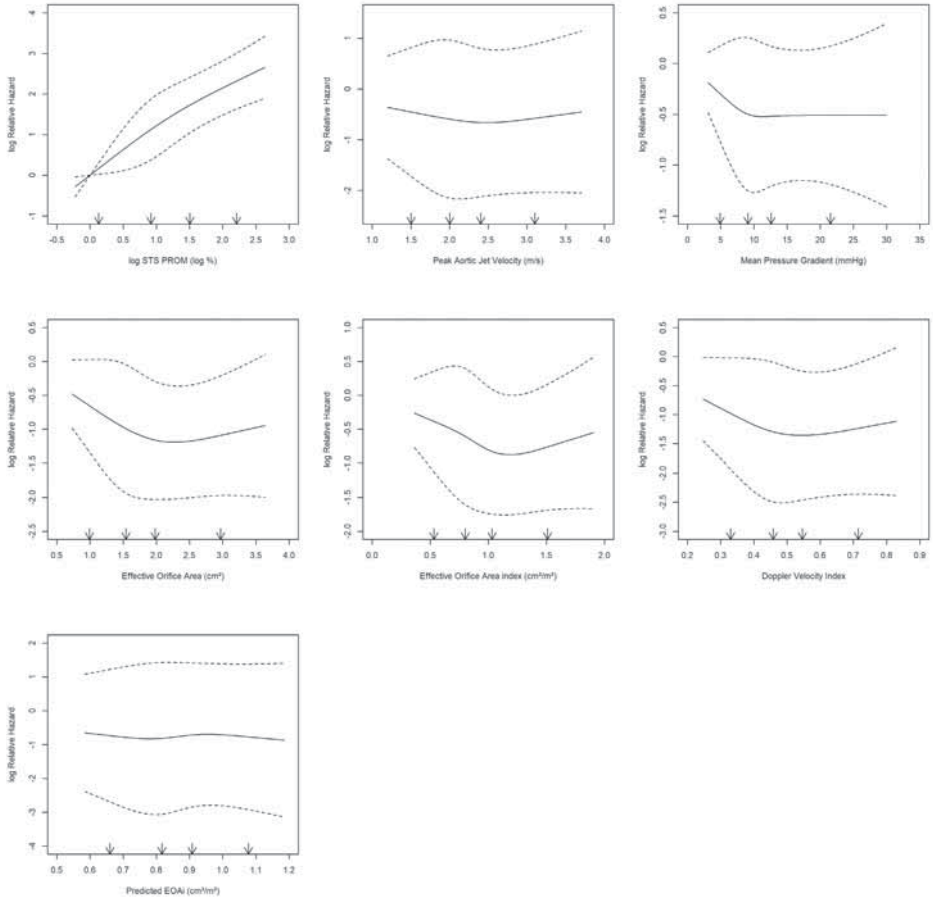
Numerical data are expressed as mean ± standard deviation or median [interquartile range], and categorical data as count (percentage). BSA, body surface area; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS PROM, Society of Thoracic Surgeons predicted risk of mortality.

Figure S1. Flowchart for the derivation of the analysis cohort.



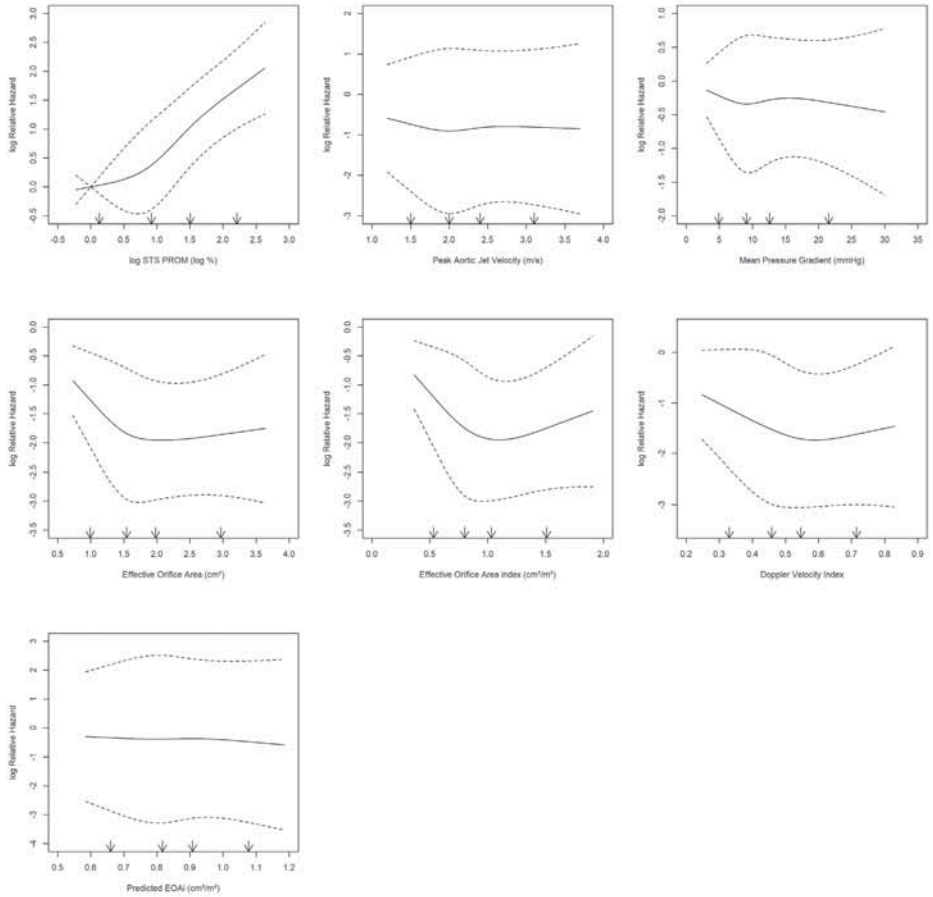
HR, high risk; LR, low risk; SAVR, surgical aortic valve replacement; SURTAVI, Surgical Replacement and Transcatheter Aortic Valve Implantation.

Figure S2. Graphical overview of the linearity assumption between continuous parameters and all-cause mortality for Cox regression.



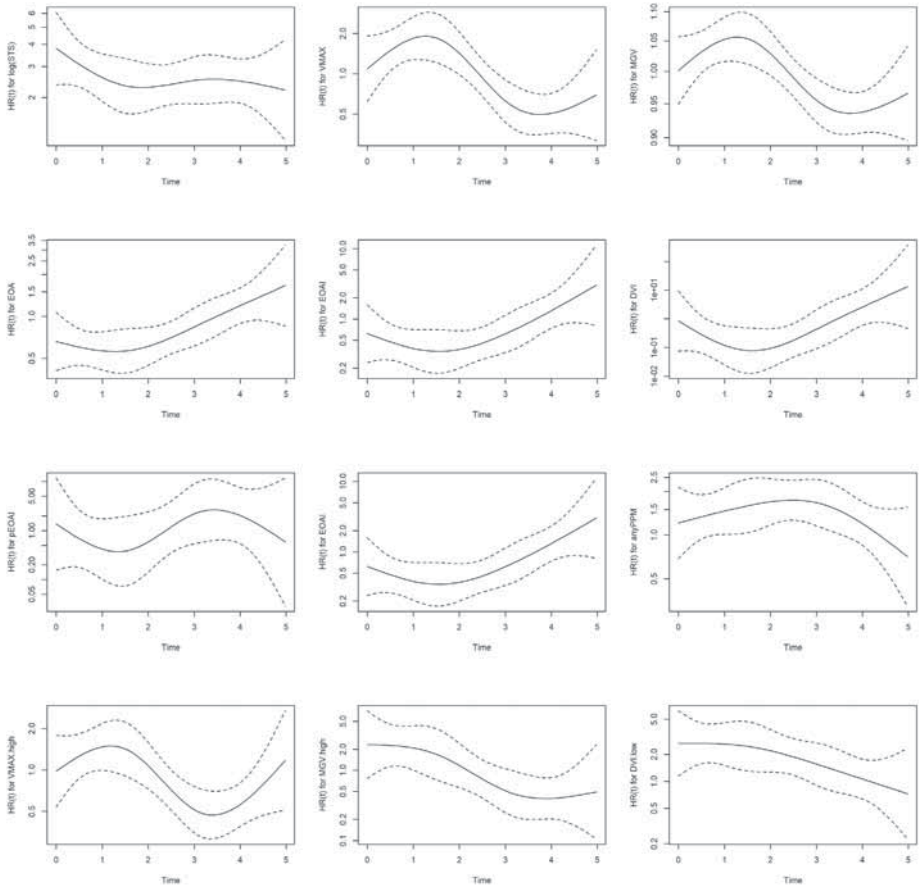
EOAi, effective orifice area index; STS PROM, Society of Thoracic Surgeons predicted risk of mortality.

Figure S3. Graphical overview of the linearity assumption between continuous parameters and cardiovascular mortality for Cox regression.



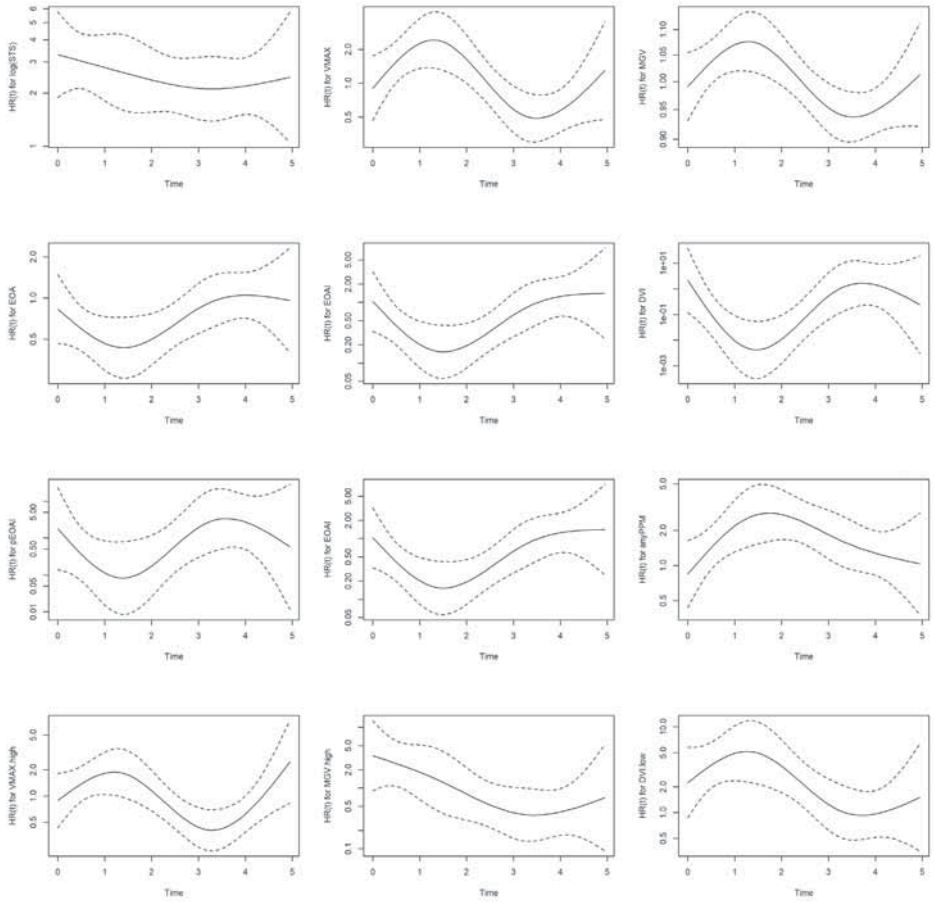
EOAi, effective orifice area index; STS PROM, Society of Thoracic Surgeons predicted risk of mortality.

Figure S4. Graphical overview of the proportional hazards assumption for Cox regression on all-cause mortality.



DVI, Doppler velocity index; DVI.low, DVI ≤ 0.35; EOA, effective orifice area; EOAi, EOA index; MGV, mean pressure gradient; MGV.high, MPG ≥20 mmHg; pEOAI, predicted EOAi; PPM, prosthesis-patient mismatch; STS PROM, Society of Thoracic Surgeons predicted risk of mortality; Vmax, peak aortic jet velocity; VMAX.high, Vmax ≥ 2.0 m/s.

Figure S5. Graphical overview of the proportional hazards assumption for Cox regression on cardiovascular mortality.



DVI, Doppler velocity index; DVI.low, DVI ≤ 0.35; EOA, effective orifice area; EOAi, EOA index; MGV, mean pressure gradient; MGV.high, MPG ≥20 mmHg; pEOAI, predicted EOAi; PPM, prosthesis-patient mismatch; STS PROM, Society of Thoracic Surgeons predicted risk of mortality; Vmax, peak aortic jet velocity; VMAX.high, Vmax ≥ 2.0 m/s.

