Optimizing

CLINICAL DECISION MAKING *in* PROSTHETIC AORTIC VALVE SELECTION

Nelleke Korteland

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COLOFON

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OPTIMIZING CLINICAL DECISION MAKING IN PROSTHETIC AORTIC VALVE SELECTION

HET OPTIMALISEREN VAN KLINISCHE BESLUITVORMING IN DE SELECTIE VAN AORTAKLEPPROTHESES

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To my mother, in loving memory

Some of these mornings
It won't be long
You are going to wake up calling me
And I'll be gone

Adapted from "Their Eyes Were Watching God"
by Zora Neale Hurston

CONTENTS

"Tell me and I forget,
teach me and I may remember,
involve me and I learn"

Benjamin Franklin

1.

General Introduction

AORTIC VALVE DISEASE

The burden of heart valve disease is increasing worldwide, due to the growth and ageing of the population, and the persistent problems caused by rheumatic heart disease. It is estimated that by 2050 the annual number of patients requiring heart valve surgery will have tripled to 850.000 [1]. Aortic valve disease is the most common heart valve disease requiring surgery [2]. In the Netherlands annually approximately 3000 aortic valve operations are carried out [3].

Aortic valve replacement is often the treatment of choice for patients with severe aortic valve disease. Since the first successful aortic valve replacement in 1960 [4], many things have changed. In the early days of heart surgery, aortic valve replacement was a salvage operation with high operative mortality. Over time however, clinical practice with regard to aortic valve replacement has changed markedly. Surgical techniques improved, and the introduction of cardiopulmonary bypass and cardioplegia contributed to a considerable decrease in mortality rates. With the development of cardiac catheterization it was possible to assess the severity of the aortic stenosis and progression over time [5]. Standardization of patient monitoring has dramatically improved the outcomes of patients after aortic valve replacement, and it is now a safe procedure with low morbidity and mortality.

PROSTHETIC VALVE CHOICE

Two main prosthetic valve types are available for aortic valve replacement: a mechanical valve prosthesis and a biological valve prosthesis (Figure 1). Both prosthetic valve types have specific advantages and disadvantages. A mechanical valve prosthesis is designed to last a lifetime but patients need to use lifelong anticoagulation due to the increased thrombogenicity of the mechanical valve prosthesis. This entails daily medication use that is monitored every few weeks by a blood test (INR test), and in case of pregnancy may result in maternal and fetal complications. Mechanical valve prostheses make a ticking sound that may be audible to the patient or other people nearby. A biological valve prosthesis does not require lifelong anticoagulation, unless another indication for anticoagulation is present. However, a biological valve prosthesis is subject to valve deterioration over time, so a patient may require one or more reoperations later in life. The durability of biological valve prostheses is improving though. Furthermore, outcome after reoperative aortic valve replacement is improved and nowadays there is the possibility of transcatheter valve-in-valve replacement in case of valve deterioration. All these factors have led to an increase in the use of biological valve prostheses [6-11].

The guidelines concerning prosthetic heart valve selection have changed accordingly over the years. At first age was the most important factor with regard to prosthetic valve choice, with an age limit of 70 for mechanical valve implantation. Although current guidelines propose a different age limit for mechanical valve implantation (European guidelines 60 years and American guidelines 50 years), this age limit has decreased significantly. Furthermore, besides clinical factors, like valve durability, hemodynamics, surgical risk and the (potential) need for long-term anticoagulation, also quality of life and patient values and preferences need to be considered [12, 13]. Informed patient preferences in the selection of a prosthetic valve are important, since each individual patient will value the advantages and disadvantages of the two prosthetic valve types in a different way. Especially the tradeoff between the risk associated with lifelong anticoagulation use and the risk of a reoperation should be discussed in detail with the patient.

FIGURE 1. Prosthetic valves. A: Mechanical valve; B: Biological valve.