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CURRENT DEFINITIONS FOR HEMODYNAMIC STRUCTURAL VALVE DETERIORATION LACK CONSISTENCY

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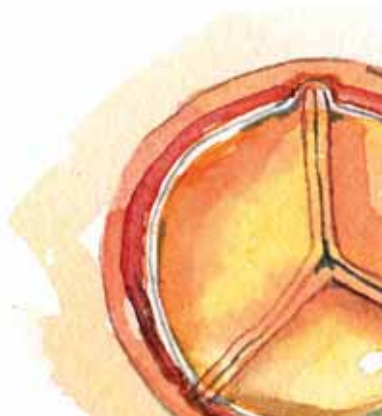
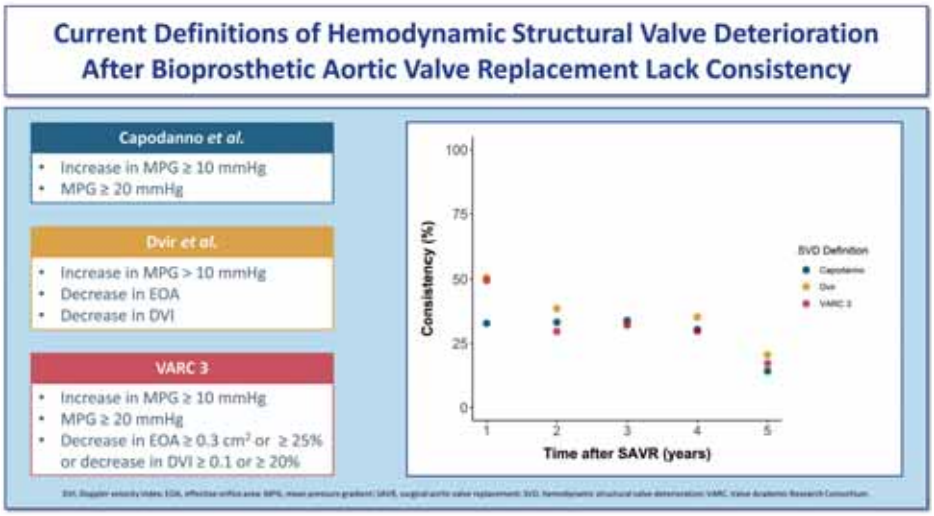
JTCVS Open 2024

Presented at the 2024 spring meeting of the Dutch Society for Cardiothoracic Surgery, Utrecht, The Netherlands



GRAPHICAL ABSTRACT



ABSTRACT

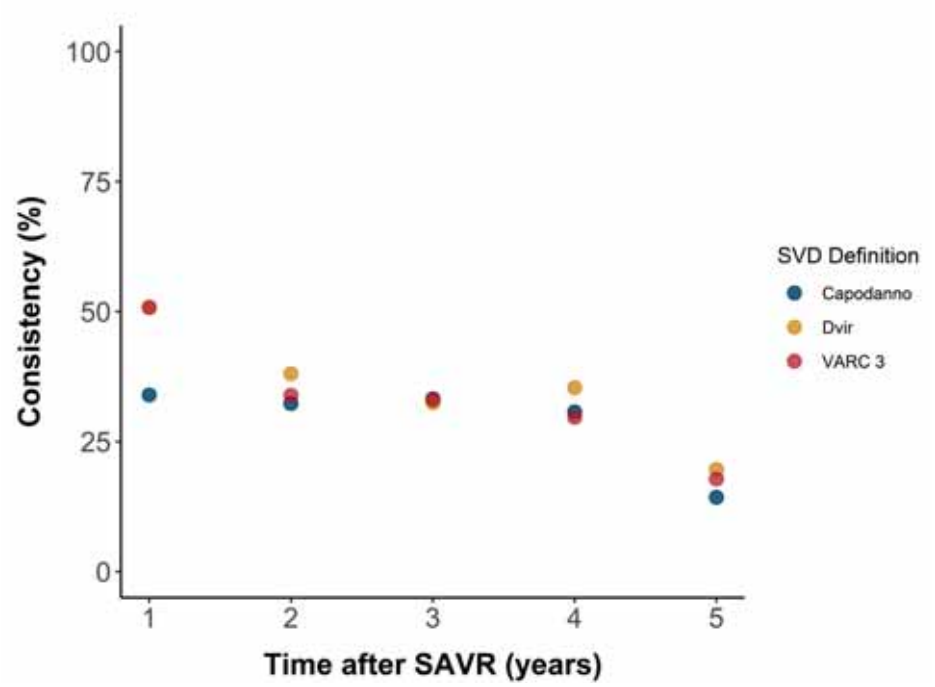
Objective: Recently, new echocardiographic definitions have been proposed for hemodynamic structural valve deterioration (SVD). We aimed to study their consistency in classifying SVD after surgical aortic valve replacement (SAVR).

Methods: Data were used of SAVR patients implanted in a multicenter, prospective cohort study with 5-year follow-up. All patients received the same stented bioprosthesis. Echocardiographic parameters were assessed by an independent core laboratory. Moderate or greater stenotic hemodynamic SVD was defined according to Capodanno *et al.*, Dvir *et al.*, and the Valve Academic Research Consortium (VARC) 3; regurgitation data was not considered in this analysis. Consistency was quantified based on SVD classification at subsequent timepoints.

Results: A total of 1118 patients were implanted. The mean age was 70 years and 75% were male. Hemodynamic SVD at any visit was present in 51 (4.6%), 32 (2.9%), and 34 (3.0%) patients according to Capodanno, Dvir, and VARC-3. 1064 (95%) patients were never labeled with SVD by any definition. After the first classification with SVD, 59%, 59%, and 65% had no subsequent SVD classification according to Capodanno, Dvir, and VARC-3, respectively.

Conclusions: The current definitions of hemodynamic SVD are strong negative predictors but inconsistent positive discriminators for the detection of stenotic hemodynamic SVD. While the diagnosis of SVD may be categorical, echocardiographic indices lack this degree of precision in the first 5-years after SAVR. The inconsistency of current SVD definitions impedes the detection of true valve degeneration, which challenges the clinical usefulness of these definitions.

CENTRAL PICTURE



The consistency, represented on the y axis, was evaluated by calculating how many patients that were classified with SVD at one timepoint were also classified with SVD at the subsequent timepoint. SAVR, surgical aortic valve replacement; SVD, hemodynamic structural valve deterioration; VARC, Valve Academic Research Consortium.

Central Message: After the first classification of hemodynamic SVD by recently proposed definitions, up to 65% of patients were not classified with SVD at the subsequent visit.

Perspective Statement: Current definitions are inconsistent positive discriminators for the detection of stenotic hemodynamic SVD. While the diagnosis of SVD may be categorical, echocardiographic indices lack this degree of precision in the first 5-years after SAVR. The observed inconsistency impedes the detection of true valve degeneration, which challenges the clinical usefulness of these definitions.

INTRODUCTION

A main concern for bioprosthetic heart valves is durability. Irreversible damage to structural elements of the prosthesis, a process called structural valve deterioration (SVD), can eventually lead to hemodynamic dysfunction, symptoms, and the potential need for reintervention. Original clinical definitions of SVD after aortic valve replacement (AVR) were based on reoperation or death and identified only the most severe cases of hemodynamic dysfunction, while subsequent hemodynamic definitions did not distinguish between structural and nonstructural causes[1]. To overcome these shortcomings, new definitions have been proposed for hemodynamic SVD by Capodanno *et al.*[2], Dvir *et al.*[3], and the Valve Academic Research Consortium (VARC) 3[4]. These definitions slightly differ but are all partially based on an increase in mean pressure gradient (MPG) compared to a reference echo performed after surgery.

Echocardiographic parameters like MPG may vary over time due to factors unrelated to bioprosthetic valve performance, such as biological fluctuations (e.g., circadian patterns, volemia, heart rate, irregular rhythms, etc.) and measurement error. Inevitably, these factors are part of clinical practice and could therefore complicate consistent classification of SVD. Moreover, even small variations in measurements could result in dramatic changes when using strict categories such as presence or absence of SVD. Hence, the aim of this study was to assess the consistency of the contemporary definitions of hemodynamic SVD after bioprosthetic AVR. Our secondary aim was to study longitudinal variability in MPG during follow-up.

METHODS

Study data

Data from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve (www.clinicaltrials.gov, NCT02088554) were used. The PERIGON Pivotal Trial is a single-armed, prospective, observational follow-up study to examine the safety and performance of the Avalus bioprosthesis (Medtronic, Minneapolis, Minnesota, USA). The design of the trial was formerly outlined in detail[5,6]. In short, patients with aortic stenosis or regurgitation and a clinical indication for SAVR were enrolled. Several concomitant procedures were allowed, including coronary artery bypass grafting (CABG), left atrial appendage ligation, and ascending aortic aneurysm or dissection repair not requiring circulatory arrest. The study was conducted at 38 centers across North America and Europe, at which local institutional review boards or ethics committees provided study approval (see supplementary files Klautz *et al.*[7] for approval number and date per center). All patients provided written informed consent. All deaths and valve-related events were adjudicated by an independent clinical events committee (Baim Institute for Clinical Research, Boston, MA, USA), and study oversight was kept by an independent data and safety monitoring board (Baim Institute). A single core laboratory (MedStar Health Research Institute, Washington,

DC, USA) assessed all echocardiographic parameters. After implant, patients were scheduled for follow-up at hospital discharge (up to 30 days), 3 to 6 months, 1 year, and annually through 5 years. A flowchart that depicts the amount of patients who completed each visit and the reasons for drop-out is provided in *Figure S1* in the supplementary files. MPG and effective orifice area (EOA) were determined using the simplified Bernoulli equation and the continuity equation, respectively. By dividing the velocity-time integral (VTI) of the left ventricular outflow tract (LVOT) by the VTI across the aortic valve, the Doppler velocity index (DVI) was derived.

Hemodynamic SVD definitions

The definitions of hemodynamic SVD that were studied were proposed by Capodanno *et al.*[2], Dvir *et al.*[3], and the VARC 3[4]. These hemodynamic SVD definitions are abbreviated throughout the manuscript as Capodanno-SVD, Dvir-SVD, and VARC3-SVD. Moderate or greater stenotic SVD was studied because we hypothesized that there would be potential variability in quantitative echocardiographic parameters for hemodynamic obstruction. For this reason and because moderate or greater regurgitation was only present in 0.2% at 5-year follow-up [7], regurgitation data were not considered in this analysis. The exact definitions as examined in this study are reported in *Figure 1*. To determine the change in echocardiographic parameters, values during follow-up were compared to a reference echo performed at hospital discharge up to 30 days. In a subanalysis, values during follow-up were compared to a reference echo performed at the first outpatient clinic visit between 3 and 6 months post-surgery.

Figure 1. Contemporary definitions of moderate or greater stenotic hemodynamic structural valve deterioration. 2-4

DVI. Doppler velocity index; EACTS, European Association for Cardio-Thoracic Surgery; EAPCI, European Association of Percutaneous Cardiovascular Interventions; EOA, effective orifice area; ESC, European Society of Cardiology; MPG; mean pressure gradient; VARC, Valve Academic Research Consortium; VIVID, Valve-in-Valve International Data.

Statistical analyses

Numerical data were presented either as mean ± standard deviation or median [interquartile range] depending on their distribution, and categorical data were presented as counts (percentages). Missing echocardiographic data are presented in *Table S1*. A complete case analysis was performed in all analyses except for graphical representation of longitudinal data. Therein, patients with missing data at one or more timepoints were not omitted.

The consistency of each hemodynamic SVD definition was evaluated by calculating how many patients that were classified with SVD at one timepoint were also classified with SVD at the subsequent timepoint. Furthermore, heatmaps were generated for each patient who was classified with SVD at least once during follow-up to illustrate whether SVD was present or absent at each follow-up visit. If SVD classification was inconsistent, we evaluated which specific condition in the definition was not met anymore (e.g., the increase in MPG). In addition, the agreement between the three SVD definitions was expressed in Cohen's kappa coefficients. In a subanalysis, patients with reintervention, endocarditis, or valve thrombosis were excluded to eliminate established clinical causes of hemodynamic alteration.

To assess longitudinal variability in MPG, patients who did not undergo reintervention were selected to guarantee that the same prosthetic valve was present at each timepoint. A 95% prediction interval was calculated for the change in MPG within individuals by subtracting their MPG value at discharge from their MPG value at 5-year follow-up. Furthermore, the change in MPG between two consecutive timepoints was repeatedly calculated for deciles of MPG at the start of the first timepoint. For example, for the change in MPG between 1-year and 2-year follow-up, deciles were created based on the values of MPG at 1-year.

While the data underlying this analysis are owned by the study sponsor, the analyses were proposed and performed by the authors, and the manuscript was written by the author group. All analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org).

RESULTS

A total of 1118 had successful valve implantation and all were included in this analysis. The mean age of the study population was 70 years, 75% were male, and the median Society of Thoracic Surgeons predicted risk of mortality was 1.60 (*Table 1*). At discharge up to 30 days, the average MPG was 13.1±4.7 mmHg, the EOA 1.54±0.36 cm^2, and the DVI 0.49±0.10. Using the initial discharge echo as the reference, 51 patients were classified with Capodanno-SVD at least once during follow-up, 32 patients with Dvir-SVD, and 34 patients with VARC3-SVD (*Table S2*). 1064 (95%) patients were never labeled with SVD by any definition.

Table 1. Patient characteristics at baseline and echocardiographic parameters at discharge for patients who underwent surgical aortic valve replacement.

	N = 1118
Patient characteristics	
Age (years)	70.2 ± 9.0
Male	840 (75%)
Body surface area (m^2)	2.0 ± 0.2
Body mass index (kg/m^2)	29.4 ± 5.4
STS PROM (%)	1.60 [1.05, 2.44]
Diabetes mellitus	298 (27%)
Hypertension	852 (76%)
Chronic obstructive pulmonary disease	130 (12%)
Left ventricle ejection fraction (%)	59 ± 10
Coronary artery disease	487 (44%)
NYHA class III/IV	472 (42%)
Previous stroke	45 (4%)
Peripheral vascular disease	81 (7%)
Renal dysfunction/insufficiency	119 (11%)
Echocardiography at discharge up to 30 days	
Mean pressure gradient (mm Hg)	13.1 ± 4.7
Effective orifice area (cm^2)	1.54 ± 0.36
Doppler velocity index	0.49 ± 0.10

Numerical data are expressed as mean ± standard deviation or median [interquartile range], and categorical data as count (percentage). STS PROM, Society of Thoracic Surgeons predicted risk of mortality.

Consistency of hemodynamic SVD definitions

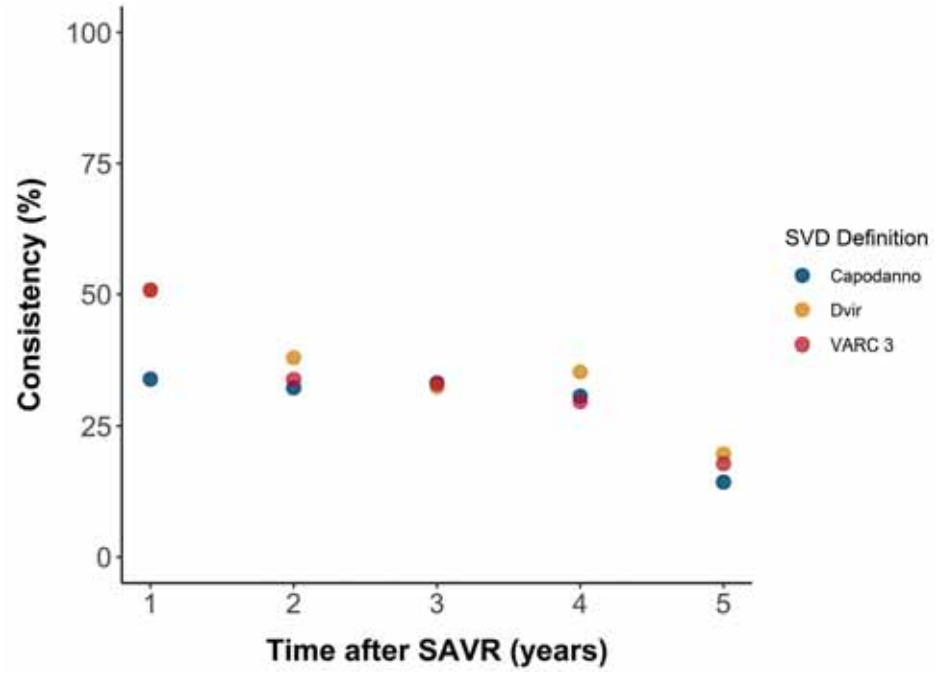
Of the patients who were classified with Capodanno-SVD at 2 years, 33% were also classified with Capodanno-SVD at 3 years. The consistency during this interval was also 33% for the definitions by Dvir *et al.* and the VARC 3. Likewise, for all intervals, the consistency per definition is reported in *Table 2* and illustrated in *Figure 2*.

Table 2. Consistency of contemporary definitions for hemodynamic structural valve deterioration after bioprosthetic aortic valve replacement.

	3-6 M to 1 y	1 y to 2 y	2 y to 3 y	3 y to 4 y	4 y to 5 y
Capodanno et al.	1/3 (33%)	4/12 (33%)	4/12 (33%)	4/13 (31%)	1/7 (14%)
Dvir et al.	1/2 (50%)	3/8 (38%)	2/6 (33%)	4/11 (36%)	1/5 (20%)
VARC 3	1/2 (50%)	3/9 (33%)	3/9 (33%)	3/10 (30%)	1/6 (17%)

Data indicate the percentage of patients labelled with hemodynamic structural valve deterioration who were also so labelled at the subsequent follow-up visit. VARC, Valve Academic Research Consortium.4

Figure 2. Consistency of contemporary definitions of hemodynamic structural valve deterioration after bioprosthetic aortic valve replacement.



The consistency, represented on the y axis, was evaluated by calculating how many patients that were classified with SVD at one timepoint were also classified with SVD at the subsequent timepoint. SAVR, surgical aortic valve replacement; SVD, hemodynamic structural valve deterioration; VARC, Valve Academic Research Consortium.

The consistency of hemodynamic SVD classification within individuals is demonstrated in heatmaps in *Figure S2* (Capodanno *et al.*), *Figure S3* (Dvir *et al.*), and *Figure 3* (VARC 3). The heatmap for VARC3-SVD is presented in the main manuscript because this definition is the most recent and the most comprehensive.

After the first classification of Capodanno-SVD, 59% had absent SVD, 16% had present SVD, and 25% had missing SVD (*Figure S2)*. The reason for inconsistent Capodanno-SVD classification was an increase in MPG <10 mmHg in 20% and not exceeding the increase threshold as well as the absolute threshold of 20 mmHg anymore in 80%.

Figure 3. The consistency of hemodynamic SVD within patients who have been labelled with SVD at least once during follow-up according to the definition of the VARC 3.

*Each row represents one patient. * indicates endocarditis, ** valve thrombosis, and *** reintervention. NA, not available; SVD, hemodynamic structural valve deterioration; VARC, Valve Academic Research Consortium.*

After the first classification of Dvir-SVD, 59% had absent SVD, 22% had present SVD, and 19% had missing SVD (*Figure S3)*. Inconsistent Dvir-SVD classification was in 89% due to an increase in MPG ≤ 10 mmHg, in 5.5% due to no decrease in EOA anymore, and in 5.5% due to an increase in MPG ≤ 10 mmHg in combination with no decrease in EOA or DVI.

After the first classification of VARC3-SVD, 65% had absent SVD, 20% had present SVD, and 15% had missing SVD (*Figure 3)*. The reason for inconsistent VARC3-SVD classification was in 23% an increase in MPG <10 mmHg, in 9% related to the MPG increase in combination with EOA/DVI decrease criteria, in 41% not exceeding both the increase and absolute MPG threshold, in 23% not fulfilling both MPG criteria and the EOA/DVI criterium, and in 4% related to the EOA/DVI decrease criterium only.

The agreement on classification during follow-up between Capodanno-SVD and Dvir-SVD, expressed in Cohen's kappa coefficients, ranged between 0.60 and 0.92 (*Table S3*). For

Capodanno-SVD and VARC3-SVD, the coefficients ranged between 0.80 and 0.91, while for Dvir-SVD and VARC3-SVD, these ranged between 0.70 and 1.00.

Longitudinal variability in mean pressure gradient

The mean MPG at discharge was 13.1±4.7 mmHg (*Table 1*), and the change in MPG throughout 5-year follow-up was on average -1.1 mmHg. The corresponding 95% prediction interval for the change within individuals ranged between -9.6 and 7.5 mmHg. To give an example of variability during follow-up, the course of MPG is plotted for 5 randomly sampled patients with complete data (*Figure 4*). The change in MPG between consecutive timepoints is demonstrated per decile in *Figure 5* and *Table S4*. At each interval, the MPG increased most in the lowest decile, while the MPG decreased most in the highest decile. For the deciles with lowest MPG, the average increase ranged between 1.2 and 2.3 mmHg. For the deciles with highest MPG, the average decrease ranged between 1.0 and 5.9 mmHg.

Figure 4. Change in mean pressure gradient for 5 randomly sampled patients who did not undergo reintervention.

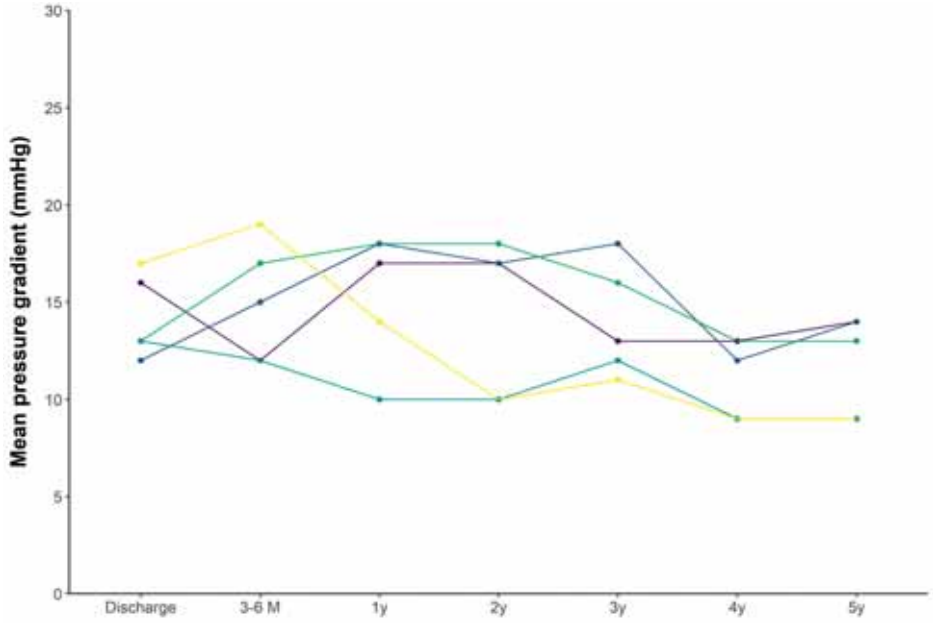
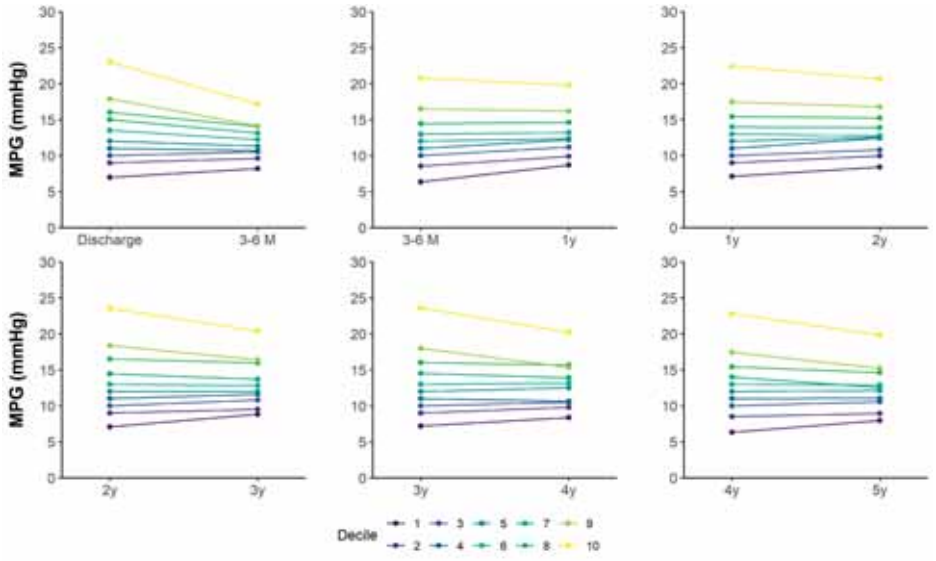


Figure 5. Change in mean pressure gradient between subsequent follow-up visits stratified by deciles of mean pressure gradient at the start of each period.



MPG, mean pressure gradient.

Subanalysis: reference echo at first outpatient clinic visit

When the echo at the first outpatient clinic visit instead of discharge was used as reference, 65 patients were classified with Capodanno-SVD at least once during follow-up, 31 patients with Dvir-SVD, and 42 patients with VARC3-SVD (*Table S5*). The consistency of the SVD definitions is reported in *Table S6* and the between-definition agreement in *Table S7*. The heatmaps demonstrated within-patient inconsistency for all three definitions of SVD that was comparable to the observation with the discharge echo as the reference (*Figures S4-6*).

Subanalysis: patients without reintervention, valve thrombosis, or endocarditis

For patients without reintervention, valve thrombosis, or endocarditis, the number of subjects that were classified with SVD are presented in *Table S8*. The consistency of the SVD definitions is reported in *Table S9* and the between-definition agreement in *Table S10*. After the first classification of present Capodanno-SVD, 25 patients (63%) had absent SVD (*Figure S7*). After the first classification of present Dvir-SVD and VARC3-SVD, 17 (65%, *Figure* S8) and 20 patients (71%, *Figure S9*) had absent SVD, respectively.

DISCUSSION

In this analysis of 1118 patients who underwent SAVR with core laboratory-adjudicated echo data, the consistency of the classification of hemodynamic SVD using contemporary definitions was poor. After the first classification of hemodynamic SVD, up to 65% of patients were not classified with SVD at the subsequent visit.

Accurate diagnosis of SVD is challenging. Definitions based on clinical outcomes fall short in detecting dysfunction at times that are relevant to patients and may underestimate the occurrence of SVD[1]. While hemodynamic definitions seem to offer a solution to these problems, these could also capture nonstructural dysfunction and noise variation due to imprecise measurements or due to natural variation. Capodanno *et al.*[2] proposed to include a change in MPG to distinguish between structural and nonstructural causes like prosthesis-patient mismatch. Thereafter, Dvir *et al.*[3] and the VARC 3[4] suggested incorporating additional parameters to prevent capturing noise: an increase in MPG should be accompanied by a decrease in EOA or DVI. Whether these new echocardiographic definitions of SVD correspond with adverse clinical outcomes is undetermined. One recent analysis suggests that the Capodanno *et al.*[2] and the VARC 3[4] definitions of hemodynamic SVD, after additional verification of all potential cases by a panel of clinical experts, are associated with increased mortality[8].

The underlying hypothesis of SVD is that prosthetic valve performance declines over time due to structural degeneration of the prosthesis caused by mechanical wear and/or immunological mechanisms. These irreversible processes do not resolve without re-intervention and are assumed to be progressive over time. Therefore, a solid definition of SVD should consistently classify a patient with SVD after the initial diagnosis. In the current study, our aim was to test whether new echocardiographic definitions fulfill this requirement. However, because up to 65% of patients initially diagnosed were classified inconsistently over time, we conclude that none of the hemodynamic definitions of SVD capture structural degeneration of the prosthesis accurately. Surprisingly, the amount of inconsistency was largely equal between definitions even though Dvir *et al.*[3] and the VARC 3[4] proposed more comprehensive definitions including EOA and DVI in addition to MPG. For these reasons, the results of the current study do not justify recommending any of these definitions as the most accurate one.