SHARED DECISION MAKING IN PROSTHETIC VALVE CHOICE

Including patient values and preferences for aortic valve choice in the current guidelines is driven by the fact that shared decision making is becoming more and more important in medicine. Shared decision making is a process in which physicians and patients make decisions together using the best available evidence [14]. It can reduce health care costs, as patients who participate in decision making choose more conservative treatment than patients who are not involved [15]. Patients want to be informed about their treatment options and participate in decision making to receive the treatment

that best fits their values and preferences [16-18]. At the same time, physicians have the responsibility to inform the patient. Nowadays informed consent and patient–centered care are important concepts in daily clinical practice [19].

According to the godfather of evidence-based medicine, David Sackett, ideally there are three essential components of medical decision making: clinical experience, clinical research and patient preferences (Figure 2) [20]. This particularly applies to prosthetic heart valve selection, since this is highly preference sensitive. However, no framework to apply shared decision making in the setting of prosthetic heart valve selection is currently available. Therefore, the Dutch Association for Cardiothoracic Surgery, in cooperation with the Netherlands Society of Cardiology, the Dutch Heart Foundation and the Hart&Vaatgroep, initiated a quality improvement project with the aim to develop and test a patient decision aid to support a shared decision making process for prosthetic heart valve selection.

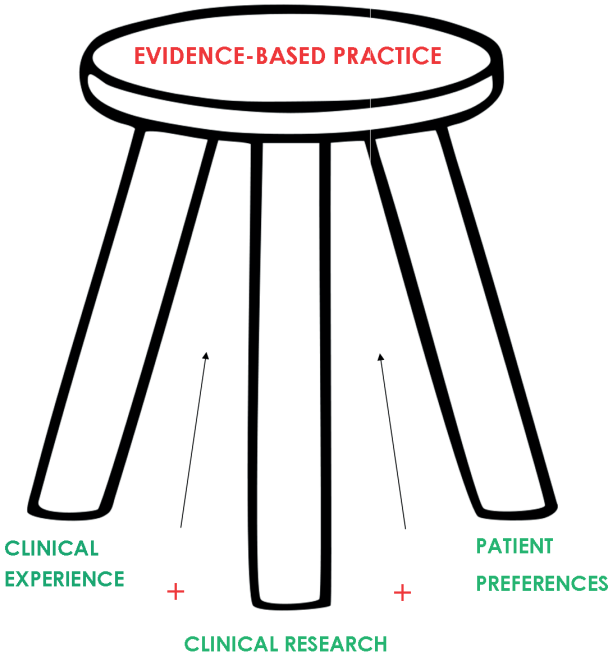

FIGURE 2. Three-legged stool of evidence-based practice.

AIM

This thesis aims to provide insight in current prosthetic heart valve selection and outcomes in non-elderly adults and introduces a tool to support shared decision making in this setting.

This was done by obtaining evidence on clinical and quality of life outcomes after aortic valve replacement in non-elderly adults, by exploring patient and physician attitudes toward shared decision making, and by testing the efficacy of a decision aid for prosthetic heart valve replacement in a randomized controlled trial setting.

OUTLINE

Chapter 2 is a systematic review and microsimulation after mechanical aortic valve replacement in non-elderly adult patients.

In Chapter 3 a systematic review and meta-analysis was performed to provide a detailed overview of outcome after the Bentall procedure using a mechanical valve prosthesis.

Chapter 4 is a cross-sectional cohort study that assesses quality of life in relation to prosthetic aortic valve selection and preferences for shared decision making among non-elderly adult patients after aortic valve replacement.

Chapter 5 presents a case report about a patient with Marfan syndrome who has undergone a Bentall procedure with a mechanical valve prosthesis.

Chapter 6 is a survey among Dutch cardiothoracic surgeons and cardiologists. It assesses and compares their opinion on (1) patient involvement, (2) risk conveyance in aortic valve selection, and (3) aortic valve preferences.

Current patient experience, preferences and knowledge with regard to prosthetic heart valve selection are presented in Chapter 7.