A potential explanation for inconsistent classification is within-patient variability in echocardiographic parameters. These parameters are proxies for prosthetic valve performance but are also affected by patient characteristics, for example, through blood flow and biological mechanisms such as circadian patterns, and by (random) measurement error. As a result, extreme echocardiographic values are likely to be followed by less extreme values during follow-up. This phenomenon, called regression toward the mean[9], at least partially explains our results (*Figure 5*). Transient clinical events like successfully treated endocarditis,

valve thrombosis, or hypo-attenuated leaflet thickening (HALT) could also temporarily bring about abnormal echocardiographic parameters. However, inconsistency remained after excluding the first two sources in a subanalysis. Information on HALT was not available because the PERIGON trial lacked protocolized computed tomography examinations, but HALT is unlikely to explain such a large inconsistency in SVD classification[10,11]. In this analysis, inconsistent classification of SVD by any definition was predominantly related to not exceeding the increase and absolute thresholds for MPG anymore and to a lesser extent related to the criteria for EOA or DVI.

In this study, we focused on consistency of present SVD classification because this was considered clinically most relevant and aligns with the underlying hypothesis about SVD that is described above. Moreover, in daily practice, hemodynamic SVD definitions are used to identify those patients that might benefit from a reintervention. Hence, we did not focus on the consistency of absent SVD since we believe that it will hardly ever occur that a patient with a structurally degenerated valve would have normal echocardiographic parameters. As expected, the consistency of absent SVD was very high, i.e., 1064 of the 1118 were never classified with SVD by any definition throughout 5-year follow-up.

In theory, inconsistent SVD classification could lead to unnecessary reinterventions. However, as the decision to reoperate is predominantly based on clinical symptoms, we do not expect this to occur often. In addition, the VARC 3[4] states that "a definite diagnosis of SVD should not rely on the measurement of a single haemodynamic parameter, and preferably should incorporate evidence from at least two serial echocardiograms." Furthermore, this consortium recommends distinguishing bioprosthetic valve dysfunction, such as hemodynamic SVD, from bioprosthetic valve failure, which is the relevant and clinically meaningful variant for the patient. We demonstrated that dysfunction can be highly unreliable; hence, it is crucial to repeat measurements, assess valve leaflet morphology, and investigate the burden for the patient when considering reintervention.

For the research setting, hemodynamic SVD is proposed by the VARC 3 as an appropriate endpoint for durability of prosthetic valves[4]. However, this setting lacks the important nuances mentioned above because generally researchers can rely only on numerical values of echocardiographic parameters to adjudicate SVD. Considering our results, hemodynamic SVD, as currently defined, will be an unreliable endpoint for prosthetic valve durability in scientific research.

To develop more robust definitions, future research should investigate which definition of hemodynamic SVD corresponds best with clinically relevant outcomes like bioprosthetic valve failure (BVF), valve-in-valve reinterventions or redo surgery. Although this sounds like a suggestion to return to previous clinical definitions, it is not. Revised definitions should still be based on hemodynamic criteria, though altered to correspond best to clinical events and not based on the events themselves. Such revised definitions would not only

be applicable to the most severe cases because BVF is included, which is independent of eligibility for reinterventions. For example, BVF is present in case of new-onset or worsening symptoms, pathologic LV remodelling or secondary pulmonary hypertension[1]. Furthermore, accumulating experience and developments with valve-in-valve procedures and redo surgery have boosted treatments options for patients formerly unfit for reinterventions. Lastly, by adhering to hemodynamic criteria, revised definitions keep the advantage of detecting bioprosthetic dysfunction at times that are relevant to patients. We consider echocardiography to be the appropriate primary imaging modality to assess prosthetic valve performance. Any red flags detected during echocardiographic screening should be confirmed with other modalities, such as computed tomography or cardiac magnetic resonance [1].

Strengths and limitations

The current study has several potential limitations. The follow-up duration is relatively short. As follow-up progresses, the classification of SVD based on hemodynamic parameters could become more stable due to progressive degeneration of the bioprostheses. Furthermore, longer follow-up would lead to more clinical events, which would enable us to study the association between hemodynamic SVD and clinical outcomes. While adverse event information were present, the study lacked information on specific patient-reported symptoms related to SVD. Another limitation is missing data. The main reason for missing data is that not all patients had completed the 5-year follow-up visit at the time of this analysis, which we consider as missing completely at random. Loss to follow-up could bias our results, since this may not be random. As only 15 patients were lost to follow-up at 5 years, we consider this impact to be minimal. More complete information would increase the reliability of our findings on SVD consistency. Data imputations were deemed to obscure the interpretation of the results and were therefore not applied. Lastly, the results could be less generalizable to populations of intermediate or high surgical risk because the study population was restricted to relatively low-risk patients. On the contrary, the study has several strengths. All patients received the same stented bioprosthesis, and longitudinal data were gathered in a prospective manner. An independent clinical events committee adjudicated all valve-related events, and a single core lab assessed all echocardiograms. Moreover, the international, multicenter setting and the allowance of concomitant procedures like CABG boost the generalizability of the results.

Only moderate or greater stenotic hemodynamic SVD was studied in the current analysis. Hence, no conclusions can be drawn about the consistency of hemodynamic SVD due to regurgitation.

CONCLUSIONS

The current definitions of hemodynamic SVD are strong negative predictors but inconsistent positive discriminators for the detection of stenotic hemodynamic SVD. This inconsistency may be explained by large within-patient variability in echocardiographic parameters. While the diagnosis of SVD may be categorical, echocardiographic indices lack this degree of precision in the first 5-years after SAVR. The observed inconsistencies obscure the detection of true valve degeneration, which is important to consider for clinicians and researchers applying this concept. For clinical usefulness and reliability of research findings, consistency of SVD classification is key.

Acknowledgements: We thank R.J. Janse for his help with visualizing the longitudinal data.

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SUPPLEMENTARY FILES

Available at https://doi.org/10.1016/j.xjon.2024.02.023.

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SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

SUMMARY

Throughout this thesis, different hemodynamic concepts in aortic valve replacement are critically evaluated for their accuracy, robustness, and validity for clinical practice. While the invaluable role of echocardiography is acknowledged, limitations and challenging scenarios are further explored. These comprehensive insights enhance the interpretation of echocardiography and support clinical decision-making by cardiologists and cardio-thoracic surgeons concerning the native and bioprosthetic aortic valve.

Chapter 1 serves as the introduction to this thesis. Echocardiographic concepts in pre-, peri- and postoperative care are described and the aim of this work is presented. In **Chapter 2**, it is shown that measurement error in the echocardiographic assessment of aortic stenosis (AS) severity is underrecognized in literature. While potential erroneous sources have been described before [1], their magnitude was still unclear. This study provides these insights; for example, the interobserver variability in effective orifice area is way larger than in mean pressure gradient. To demonstrate the clinical implications of measurement error, various simulations were performed. With expanding echocardiography-based indications for asymptomatic patients with AS, it is crucial to acknowledge the presence and magnitude of measurement error and its implications to adequately refer patients to undergo an intervention. Obtaining the right diagnosis is not only a challenge in asymptomatic patients but also in symptomatic patients with low cardiac output, i.e. low-flow status. The diagnosis of true severe AS is challenging in this subgroup, hence, a classification based on stroke volume (SV) and mean gradient has been proposed [2]. In **Chapter 3**, poor agreement in flow-gradient classification is demonstrated as a result of large differences between echocardiographic SV measurement at the left ventricular outflow tract (LVOT) and at the left ventricle using the Simpson's method. Hence, these methods are not suitable for corroboration of each other. Furthermore, the sensitivity of this classification to small measurement errors is exemplified; after the introduction of a 1 mm overestimation in LVOT diameter, the number of patients in low-flow groups decreased by 50%. **Chapter 4** outlines that the classification of paradoxical low-flow severe (PLF) AS is dependent on body surface area (BSA). Patients with large BSA have a higher probability to be classified with PLF than patients with small BSA. This finding is clinically relevant since patients with normal flow and a low gradient do not have an indication for intervention [3,4]. The results of **Chapters 3 and 4** reinforce that for challenging clinical entities like low-flow patients, an integrated approach considering parameters beyond the flow-gradient classification is needed to accurately determine whether AS is truly severe and the patient will benefit from valve replacement. **Chapter 5** reveals that there is high agreement between the echocardiographic core laboratory and clinical centers on continuous-wave Doppler related measurements like peak aortic jet velocity and mean pressure gradient. On the contrary, agreement is low for parameters which involve measurement of the LVOT diameter (e.g., SV, EOA, and EOAi), highlighting its limited reproducibility.

In **Chapters 6 and 7**, the hemodynamic and clinical effects of different strategies for surgical aortic valve replacement (SAVR) are compared. In **Chapter 6**, a minimally invasive approach

via right anterior thoracotomy or hemisternotomy led to similar 3-year outcomes as compared to conventional full sternotomy. In **Chapter 7,** pledgeted sutures yielded comparable 5-year clinical results to nonpledgeted sutures, though the effective orifice area might be slightly smaller during follow-up when pledgeted sutures are used. **Chapter 8** is a systematic review and meta-analysis summarized all available literature on the risks and benefits of pledget-reinforced sutures during SAVR. Evidence is scarce and at high risk of bias, and the pooled results do not indicate superiority for either sutures with or without pledgets for multiple clinical and hemodynamic outcomes. In **Chapter 9**, surgical insights for the implantation of a stentless bioprosthesis are provided. Specific attention is paid to appropriate positioning of the prosthetic valve in case of a native bicuspid aortic valve. **Chapter 10** provides an overview of patients that underwent SAVR in North America and Europa. Significant intercontinental differences were observed in disease severity at baseline, procedural characteristics, antithrombotic regime, and timing of discharge. The 30-day rehospitalization risk was 8.5% in Europe and 15.9% in North America. These results stress that geographical setting must be considered during design of trials on SAVR and during the interpretation of their results. In **Chapter 11**, it is found that the quality of reporting on confounding adjustment is subpar in many observational studies on cardiothoracic interventions. The methodological practice requires improvement because these observational studies form the framework on which interventional recommendations for daily clinical practice are based. Therefore, comprehensive recommendations are delineated for the design and the execution of such studies.

While a range of hemodynamic parameters to assess prosthetic performance are available, prosthesis-patient mismatch is exclusively defined by thresholds of indexed effective orifice area. In **Chapter 12**, the incremental prognostic value of various postoperative echocardiographic parameters to a preoperative risk score, the Society of Thoracic Surgeons (STS) predicted risk of mortality, is demonstrated to be limited for the prediction of 5-year mortality after SAVR. A potential explanation could be that echocardiographic parameters are imperfect proxies for valvular performance as these parameters also reflect the health of the patient. The only parameter that did provide minor predictive improvement in a post-hoc analysis was Doppler velocity index (DVI) ≤ 0.35, but even this parameter did not improve the discrimination between patients that died or survived throughout 5-year follow-up. In **Chapter 13**, the results of the preceding chapter were validated in data of three randomized controlled trials. In this cohort, DVI ≤ 0.35 was again the only parameter that provided some predictive improvement to the STS score, but this parameter did not improve the discrimination. These results stress the importance of considering patient characteristics when interpreting hemodynamic parameters for prognostic purposes. **Chapter 14** depicts that current definitions for hemodynamic structural valve deterioration (SVD) lack consistency. After the first classification of SVD, up to 65% of the patients does not have SVD at subsequent visits. These findings strike with the underlying hypothesis that SVD implies permanent intrinsic damage to the prosthesis and therefore challenge the clinical usefulness of these definitions.

Aortic Valve Replacement	Main challenge addressed in this thesis	Insights provided in this thesis
Preoperative assessment	• The diagnosis of severe aortic stenosis in asymptomatic patients • The diagnosis of severe aortic stenosis in low-flow patients	• The magnitude and clinical impact of potential echocardiographic measurement errors are shown • The classification of paradoxical low-flow AS is dependent on SV measurement (location and accuracy) and BSA
Perioperative management	• The surgical strategy to optimize hemodynamic performance • The research methods to determine optimal surgical strategies	• For SAVR, a minimally invasive approach or pledget-reinforced sutures do not alter hemodynamic and clinical outcomes • The quality of reporting and conduct is insufficient in the majority of observational studies on cardiothoracic interventions
Postoperative assessment	• The prognostic value of prosthesis-patient mismatch and other parameters for residual hemodynamic obstruction • The diagnosis of hemodynamic structural valve deterioration	• DVI ≤ 0.35 associates most strongly with mortality after SAVR, however, prosthetic valve performance parameters provide limited incremental prognostic value to patient characteristics • Current definitions of hemodynamic SVD do not accurately capture structural degeneration of a bioprosthesis

DISCUSSION AND FUTURE PERSPECTIVES

The main findings of this thesis are put in a broader perspective in this section. Current concepts with regard to hemodynamic performance are reviewed and evidence gaps are addressed. The discussion follows the same chronological order as the introduction of this thesis: it starts with the diagnosis of native aortic valve disease and ends with failure of the bioprosthesis.

Risk stratification and timing of intervention in aortic stenosis

In preoperative care, the main goal is to optimize the timing of intervention [5,6]. On the one hand, interventions need to be performed early to prevent irreversible damage to the heart. On the other hand, the operative risks of redundant interventions and subsequent prosthetic valve complications must be avoided. We need to find the balance between these two to detect the sweet spot for intervention. Particularly challenging clinical entities comprise asymptomatic patients, low-flow subgroups, and patients with moderate AS. The symptoms which patients experience, correspond only modestly to cardiac damage which underpins the pivotal role of imaging parameters [7]. Critically abnormal echocardiographic values of peak aortic jet velocity have been established as a useful intervention threshold for asymptomatic patients [8,9]. Transvalvular flow rate, the ratio of stroke volume to ejection time, was found to be a marker with superior prognostic value to AVA, specifically at low flow rates [10]. Patients with moderate AS seems to have a poor prognosis which is not that distinct from severe AS [11,12]. To accurately diagnose patients with moderate AS, comprehensive diagnostic pathways including multimodality imaging and investigations of cardiac damage have been proposed [12]. For example, acute and chronic markers of elevated LV filling pressure are linked to worse outcomes and potentially appropriate future targets for intervention in moderate AS [13]. By shifting the focus to the myocardium and the extent of cardiac damage, new imaging biomarkers have been identified such as longitudinal strains and work indices, calcium scores on computed tomography (CT), and fibrosis assessment on cardiac magnetic resonance [14-16]. These parameters seem promising and will contribute to the optimization of risk stratification in AS.

Further improvements to patient care in AS relies on the prevention of underdiagnosis and undertreatment [17,18]. Undertreatment occurs in up to 67% of patients with low-gradient AS, in 20-33% in symptomatic AS with a class I indication for intervention, and more frequently in women [19-21]. The latter could be due to the fact that women present with less calcification but more fibrosis at the same level of AS severity [22-24], hence, sex-specific thresholds for severe AS are suggested [25]. Underdiagnosis can be reduced through raising awareness, education and technical innovations, among others. Moreover, contemporary population-based studies could provide valuable insights into the prevalence and outcomes in AS because the field is rapidly progressing [17], for example in the Netherlands by linking data sources of Statistics Netherlands to the Netherlands Heart Registration.

For timely interventions, an integrated approach by the multidisciplinary heart team, preferably in designated heart valve centers, is essential [26]. Dedicated cardiologists and cardio-thoracic surgeons should be aware of evolving indications and not be fooled in their diagnostic work-up by natural variability or measurement error. Especially for challenging clinical entities, the heart team needs to consider additional echocardiographic, functional and anatomical parameters to diagnose true severe AS and identify the patients that will benefit from AVR [3,4].

Ongoing trials will aid decision-making in AS. The EARLY-TAVR (NCT03042104), ESTIMATE (NCT02627391) and EASY-AS (NCT04204915) trial study the effect of early TAVR or SAVR versus surveillance in asymptomatic severe AS. The Evolved (NCT03094143) trial targets the same asymptomatic severe AS patients but includes fibrosis assessment using cardiac magnetic resonance before participants are randomized. The DANAVR (NCT03972644) also investigates the benefits of early intervention and focusses on asymptomatic severe AS with preserved LVEF but with high filling pressures, large left atrial volume index, or impaired LV GLS. For moderate AS, TAVR versus optical medical therapy is studied in the TAVR UNLOAD (NCT02661451), PROGRESS (NCT04889872), and Evolut EXPAND TAVR II (NCT05149755) trials. The DETECT AS (NCT05230225) trial investigates whether electronic notification of severe AS detection on echocardiography leads to higher AVR utilization and includes predefined subgroup analyses for women, low-gradient AS, and racial/ethnic minorities, among others. Today, there are no pharmacotherapeutic agents that could slow down, stop or reverse AS progression [27]. Randomized studies on the effect of statins, denosumab and alendronic acid all failed to show benefit [28-31]. New drugs targeting lipoprotein(a) seem promising but their clinical value has yet to be proven [32-34]. Pharmacotherapy has a large potential for AS as well as for the conservation of prosthetic valve durability.

Periprocedural AVR strategies to optimize hemodynamic and clinical outcomes

In perioperative care, the main challenge is to tailor interventional strategies and prosthetic valve selection to individual patients. Hemodynamic performance is a very important aspect, though other clinical aspects, e.g., conduction problems and valve durability, cannot be left unconsidered. In the end, a combination of all aspects determines the prognosis and quality of life for the patient. The effect of TAVR versus SAVR has been studied across the entire range of risk, however, long-term results have yet to be established, especially for low-risk individuals [35-41]. In most studies, the gradients are lower and effective orifice areas larger after TAVR, though paravalvular leak and conduction disturbances occur more frequently [35-40,42]. Patient characteristics that favor either SAVR or TAVR comprise the extent of calcification, the anatomy, and the need for concomitant surgery to the coronary arteries, other heart valves and the aorta [43]. Some patient groups have systematically been excluded from the randomized trials, for example with a bicuspid aortic valve (BAV). BAV patients represent 5-10% of the elderly patients currently treated with TAVR [44] and often require concomitant aortic surgery [45]. Hemodynamic performance of TAVR valves in BAV patients seems comparable to tricuspid

aortic valve patients[46]. However, recent results from the NOTION-2 trial suggest cautious use of TAVR in young BAV patients [47]. Moreover, clinical outcomes for TAVR in BAV may depend on the valve morphology [48]. For patients with low-flow low-gradient AS, the optimal interventional strategy is undetermined and requires further investigation [49-51]. Another AS subgroup for which hemodynamic performance is considered to be of utmost importance, are the patients with a small aortic annulus [52]. These patients are at risk for residual hemodynamic obstruction after AVR because the pressure gradient is inversely and exponentially related to the radius in tubular structures (Poiseuille's law) such as the outflow tract of the heart, In a subanalysis of the PARTNER trial, the risk of mortality was comparable between TAVR and SAVR although hemodynamic performance was in favor of TAVR [53]. The VIVA (NCT03383445) trial investigated the effect of TAVR versus SAVR specifically for elderly with a small annular diameter. In this small RCT, no differences were observed in clinical and hemodynamic outcomes. The RHEIA (NCT04160130) trial specifically studies the effect of TAVR vs SAVR in women with severe AS. Other ongoing trials on TAVR versus SAVR for low-risk patients include the DEDICATE (NCT03112980) trial, an investigate-initiated trial explicitly targeting "all-comers". The 1-year results indicate that TAVR was non-inferior with regard to death from any cause or stroke [54] but longer term results will follow. For BAV patients, the effect of TAVR vs. SAVR will be investigated in the NAVIGATE, BELIEVERS, and YOUNG TAVR trial. For severe AS patients with multivessel coronary artery disease, the TCW (NCT03424941) trial compares whether TAVR + percutaneous coronary intervention is non-inferior to SAVR + concomitant coronary artery bypass grafting.

Apart from the question whether a transcatheter or surgical strategy is preferred, the procedural details for both treatments also require attention. For SAVR, the prosthetic valve of choice, the surgical approach and the suturing technique are potential contributing factors to clinical outcomes. Stented biological valves are used most often but alternatives include sutureless, stentless, or mechanical prostheses. In the following section, evidence for comparisons is discussed for patients that are eligible for both conventional (i.e. stented bioprosthesis) and alternative prosthetic valves. Observational studies suggest that sutureless valves yield better hemodynamic performance but come with an increased risk of pacemaker implantation [55,56]. In the PERSIST-AVR trial, however, sutureless valves were noninferior to stented valves with regard to major cerebral and cardiovascular adverse clinical events [57]. Randomized trials for the comparison between stentless and stented valves originate from the early 2000's and demonstrated comparable prognosis despite a better hemodynamic profile for stentless valves [58-60]. These results were also found in a recent observational study [61]. According to an expert consensus statement, sutureless valves could specifically be used in elderly patients with comorbidities, porcelain aorta or those requiring concomitant surgery to reduce cross-clamp and cardiopulmonary bypass times [62]. In the choice between biological and mechanical valves, aspects like anticoagulation and durability are as important as hemodynamic performance. The age limit below which mechanical valves should be preferred is highly debated [63] and even differs between American and European guidelines [3,4]. Performing an annular enlargement, through the traditional Nicks [64], Manouguian [65], or

recently introduced Y-incision procedure [66], is another way to improve hemodynamics. According to the Society of Thoracic Surgeons data, enlargements are currently performed in only 2.9% of patients aged 65 years and older [67]. Literature consists solely of observational studies likely biased by confounding by indication and yields conflicting results for outcomes such as perioperative mortality [67-72]. The safety of these procedures as well as their long-term benefits and reproducibility are areas which require further research. Lastly, the optimal suturing technique for prosthetic valve implantation lacks consensus and is primarily based on surgeon preference and training. For example, different studies suggest pledget-reinforced mattress [73], simple interrupted [74], or continuous sutures to be optimal [75].

Hemodynamic performance of transcatheter prostheses is affected by the implantation location and the valve's design. Supra-annular implantation with a self-expandable valve provided better hemodynamics but similar clinical outcomes compared to intra-annular implantation with a balloon-expandable valve in different trials [76-79]. In the ongoing SMART (NCT04722250) trial, patients with a small native aortic annulus based on CT are randomized to the latest commercially available self-expandable or balloon-expandable valves. The LYTEN trial shows that self-expandable valves had superior hemodynamic performance in failed surgical bioprosthesis below size 23 mm, but that short-term clinical outcomes were again comparable [80]. In failed stented bioprosthesis, valve fracture for valve-in-valve implantation might improve hemodynamic performance but proof of clinical benefit has yet to be established [81]. An overview of normal transcatheter function for different valves was provided by Hahn *et al.* to serve as reference for clinical practice [82].

Imaging of prosthetic heart valves is complicated and requires clinical competence as well as knowledge of common pitfalls [83,84]. Specific recommendations are proposed in international echo guidelines and expert consensus documents [85,86]. Echocardiography was validated against cardiac catheterization in the setting of native AS, hence, some calculations like the simplified Bernoulli formula might be less accurate in well-functioning prosthetic valves [87]. The DISCORDANCE (NCT04827238) trial further investigates discrepancies between echocardiographic measurements and their catheterization counterparts.

The importance of lifetime management has been increasingly emphasized: future procedures should already be considered at the time of the primary intervention [43]. These considerations involve, next to valvular performance, preservation of coronary access. TAVR explantation can be surgically challenging and often requires root repair / replacement or mitral valve interventions [88,89]. Valve-in-valve TAVR requires careful planning and implantation. An amplification of clinical insights is expected in the coming years [90,91]. In lifetime management, information on life expectancy and the likelihood of lifetime events for individuals is essential. Microsimulation could be helpful here [92].

Prosthesis-patient mismatch and hemodynamic structural valve deterioration

In postoperative management of SAVR patients, two pivotal echocardiographic concepts are prosthesis-patient mismatch (PPM) and hemodynamic structural valve deterioration (SVD). The problem of PPM was brought up by Rahimtoola, already in 1978 [93]. Later, a formal definition of PPM was proposed using effective orifice area index (EOAi) thresholds which corresponded to elevated pressure gradients [94]. Meta-analyses showed that severe PPM, using these EOAi-based definitions, is associated with decreased survival after SAVR and TAVR [95-97]. However, recent studies have outlined several pitfalls concerning the current definition of PPM and its clinical value for individual patients. These include unsatisfactory agreement between projected PPM depicted by valve charts and measured PPM after AVR [98] but also invalid categorization of EOAi as well as poor correspondence with hemodynamic obstruction by other parameters [99], and disproportional indexation to body surface area (BSA) [100]. A clear example of erroneous PPM classification due to fallacious BSA indexation is outlined in this letter [101]: in a study among an Asian and Western population, the Asian had significantly *higher* velocities and gradients after AVR but a significantly *lower* incidence of PPM. The problems identified by the studies above underscore that, although PPM is associated with worse prognosis on group level in most studies, the concept as currently defined could be deceptive for individual patients (and unfortunately we cannot predict for which). Surrogate concepts like PPM require additional assumptions on top of the ones that are already made for standard echocardiographic measurements. The parameters that are most valuable for clinical assessment of prosthetic valve performance are the ones that are measured most accurate and correspond best to relevant clinical outcomes. The results presented in this thesis suggest that DVI $\leq$ 0.35 associates stronger with all-cause and cardiovascular mortality than severe PPM and could therefore be a superior marker for clinically relevant hemodynamic obstruction after SAVR (Chapter 12[102] & 13). To note, the impact of flow challenges uniform criteria [103,104] and will need to be integrated into assessment algorithms of prosthetic valves similar to the diagnosis of native AS.

The second echo concept in this setting is hemodynamic SVD. Over the past few years, definitions for hemodynamic SVD have been proposed by several international associations and expert panels, mainly based on changes in echo parameters over time [105-107]. The occurrence of hemodynamic SVD after TAVR and SAVR has been investigated [108,109], though one can wonder whether the definitions equally apply to TAVR and SAVR patients. After the intervention, the hemodynamic profile is different in favor of TAVR, hence, exceeding the absolute mean gradient thresholds of 20 mmHg implies a larger relative change for transcatheter valves. Put differently, surgical valves will exceed this threshold more easily with less relative degeneration. To note, this even holds in trials because the time of randomization, i.e., before implantation of the prosthetic valve, does not concur with the reference point for the hemodynamic SVD definitions, i.e., after implantation of the prosthetic valve. Furthermore, current SVD classification is inconsistent in up to 65% as outlined in the body of this thesis [110]. Echocardiography as first-line detection tool for bioprosthetic valve dysfunction is justified by the possibility to assess the leaflets and to rule out valve thrombosis or endocarditis in a

quick and non-invasive manner. However, quantitative criteria for the detection of prosthetic degeneration require further optimization, for example by investigating their link with relevant outcomes like valve-related symptoms, redo surgery or valve-in-valve reinterventions. For clinical practice, echocardiographic red flags for suspected SVD need careful confirmation and an investigation of the burden for the patient [84,107]. CT imaging could be used to assess calcification, though, artefacts due to metallic components of prosthetic valves could complicate evaluation. Invasive measurements by means of cardiac catheterization may be considered before reintervention in case of abnormal echo values but absent leaflet abnormalities on echo and CT despite the presence of valve-related symptoms [76]. This is backed up by the finding that in 70% of the patients with a mean gradient ≥20 mmHg on echo, the mean gradient was not elevated at cardiac catheterization [87]. Moreover, modern imaging tools such as ^{18}F-fluoride positron emission tomography CT revealed valve degeneration that was not detected through echocardiography or CT alone and was found to be a strong predictor of subsequent deterioration [111]. With evolving knowledge on the benefit of AVR in asymptomatic (and potentially moderate) AS and low-risk patients, the widespread adaptation of TAVR, the decrease of mechanical valve implantation, and increasing life expectancy, more and younger patients will receive bioprosthetic valves in the near future. Therefore, the burden of SVD will amplify and its management increasingly important.