Chapter 8 is a multicenter randomized controlled trial that assesses whether use of the patient decision aid results in optimization of shared decision making in prosthetic heart valve selection.

REFERENCES

1. Yacoub, M.H. and J.J. Takkenberg, *Will heart valve tissue engineering change the world?* Nat Clin Pract Cardiovasc Med, 2005. 2(2): p. 60-1.
2. Iung, B., et al., *A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease.* Eur Heart J, 2003. 24(13): p. 1231-43.
3. www.bhn-registratie.nl
4. Harken, D.E., et al., *Aortic valve replacement with a caged ball valve.* Am J Cardiol, 1962. 9: p. 292-9.
5. Lester, S.J., et al., *The natural history and rate of progression of aortic stenosis.* Chest, 1998. 113(4): p. 1109-14.
6. Ruel, M., et al., *Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age.* Circulation, 2007. 116(11 Suppl): p. I294-300.
7. Niclauss, L., L.K. von Segesser, and E. Ferrari, *Aortic biological valve prosthesis in patients younger than 65 years of age: transition to a flexible age limit?* Interact Cardiovasc Thorac Surg, 2013. 16(4): p. 501-7.
8. Une, D., M. Ruel, and T.E. David, *Twenty-year durability of the aortic Hancock II bioprosthesis in young patients: is it durable enough?* Eur J Cardiothorac Surg, 2014. 46(5): p. 825-30.
9. Potter, D.D., et al., *Operative risk of reoperative aortic valve replacement.* J Thorac Cardiovasc Surg, 2005. 129(1): p. 94-103.
10. Davierwala, P.M., et al., *Reoperation is not an independent predictor of mortality during aortic valve surgery.* J Thorac Cardiovasc Surg, 2006. 131(2): p. 329-35.
11. Bourguignon, T., et al., *Very Long-Term Outcomes of the Carpentier-Edwards Perimount Aortic Valve in Patients Aged 60 or Younger.* Ann Thorac Surg, 2015. 100(3): p. 853-9.
12. Baumgartner, H., et al., *2017 ESC/EACTS Guidelines for the management of valvular heart disease.* Eur Heart J, 2017. 38(36): p. 2739-2791.
13. Nishimura, R.A., et al., *2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* Circulation, 2017. 135(25): p. e1159-e1195.
14. Elwyn, G., et al., *Implementing shared decision making in the NHS.* BMJ, 2010. 341: p. c5146.
15. Stacey, D., et al., *Decision aids for people facing health treatment or screening decisions.* Cochrane Database Syst Rev, 2014(1): p. CD001431.
16. Janz, N.K., et al., *Patient-physician concordance: preferences, perceptions, and factors influencing the breast cancer surgical decision.* J Clin Oncol, 2004. 22(15): p. 3091-8.
17. Manson, N.C., *Why do patients want information if not to take part in decision making?* J Med Ethics, 2010. 36(12): p. 834-7.
18. van Til, J.A., A.M. Stiggelbout, and M.J. Ijzerman, *The effect of information on preferences stated in a choice-based conjoint analysis.* Patient Educ Couns, 2009. 74(2): p. 264-71.
19. Krumholz, H.M., *Informed consent to promote patient-centered care.* JAMA, 2010. 303(12): p. 1190-1.

20. Sackett, D.L., et al., *Evidence based medicine: what it is and what it isn't.* BMJ, 1996. 312(7023): p. 71-2.

"No decision about me, without me"

Angela Coulter & Alf Collins

2.

Mechanical aortic valve replacement in non-elderly adults: meta-analysis and microsimulation

Korteland NM, Etnel JRG, Arabkhani B, Mokhles MM, Mohamad A, Roos-Hesselink JW, Bogers AJJC, Takkenberg JJM.

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ABSTRACT

Aims. To support decision-making regarding prosthetic valve selection in non-elderly adults, we aim to provide a detailed overview of outcome after contemporary mechanical aortic valve replacement (AVR).