Closing remarks on hemodynamic concepts in aortic valve replacement

Echocardiography is a valuable, if not the most valuable, tool to assess the performance of the native and bioprosthetic aortic valve. That said, quantitative echocardiographic measurements should be interpreted with care. Measurements are affected by various sources of measurement error, natural variation and by patient characteristics which often have larger impact than expected. This thesis consistently highlights that diagnostic echocardiographic criteria, which seem theoretically valid, can turn out to be unreliable in clinical practice. Validation studies are essential to investigate whether echocardiographic definitions capture what they should capture and if theoretical definitions associate with clinically relevant outcomes for patients. This will lead to continuing advancement in diagnostic algorithms and to increased awareness about limitations and uncertainties which further improve clinical care for patients with aortic valve disease.

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16

NEDERLANDSE SAMENVATTING

SAMENVATTING

In dit proefschrift worden verschillende hemodynamische concepten met betrekking tot aortaklepvervanging kritisch geëvalueerd op hun nauwkeurigheid, robuustheid en validiteit voor de klinische praktijk. Hoewel de onschatbare rol van echocardiografie wordt erkend, worden de beperkingen en uitdagende scenario's verder onderzocht. Deze uitgebreide inzichten verbeteren de interpretatie van echocardiografie en ondersteunen het klinische besluitvormingsproces door cardiologen en cardio-thoracale chirurgen met betrekking tot de native en biologische aortaklep.

Hoofdstuk 1 fungeert als inleiding van dit proefschrift. Echocardiografische concepten in de pre-, peri- en postoperatieve zorg worden beschreven en het doel van dit werk wordt gepresenteerd. In **Hoofdstuk 2** wordt aangetoond dat meetfouten bij de echocardiografische beoordeling van de ernst van aortaklepstenose (AoS) onvoldoende erkend worden in de literatuur. Hoewel mogelijke foutbronnen eerder zijn beschreven [1], was de omvang en impact van de fouten nog onduidelijk. Deze studie biedt nieuwe inzichten; bijvoorbeeld, de interobservervariabiliteit in de effectieve openingsoppervlakte is veel groter dan in de gemiddelde drukgradiënt. Om de klinische implicaties van meetfouten te demonstreren, werden verschillende simulaties uitgevoerd. Gezien de toenemende echocardiografische indicaties voor asymptomatische patiënten met AoS, is het van cruciaal belang de aanwezigheid en de omvang van meetfouten en de implicaties ervan te kennen om patiënten adequaat door te verwijzen voor interventie. Het verkrijgen van de juiste diagnose is niet alleen een uitdaging bij asymptomatische patiënten, maar ook bij symptomatische patiënten met een lage slagvolume, d.w.z. een lage flow status. Een valide diagnose van ernstige AoS is een uitdaging in deze subgroep, daarom is er een classificatie op basis van slagvolume (SV) en gemiddelde drukgradiënt voorgesteld [2]. In **Hoofdstuk 3** wordt een slechte overeenstemming in de flow-gradiënt classificatie aangetoond als gevolg van grote verschillen tussen de echocardiografische SV metingen in de linker ventrikel uitstroombaan en in de linker ventrikel zelf met de Simpson methode. Daarom zijn deze methoden niet geschikt voor wederzijdse bevestiging. Verder wordt de gevoeligheid van deze classificatie voor kleine meetfouten geïllustreerd; na de introductie van een overschatting van 1 mm in de diameter van de uitstroombaan, nam het aantal patiënten in de lage flow groepen met 50% af. **Hoofdstuk 4** schetst dat de classificatie van paradoxale lage flow (PLF) ernstige AoS afhankelijk is van het lichaamsoppervlakte (oftewel de body surface area [BSA]). Patiënten met een grotere BSA hebben een grotere kans om te worden geclassificeerd met PLF dan patiënten met een kleinere BSA. Deze bevinding is klinisch relevant aangezien patiënten met normale flow en een lage gradiënt geen indicatie hebben voor een interventie [3,4]. De resultaten van **Hoofdstukken 3 en 4** benadrukken dat voor uitdagende klinische entiteiten zoals patiënten met een lage flow, een geïntegreerde benadering, waarin parameters buiten de flow-gradiënt classificatie mee worden genomen, noodzakelijk is om nauwkeurig te bepalen of AoS daadwerkelijk ernstig is en of de patiënt zal profiteren van een klepvervanging. **Hoofdstuk 5** toont dat er een hoge overeenkomst is tussen de echocardiografische

metingen van een centraal core laboratorium en klinische centra voor continuous-wave Doppler parameters zoals de maximale snelheid en de gemiddelde drukgradiënt over de aortaklep. Daarentegen is de overeenstemming laag voor parameters die de meting van de linker ventrikel uitstroombaandiameter betreffen (bijv. SV en de [geïndexeerde] effectieve openingsoppervlakte), wat wijst op de beperkte reproduceerbaarheid van deze metingen.

In **Hoofdstukken 6 en 7** worden de hemodynamische en klinische effecten van verschillende strategieën voor chirurgische aortaklepvervanging vergeleken. In **Hoofdstuk 6** leidde een minimaal invasieve benadering via een rechter anterieure thoracotomie of hemisternotomie tot vergelijkbare 3-jaar uitkomsten in vergelijking met de conventionele volledige sternotomie. In **Hoofdstuk 7** toonden hechtingen met vilt vergelijkbare 5-jaar klinische resultaten als hechtingen zonder vilt, hoewel de effectieve openingsoppervlakte mogelijk iets kleiner was tijdens follow-up wanneer vilt werd gebruikt. **Hoofdstuk 8** is een systematische review en meta-analyse die alle beschikbare literatuur samenvat over de risico's en voordelen van hechtingen met vilt tijdens chirurgische aortaklepvervanging. Het bewijs is schaars en heeft een hoog risico op bias, en de samengevoegde resultaten wijzen niet op superioriteit van hechtingen met of zonder vilt voor verschillende klinische en hemodynamische uitkomsten. In **Hoofdstuk 9** worden chirurgische inzichten voor de implantatie van een stentless bioprothese gepresenteerd. Er wordt specifieke aandacht besteed aan de juiste positionering van de prothetische klep in het geval van een native bicuspide aortaklep. **Hoofdstuk 10** biedt een overzicht van patiënten die een chirurgische aortaklepvervanging ondergingen in Noord-Amerika en Europa. Er werden significante intercontinentale verschillen waargenomen in ziekte ernst voor de operatie, procedurele kenmerken, antitrombotisch regime en het moment van ontslag. Het 30-dagen heropname risico was 8,5% in Europa en 15,9% in Noord-Amerika. Deze resultaten benadrukken dat de geografische setting mee moet worden genomen bij het ontwerpen van trials over chirurgische aortaklepvervanging en bij de interpretatie van resultaten. In **Hoofdstuk 11** wordt vastgesteld dat de kwaliteit van de rapportage over confounding correctie in veel observationele studies over cardiothoracale ingrepen onvoldoende is. De methodologie moet verbeterd worden omdat deze observationele studies de basis vormen voor de aanbevelingen voor interventie in de dagelijkse klinische praktijk. Daarom worden uitgebreide aanbevelingen geformuleerd voor het ontwerp en de uitvoering van dergelijke studies.

Hoewel een reeks hemodynamische parameters beschikbaar is om de prestatie van de prothese te beoordelen, wordt prothese-patiënt mismatch uitsluitend gedefinieerd op basis van de geïndexeerde effectieve openingsoppervlakte. In **Hoofdstuk 12** wordt aangetoond dat de incrementele prognostische waarde van verschillende postoperatieve echocardiografische parameters ten opzichte van een preoperatieve risicoscore, de Society of Thoracic Surgeons (STS) voorspelde mortaliteit, beperkt is voor de voorspelling van de 5-jaar mortaliteit na chirurgische aortaklepvervanging. Een mogelijke verklaring zou kunnen zijn dat echocardiografische parameters afgeleide indicatoren zijn voor de kleppprestatie, aangezien deze parameters ook de gezondheid van de patiënt weerspiegelen.

De enige parameter die enige verbetering in voorspelling bood in een post-hoc analyse was een Doppler velocity index (DVI) ≤ 0.35, maar zelfs deze parameter verbeterde de discriminatie tussen patiënten die stierven of overleefden gedurende de 5-jaar follow-up niet. In **Hoofdstuk 13** werden de resultaten van het vorige hoofdstuk gevalideerd in data van drie gerandomiseerde gecontroleerde trials. In dit cohort was DVI ≤ 0.35 opnieuw de enige parameter die enige verbetering in voorspelling bood ten opzichte van de STS score, maar deze parameter verbeterde weer de discriminatie niet. Deze resultaten benadrukken het belang van het overwegen van patiëntkenmerken bij de interpretatie van hemodynamische parameters voor prognostische doeleinden. **Hoofdstuk 14** laat zien dat de huidige definities voor hemodynamische structurele klepdegeneratie (SVD) inconsistent zijn. Na de eerste classificatie van SVD heeft tot 65% van de patiënten geen SVD bij volgende bezoeken. Deze bevindingen botsen met de onderliggende hypothese dat SVD permanente intrinsieke schade aan de prothese impliceert en werpen dus vraagtekens bij de klinische waarde van deze definities.

Aortaklepvervanging	Klinisch probleem behandeld in dit proefschrift	Inzichten verschaft in dit proefschrift
Preoperatieve beoordeling	• De diagnose van ernstige aortaklep-stenose bij asymptomatische patiënten	• De omvang en klinische impact van potentiële echocardiografische meetfouten worden aangetoond
	• De diagnose van ernstige aortaklep-stenose bij lage-flow patiënten	• De classificatie van paradoxale lage flow AoS is afhankelijk van slagvolume meting (locatie en nauwkeurigheid) en BSA
Perioperatief management	• De chirurgische strategie om hemodynamische prestaties te optimaliseren	• Een minimaal invasieve benadering of hechtingen met vilt veranderen hemodynamische en klinische uitkomsten niet
	• De onderzoeksmethoden om optimale chirurgische strategieën te bepalen	• De kwaliteit van rapportage en uitvoering is onvoldoende in de meeste observationele studies over cardiothoracale ingrepen
Postoperatieve beoordeling	• De prognostische waarde van prothese-patiënt mismatch en andere parameters voor residuele hemodynamische obstructie	• DVI ≤ 0.35 heeft de sterkste associatie met mortaliteit na SAVR, maar hemodynamische parameters van de hartklepprothese bieden beperkte incrementele prognostische waarde ten opzichte van patiëntkenmerken
	• De diagnose van hemodynamische structurele klepdegeneratie	• De huidige definities van hemodynamische SVD vangen structurele degeneratie van een bioprothese niet accuraat

DISCUSSIE EN TOEKOMSTPERSPECTIEF

De belangrijkste bevindingen van dit proefschrift worden in dit hoofdstuk in een breder perspectief geplaatst. Hedendaagse concepten met betrekking tot hemodynamische prestaties worden besproken en leemtes in het bewijs worden aangekaart. De discussie volgt de chronologische volgorde van de inleiding van dit proefschrift: het begint met de diagnose van native aortaklepziekte en eindigt met het falen van de bioprothese.

Risicostratificatie en timing van interventie voor aortaklepstenose

In de preoperatieve zorg is het belangrijkste doel het optimaliseren van het tijdstip van interventie [5,6]. Enerzijds moeten ingrepen vroeg worden uitgevoerd om onomkeerbare schade aan het hart te voorkomen. Anderzijds moeten de operatierisico's van overbodige ingrepen en de complicaties van prothetische kleppen worden vermeden. Het is noodzakelijk om de balans te vinden tussen deze twee aspecten om het ideale moment voor interventie te bepalen. Bijzondere klinische uitdagingen vormen asymptomatische patiënten, subgroepen met lage flow en patiënten met matige AoS. De symptomen die patiënten ervaren, correleren slechts in beperkte mate met de hartbeschadiging, wat de cruciale rol van beeldvormende parameters benadrukt [7]. Kritiek afwijkende echocardiografische waarden van de maximum snelheid over de aortaklep zijn vastgesteld als een nuttige interventiedrempel voor asymptomatische patiënten [8,9]. De transvalvulaire flow, de verhouding van slagvolume tot ejectietijd, bleek een marker te zijn met superieure prognostische waarde ten opzichte van de effectieve openingsoppervlakte, met name bij lage stroomsnelheden [10]. Patiënten met matige AoS lijken een slechte prognose te hebben, die niet veel verschilt van die van ernstige AoS [11,12]. Om patiënten met matige AoS nauwkeurig te diagnosticeren, zijn uitgebreide diagnostische trajecten voorgesteld met multimodale beeldvorming en onderzoeken naar hartbeschadiging [12]. Bijvoorbeeld, acute en chronische markers van verhoogde vullingsdruk van de linker ventrikel worden geassocieerd met slechtere uitkomsten en zijn mogelijk geschikte toekomstige interventiedrempels bij matige AoS [13]. Door de focus te verleggen naar het myocard en de mate van hartbeschadiging, zijn nieuwe beeldvormende biomarkers geïdentificeerd, zoals longitudinale strain en werkindices, calciumscores op computertomografie (CT) en het beoordelen van fibrose met cardiale magnetische resonantie [14-16]. Deze parameters lijken veelbelovend en zullen bijdragen aan de optimalisatie van de risicostratificatie bij patiënten met AoS.

Verder verbeteren van de patiëntenzorg bij AoS vereist de preventie van onderdiagnose en onderbehandeling [17,18]. Onderbehandeling komt voor bij tot 67% van de patiënten met lage-gradient AoS, bij 20-33% van de symptomatische AoS patiënten met een klasse I indicatie voor interventie, en vaker bij vrouwen [19-21]. Dit laatste kan te maken hebben met het feit dat vrouwen minder calcificatie maar meer fibrose vertonen bij dezelfde AoS ernst [22-24], en daarom worden geslacht specifieke drempels voor ernstige AoS voorgesteld [25]. Onderdiagnose kan worden verminderd door bewustwording, onderwijs en technische innovaties. Bovendien kunnen hedendaagse populatie-gebaseerde studies waardevolle inzichten bieden in de prevalentie en uitkomsten van AoS, omdat het vakgebied snel

vordert [17], bijvoorbeeld in Nederland door data van het Centraal Bureau voor de Statistiek te koppelen aan de Nederlandse Hartregistratie.

Voor tijdige interventies is een geïntegreerde aanpak door het multidisciplinaire hartteam, bij voorkeur in gespecialiseerde hartklepcentra, essentieel [26]. Toegewijde cardiologen en cardio-thoracale chirurgen moeten zich bewust zijn van de evoluerende indicaties en zich niet laten misleiden in hun diagnostische work-up door natuurlijke variabiliteit of meetfouten. Vooral voor uitdagende klinische entiteiten moet het hartteam aanvullende echocardiografische, functionele en anatomische parameters overwegen om de werkelijke ernstige AoS te diagnosticeren en de patiënten te identificeren die zullen profiteren van aortaklepvervanging [3,4].

Lopende trials zullen de besluitvorming bij AoS ondersteunen. De EARLY-TAVR (NCT03042104), ESTIMATE (NCT02627391) en EASY-AS (NCT04204915) trials onderzoeken het effect van vroege TAVR of SAVR versus surveillance bij asymptomatische ernstige AoS. De Evolved (NCT03094143) trial richt zich op dezelfde asymptomatische ernstige AoS patiënten, maar omvat ook fibrosebeoordeling via cardiale magnetische resonantie voordat de deelnemers worden gerandomiseerd. De DANAVR (NCT03972644) onderzoekt eveneens de voordelen van vroege interventie en richt zich op asymptomatische ernstige AoS met bewaarde linker ventrikel ejectiefractie (LVEF), maar met hoge vullingsdrukken, een groot geïndexeerd linker atrium volume, of verstoorde linker ventrikel globale longitudinale strain (GLS). Voor matige AoS worden in de TAVR UNLOAD (NCT02661451), PROGRESS (NCT04889872) en Evolut EXPAND TAVR II (NCT05149755) trials TAVR versus optimale medische therapie bestudeerd. De DETECT AS (NCT05230225) trial onderzoekt of elektronische notificatie van de detectie van ernstige AoS op echocardiografie leidt tot een hoger gebruik van aortaklepvervanging en omvat vooraf gedefinieerde subgroep analyses voor onder andere vrouwen, lage-gradiënt AoS en raciale/etnische minderheden.

Vandaag de dag zijn er geen farmacotherapeutische middelen die de voortgang van AoS kunnen vertragen, stoppen of omkeren [27]. Gerandomiseerde studies naar het effect van statines, denosumab en alendroninezuur hebben geen voordeel aangetoond [28-31]. Nieuwe geneesmiddelen die gericht zijn op lipoproteïne(a) lijken veelbelovend, maar hun klinische waarde moet nog bewezen worden [32-34]. Farmacotherapie heeft een groot potentieel voor AoS, evenals voor het tegengaan van degeneratie van prothetische hartkleppen.

Periprocedurele AVR-strategieën voor het optimaliseren van hemodynamische en klinische uitkomsten

In de perioperatieve zorg is de belangrijkste uitdaging het afstemmen van interventiestrategieën en de keuze van de prothetische klep op de individuele patiënt. Hemodynamische prestaties zijn een zeer belangrijk aspect, hoewel andere klinische factoren, zoals geleidingsproblemen en klepduurzaamheid, niet over het hoofd mogen worden gezien. Uiteindelijk wordt de

prognose en kwaliteit van leven van de patiënt bepaald door een combinatie van al deze aspecten. Het effect van transkatheter versus chirurgische aortaklepvervanging (TAVR versus SAVR) is onderzocht over het gehele risicospectrum, maar de langetermijnresultaten moeten nog worden vastgesteld, vooral voor patiënten met een laag risico [35-41]. In de meeste studies zijn de gradiënten lager en de effectieve openingsoppervlakten groter na TAVR, hoewel paravalvulaire lekkage en geleidingsstoornissen vaker voorkomen [35-40,42]. Patiëntkenmerken die respectievelijk SAVR of TAVR ten faveure stellen, omvatten de mate van calcificatie, de anatomie en de noodzaak voor aanvullende chirurgie aan de coronairen, andere hartkleppen en de aorta [43]. Sommige patiëntengroepen zijn systematisch uitgesloten van gerandomiseerde trials, zoals patiënten met een bicuspide aortaklep (BAV). BAV patiënten vertegenwoordigen 5-10% van de ouderen die momenteel met TAVR worden behandeld [44] en vereisen vaak aanvullende aortachirurgie [45]. De hemodynamische prestaties van TAVR kleppen bij BAV patiënten lijken vergelijkbaar te zijn met die bij patiënten met een tricuspide aortaklep [46]. Recente resultaten van de NOTION-2 trial suggereren echter een voorzichtige toepassing van TAVR bij jonge BAV patiënten [47]. Bovendien kunnen de klinische uitkomsten van TAVR bij BAV afhankelijk zijn van de klepmorfologie [48]. Voor patiënten met lage flow, lage-gradiënt AoS is de optimale interventiestrategie nog onbepaald en is verder onderzoek vereist [49-51]. Een andere AoS subgroep waarvoor hemodynamische prestaties van het grootste belang worden geacht, zijn de patiënten met een kleine annulus van de aortaklep [52]. Deze patiënten lopen risico op residuele hemodynamische obstructie na AVR, omdat de gradiënt in omgekeerde en exponentiële verhouding staat tot de straal in buisvormige structuren (de Wet van Poiseuille), zoals de uitstroombaan van het hart. In een subanalyse van de PARTNER trial was het risico op mortaliteit vergelijkbaar tussen TAVR en SAVR, hoewel de hemodynamische prestaties in het voordeel van TAVR waren [53]. De VIVA (NCT03383445) trial onderzocht het effect van TAVR versus SAVR specifiek voor ouderen met een kleine annulus diameter. In deze kleine gerandomiseerde trial werden geen verschillen waargenomen in klinische en hemodynamische uitkomsten. De RHEIA (NCT04160130) trial bestudeert specifiek het effect van TAVR versus SAVR bij vrouwen met ernstige AoS. Andere lopende trials over TAVR versus SAVR voor patiënten met een laag risico zijn de DEDICATE (NCT03112980) trial, een door onderzoekers geïnitieerde trial die zich expliciet richt op "all-comers". De 1-jaarsresultaten geven aan dat TAVR niet inferieur was wat betreft overlijden of beroerte [54], maar de langetermijnresultaten moeten nog volgen. Voor BAV patiënten wordt het effect van TAVR versus SAVR onderzocht in de NAVIGATE, BELIEVERS en YOUNG TAVR trials. Voor ernstige AoS patiënten met multivessel coronairlijden vergelijkt de TCW (NCT03424941) trial of TAVR + percutane coronaire interventie niet inferieur is aan SAVR + aanvullende coronaire bypassoperatie.

Afgezien van de vraag of een transkatheter of chirurgische strategie de voorkeur heeft, verdienen ook de procedurele details van beide behandelingen aandacht. Bij SAVR zijn de keuze van de prothetische klep, de chirurgische benadering en de hechtingstechniek mogelijke bijdragende factoren voor klinische uitkomsten. Gestente biologische kleppen worden het vaakst gebruikt, maar alternatieven zijn sutureless, stentless of mechanische

protheses. In de volgende sectie worden de bewijsstukken besproken voor de vergelijkingen van patiënten die in aanmerking komen voor zowel conventionele (d.w.z. gestente bioprotheses) als alternatieve prothetische kleppen. Observatiestudies suggereren dat sutureless kleppen betere hemodynamische prestaties opleveren, maar gepaard gaan met een verhoogd risico op pacemakerimplantatie [55,56]. In de PERSIST-AVR trial waren sutureless kleppen echter niet inferieur aan gestente kleppen wat betreft majeure cerebrale en cardiovasculaire nadelige klinische gebeurtenissen [57]. Gerandomiseerde trials voor de vergelijking tussen stentless en gestente kleppen stammen uit de vroege jaren 2000 en toonden een vergelijkbare prognose aan ondanks een beter hemodynamisch profiel voor stentless kleppen [58-60]. Deze resultaten werden ook gevonden in een recente observationele studie [61]. Volgens een expertconsensusverklaring zouden sutureless kleppen specifiek gebruikt kunnen worden bij ouderen met comorbiditeiten, een porseleinen aorta of patiënten die aanvullende chirurgie nodig hebben om de tijd voor het klemmen van de aorta en de hartlongmachine te verkorten [62]. Bij de keuze tussen biologische en mechanische kleppen zijn aspecten zoals anticoagulatie en duurzaamheid even belangrijk als de hemodynamische prestaties. De leeftijdsgrens waaronder mechanische kleppen de voorkeur zouden moeten krijgen, is uitvoerig bediscussieerd [63] en verschilt zelfs tussen Amerikaanse en Europese richtlijnen [3,4]. Het uitvoeren van een annulusvergroting, via de traditionele Nicks [64], Manouguian [65], of recent geïntroduceerde Y-incisie procedure [66], is een andere manier om de hemodynamiek te verbeteren. Volgens de gegevens van de Society of Thoracic Surgeons worden vergrotingen momenteel uitgevoerd bij slechts 2,9% van de patiënten van 65 jaar en ouder [67]. De literatuur bestaat uitsluitend uit observationele studies die waarschijnlijk vertekend zijn door confounding en levert conflicterende resultaten op voor uitkomsten zoals perioperatieve mortaliteit [67-72]. De veiligheid van deze procedures, evenals de voordelen op lange termijn en de reproduceerbaarheid, zijn gebieden die verder onderzoek vereisen. Ten slotte ontbreekt consensus over de optimale hechtingstechniek voor het implanteren van een aortaklepprothese, en in de praktijk is deze voornamelijk gebaseerd op de voorkeur en opleiding van de chirurg. Bijvoorbeeld, verschillende studies suggereren met vilt versterkte matrashechtingen [73], simple-interrupted [74], of continue hechtingen als optimaal [75].

De hemodynamische prestaties van transkatheterprotheses worden beïnvloed door de implantatieplaats en het ontwerp van de klep. Supra-annulaire implantatie met een zelf-expanderende klep leverde betere hemodynamica op, maar vergelijkbare klinische uitkomsten in vergelijking met intra-annulaire implantatie met een ballon-expanderende klep in verschillende trials [76-79]. In de lopende SMART (NCT04722250) trial worden patiënten met een kleine native aortaklep op basis van CT gestrand om te worden gerandomiseerd naar de nieuwste commercieel beschikbare zelf-expanderende of ballon-expanderende kleppen. De LYTEN trial toont aan dat zelf-expanderende kleppen superieure hemodynamische prestaties hadden bij gefaalde chirurgische bioprotheses met een maat kleiner dan 23 mm, maar dat de korte termijn klinische uitkomsten opnieuw vergelijkbaar waren [80]. Bij gefaalde gestente bioprotheses kan een het breken van de stent voor een valve-in-valve-implantatie de hemodynamische prestaties verbeteren, maar het klinische voordeel moet nog worden

bewezen [81]. Een overzicht van de normale transkatheterfunctie voor verschillende kleppen werd verstrekt door Hahn et al. als referentie voor de klinische praktijk [82].

Beeldvorming van hartklepprotheses is complex en vereist klinische competentie evenals kennis van veelvoorkomende valkuilen [83,84]. Specifieke aanbevelingen worden voorgesteld in internationale echo-richtlijnen en expertconsensusdocumenten [85,86]. Echocardiografie werd gevalideerd tegen hartkatheterisatie in de setting van native AoS, daarom kunnen sommige berekeningen, zoals de vereenvoudigde Bernoulli formule, minder nauwkeurig zijn bij goed functionerende hartklepprotheses [87]. De DISCORDANCE (NCT04827238) trial zoekt de discrepanties tussen echocardiografische- en katheterisatie metingen verder uit.

Het belang van levenslange zorg wordt steeds meer benadrukt: toekomstige procedures moeten al bij de primaire interventie in acht worden genomen [43]. Deze overwegingen omvatten, naast de klepfunctie, het behoud van toegang tot de coronairen. Explantatie van traskatheterkleppen kan chirurgisch uitdagend zijn en vereist vaak wortelreparatie / vervanging of ingrepen aan de mitralisklep [88,89]. Valve-in-valve TAVR vereist zorgvuldige planning en implantatie. Een verdere verfijning van klinische inzichten wordt in de komende jaren verwacht [90,91]. Bij levenslange zorg is informatie over de levensverwachting en de waarschijnlijkheid van klepgerelateerde complicaties voor individuele patiënten essentieel. Microsimulatie zou hierbij behulpzaam kunnen zijn [92].

Prothese-patiënt mismatch en hemodynamische structurele klepdegeneratie

Postoperatief management van SAVR patiënten omvat twee belangrijke echocardiografische concepten: prothese-patiënt mismatch (PPM) en hemodynamische structurele klepdegeneratie (SVD). Het probleem van PPM werd voor het eerst naar voren gebracht door Rahimtoola in 1978 [93]. Later werd een formele definitie van PPM voorgesteld, gebaseerd op waarden van de geïndexeerde effectieve openingsoppervlakte (EOAi), die overeenkwamen met verhoogde gradiënten [94]. Meta-analyses hebben aangetoond dat ernstige PPM, op basis van deze EOAi-gebaseerde definities, geassocieerd is met verminderde overleving na SAVR en TAVR [95-97]. Recente studies hebben echter verschillende limitaties geïdentificeerd met betrekking tot de huidige definitie van PPM en de klinische waarde ervan voor individuele patiënten. Deze limitaties omvatten ontevredenheid over de overeenstemming tussen de geprojecteerde PPM, zoals weergegeven in klepdiagrammen, en gemeten PPM na AVR [98], maar ook onjuiste categorisering van EOAi en een slechte overeenkomst met hemodynamische obstructie door andere parameters [99], en disproportionele indexatie naar BSA [100]. Een duidelijk voorbeeld van onjuiste PPM-classificatie door foutieve BSA-indexatie wordt besproken in deze brief [101]: in een studie bij een Aziatische en Westerse populatie hadden de Aziaten aanzienlijk hogere snelheden en gradiënten na AVR, maar een aanzienlijk lagere incidentie van PPM. De problemen die in de bovengenoemde studies worden geïdentificeerd, benadrukken dat hoewel PPM op groepsniveau geassocieerd is met een slechtere prognose in de meeste studies, het concept zoals het momenteel gedefinieerd is, misleidend kan zijn voor individuele patiënten (en helaas kunnen we niet voorspellen voor welke). Surrogaatconcepten zoals

PPM vereisen aanvullende aannames bovenop de reeds gemaakte aannames voor standaard echocardiografische metingen. De parameters die het meest waardevol zijn voor de klinische beoordeling van de prestaties van een hartklepprothese, zijn de parameters die het meest nauwkeurig worden gemeten en het beste overeenkomen met relevante klinische uitkomsten. De resultaten gepresenteerd in dit proefschrift suggereren dat een DVI ≤ 0.35 sterker geassocieerd is met (cardiovasculaire) mortaliteit dan ernstige PPM en daardoor een superieure marker kan zijn voor klinisch relevante hemodynamische obstructie na SAVR (Hoofdstuk 12 [102] & 13). De impact van flow op hemodynamische metingen maakt uniforme criteria uitdagend [103,104] en moet worden geïntegreerd in de beoordelingsalgoritmen van hartklepprotheses, vergelijkbaar met de diagnose van native AoS.

Het tweede echocardiografische concept in deze context is hemodynamische SVD. In de afgelopen jaren zijn door verschillende internationale verenigingen en expertpanels definities voor hemodynamische SVD voorgesteld, voornamelijk op basis van veranderingen in echoparameters in de tijd [105-107]. Het optreden van hemodynamische SVD na TAVR en SAVR is onderzocht [108,109], hoewel men zich af kan vragen of de definities evenzeer van toepassing zijn op TAVR- en SAVR-patiënten. Na de interventie is het hemodynamische profiel anders, ten gunste van TAVR, en dus betekent het overschrijden van de absolute gemiddelde gradiëntdrempels van 20 mmHg een grotere relatieve verandering voor transkatheter kleppen. Anders gezegd, chirurgische kleppen zullen deze drempel gemakkelijker overschrijden met minder relatieve degeneratie. Het is belangrijk op te merken dat dit zelfs geldt in trials, omdat het moment van randomisatie (namelijk vóór implantatie van de hartklepprothese) niet samenvalt met het referentiepunt voor de definities van hemodynamische SVD (namelijk na implantatie van de hartklepprothese). Bovendien is de huidige SVD-classificatie in 65% van de gevallen inconsistent, zoals uiteengezet in dit proefschrift [110]. Echocardiografie als eerstelijns detectietool voor afwijkende hartklepfunctie is gerechtvaardigd door de mogelijkheid om de klepbladen te beoordelen en kleptrombose of endocarditis snel en non-invasief uit te sluiten. Echter, kwantitatieve criteria voor de detectie van klepdegeneratie vereisen verdere optimalisatie, bijvoorbeeld door hun verband met relevante uitkomsten zoals klepgerelateerde symptomen, reoperaties of valve-in-valve re-interventies te onderzoeken. Voor de klinische praktijk moeten echocardiografische alarmsignalen voor vermoedelijke SVD zorgvuldig worden bevestigd en moeten de klinische implicaties voor de patiënt worden onderzocht [84,107]. CT-beeldvorming kan worden gebruikt om calcificatie te beoordelen, maar artefacten door de metalen componenten van de hartklepprotheses kunnen de evaluatie bemoeilijken. Invasieve metingen door middel van hartkatheterisatie kunnen worden overwogen voordat een reinterventie plaatsvindt in geval van abnormale echowaarden maar afwezige klepbladafwijkingen op echo en CT, ondanks de aanwezigheid van klepgerelateerde symptomen [76]. Dit wordt ondersteund door de bevinding dat bij 70% van de patiënten met een gemiddelde gradiënt ≥20 mmHg op echocardiografie, de gemiddelde gradiënt niet verhoogd was bij hartkatheterisatie [87]. Bovendien hebben moderne beeldvormingstools, zoals 18F-fluoride positronemissietomografie CT, klepdegeneratie aan het licht gebracht die niet werd gedetecteerd door echocardiografie of CT alleen, wat een sterke voorspeller bleek te

zijn van daaropvolgende degeneratie [111]. Met de evoluerende kennis over de voordelen van AVR bij asymptomatische (en mogelijk matige) AoS- en laagrisicopatiënten, de progressieve implantatie van transkatheterkleppen, de afname van mechanische klepimplantaties en de stijgende levensverwachting, zullen meer en jongere patiënten in de nabije toekomst een biologische hartklepprothese ontvangen. Daarom zal de incidentie van SVD toenemen en zal het management ervan steeds belangrijker worden.

Conclusies over hemodynamische concepten rondom aortaklepvervanging

Echocardiografie is een waardevol, zo niet het meest waardevolle, hulpmiddel om de werking van de native en biologische aortaklep te beoordelen. Dat gezegd hebbende, moeten kwantitatieve echocardiografische metingen met de nodige voorzichtigheid worden geïnterpreteerd. Metingen worden beïnvloed door verschillende bronnen van meetfouten, natuurlijke variatie en door patiëntkenmerken, die vaak een grotere impact hebben dan verwacht. Dit proefschrift benadrukt consequent dat diagnostische echocardiografische criteria, die theoretisch valide lijken, in de klinische praktijk onbetrouwbaar kunnen zijn. Validatiestudies zijn essentieel om te onderzoeken of echocardiografische definities daadwerkelijk vangen wat ze zouden moeten vangen en of theoretische definities daadwerkelijk correleren met klinisch relevante uitkomsten voor patiënten. Dit zal leiden tot verdere vooruitgang in diagnostische algoritmen en tot een verhoogd bewustzijn van de beperkingen en onzekerheden, wat de klinische zorg voor patiënten met aortaklepziekten verder zal verbeteren.

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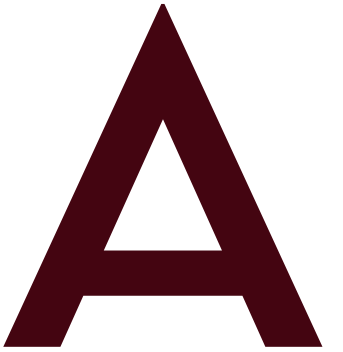

APPENDICES

ABBREVIATIONS

ACC/AHA	=	American College of Cardiology / American Heart Association
AVR	=	Aortic valve replacement
AS	=	Aortic stenosis
ATS	=	Annals of Thoracic Surgery
AVA	=	Aortic valve area
BSA	=	Body surface area
BVF	=	Bioprosthetic Valve Failure
CABG	=	Coronary artery bypass grafting
CI	=	Confidence interval
CSA	=	Cross-sectional area
CVA	=	Cerebrovascular accident
DVI	=	Doppler velocity index
ECL	=	Echo core laboratory
EJCTS	=	European Journal of Cardio-Thoracic Surgery
EOA	=	Effective orifice area
ESC/EACTS	=	European Society of Cardiology / European Association of Cardio-Thoracic Surgery
IPTW	=	Inverse probability of treatment weighting
JTCVS	=	The Journal of Thoracic and Cardiovascular Surgery
LFHG	=	Low-flow, high-gradient
LVEF	=	Left ventricular ejection fraction
LVOT	=	Left ventricular outflow tract
GRADE	=	Grading of Recommendations, Assessment, Development, and Evaluations
MD	=	Mean difference
MI-AVR	=	Minimally invasive aortic valve replacement
MPG	=	Mean pressure gradient
NF	=	Normal-flow
NYHA	=	New York Heart Association
OAC	=	Oral anticoagulant
PERIGON	=	PERIcardial SurGical AOrtic Valve ReplacemeNt Pivotal Trial for the Avalus valve
PLF	=	Paradoxical low-flow
PLFLG	=	Paradoxical low-flow, low-gradient
PPM	=	Prosthesis-patient mismatch
PRISM	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	=	Propensity score
PSA	=	Propensity score adjustment
PSM	=	Propensity score matching

PVL	=	Paravalvular leak
RR	=	Risk ratio
SAVR	=	Surgical aortic valve replacement
STS	=	Society of Thoracic Surgeons
STS PROM	=	Society of Thoracic Surgeons predicted risk of mortality
SV	=	Stroke volume
SVD	=	Structural valve deterioration
TAVR	=	Transcatheter aortic valve replacement
VARC	=	Valve Academic Research Consortium
V_{max}	=	Peak aortic jet velocity
VTI	=	Velocity-time integral

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CURRICULUM VITAE

Bart Velders was born on 1 November 1995 in Voorschoten, The Netherlands. In 2014, he graduated from secondary school (Stedelijk Gymnasium Leiden) and subsequently began his studies in Medicine at Leiden University. He completed his Master's degree with distinction (cum laude) in 2021. During his studies, he worked as a retrieval technician at BISLIFE (later renamed WUON), where he was responsible for performing surgical explantations of post-mortem human tissue, including heart valves, blood vessels, ocular tissue, and musculoskeletal tissue, for transplantation purposes.

Bart commenced his PhD in September 2021 at the Leiden University Medical Center (LUMC), under the supervision of Prof. Dr. R.J.M. Klautz from the Department of Cardiothoracic Surgery and Prof. Dr. R.H.H. Groenwold from the Departments of Clinical Epidemiology and Biomedical Data Science. In parallel with his doctoral research, he trained to become a clinical epidemiologist in the department of Prof. Dr. F.R. Rosendaal. He also contributed to the education of Bachelor's, Master's, and PhD students in research methodology, with a particular focus on causal inference for the latter group. Furthermore, he conducted a research visit to the headquarters of Medtronic and the Echocardiographic Core Laboratory at the Mayo Clinic in Minnesota, USA. In March 2024, he returned to clinical practice to work as resident not in training at the department of Cardiothoracic Surgery at the LUMC. As of December 2024, he is in training to become a cardiothoracic surgeon.

ACKNOWLEDGEMENTS

Prof. Klautz, beste Robert, bedankt voor jouw toewijding aan mijn promotietraject en de kansen om het maximale uit mijn onderzoekstijd te halen. Ik hoop tijdens mijn opleiding nog veel van je te leren op de OK.

Prof. Groenwold, beste Rolf, jouw bijdrage aan de kwaliteit van mijn proefschrift is onbeschrijfelijk. Je hebt mij gemaakt tot een onderzoeker met een rugtas vol ervaring, daar ben ik je erg dankbaar voor.

Dr. Vriesendorp, beste Michiel, jij hebt de basis gelegd voor dit onderzoek; theorieën neem je niet klakkeloos over, maar valideer je eerst voor klinisch gebruik. Ik heb genoten van al onze discussies.

Prof. Kappetein, beste Pieter, jouw bijdrage aan dit proefschrift is aanzienlijk door de onderzoeksmogelijkheden die je hebt gecreëerd. Je bent een mentor en een voorbeeld voor mij.

Simon en Jesse, dank dat jullie mijn paranimfen willen zijn. Succes met jullie eigen PhDs! Ik waardeer onze vriendschap, ook met Olivier en Bastiaan.

Collega's van de thoraxchirurgie, dank voor alles wat jullie mij hebben geleerd. Ik werk met plezier met jullie samen. Dank ook aan oud-collega's zoals Anton, Bardia, Nimrat en Thomas van Brakel voor de begeleiding bij mijn eerste stappen binnen de thoraxchirurgie.

Collega's van de epidemiologie, ik ben onder de indruk van de kennis en kwaliteit op jullie afdeling.

Dear dr. Ajmone Marsan, dear Nina, I greatly respect your expertise and passion for imaging and I enjoy collaborating with your imaging fellows. Beste PhD'ers uit de tuin, de congressen waren top! Tot in de kliniek.

Dear Medtronic, I am grateful for the collaboration and for my research visit at Mounds View. Dear prof. Oh and dr. Ito, I would also like to thank you for my research visit at the Mayo Clinic echo core laboratory. I look forward to extending our research.

Dear PERIGON participants and investigators, without you this research was impossible to conduct.

Lieve vrienden, huis- en clubgenoten, dank voor alle afleiding.

Lieve Eddo en Sabine, lieve papa en mama, ik ben erg dankbaar voor jullie steun voor mijn studie en promotietraject, en voor alles wat jullie me hebben geleerd. Lieve Anne, lieve zus, dank voor jouw support en onze momenten samen.

Lieve Feeke, jij haalt het beste in me naar boven en stuurt me bij wanneer nodig. Ik ben dankbaar voor de ruimte die ik van jou krijg en realiseer me dat dit zeker niet vanzelfsprekend is. Ik kijk uit naar onze toekomst samen.