Methods and Results. A systematic review was conducted for papers reporting clinical outcome after AVR with bileaflet mechanical valves with a mean patient age ≥18 and ≤55 years, published between 1/1/1995 and 31/12/2015. Through meta-analysis outcomes were pooled and entered into a microsimulation model to calculate (event-free) life expectancy and lifetime event risk.

Twenty-nine publications, encompassing a total of 5728 patients with 32515 patient-years of follow-up (pooled mean follow-up: 5.7 years), were included. Pooled mean age at surgery was 48.0 years. Pooled early mortality risk was 3.15% (95%CI:2.37-4.23), late mortality rate was 1.55%/year (95%CI:1.25-1.92); 38.7% of late deaths were valve-related. Pooled thromboembolism rate was 0.90%/year (95%CI:0.68-1.21), major bleeding 0.85%/year (95%CI:0.65-1.12), nonstructural valve dysfunction 0.39%/year (95%CI:0.21-0.76), endocarditis 0.41%/year (95%CI:0.29-0.57), valve thrombosis 0.14%/year (95%CI:0.08-0.25), structural valve deterioration 0.00%/year (zero events observed), and reintervention 0.51%/year (95%CI:0.37-0.71), mostly due to nonstructural valve dysfunction and endocarditis. For a 45-year-old, for example, this translated to an estimated life expectancy of 19 years (general population: 34 years) and lifetime risks of thromboembolism, bleeding and reintervention of 18%, 15% and 10%, respectively.

Conclusions. This study demonstrates that outcome after mechanical AVR in non-elderly adults is characterized by suboptimal survival and considerable lifetime risk of anticoagulation-related complications, but also reoperation. Non-elderly adult patients who are facing prosthetic valve selection are entitled to conveyance of evidence-based estimates of the risks and benefits of both mechanical and biological valve options in a shared decision-making process.

INTRODUCTION

Aortic valve replacement (AVR) is the most widely used surgical treatment for aortic valve disease in non-elderly adults. When valve repair is not possible, two types of valve substitutes are available: mechanical and biological valves. The primary advantage of mechanical valves is their durability. They do, however, require lifelong anticoagulation due to their increased thrombogenicity, which gives rise to a substantial risk of thromboembolic and bleeding complications that may have an important impact on quality of life [1]. Furthermore, patients are faced with the hassle of INR regulation, the valve sound and, in the case of a woman with pregnancy wishes, the hazards of anticoagulation during pregnancy. Biological valves do not require long-term anticoagulation unless another indication is present. However, they are subject to valve deterioration over time and young patients, in particular, may require a reoperation later in life [2].

Since all currently available valve substitutes have important limitations, younger patients who require AVR are facing a difficult choice. A mechanical valve is often recommended in non-elderly adult patients due to the lower, though not absent, rate of reoperation compared with biological valves. Subsequently, most non-elderly adult patients will face a lifelong risk of bleeding and thromboembolic events after their mechanical AVR. To improve decision-making with regard to prosthetic valve selection in non-elderly adults, detailed and up-to-date information on mechanical valve-related morbidity and mortality is required. To gain insight in morbidity and mortality after contemporary mechanical AVR in non-elderly adults, we aim to provide an overview of published evidence by conducting a systematic review and meta-analysis of reported outcome. Furthermore, we aim to estimate age-specific life expectancy and lifetime risk of valve-related events with the use of a microsimulation model based on the results of our meta-analysis.

METHODS

This systematic review was conducted according to the PRISMA guidelines [3]. This study was approved by the institutional review board and informed consent was waived (MEC-2015-170).

Literature search

On December 7, 2015, a systematic literature search was conducted in Embase, MEDLINE, The Cochrane Collaboration and Web of Science by a biomedical information specialist

(Supplement 1). All studies were screened by two independent reviewers (NMK, JRGE). Studies reporting survival after contemporary AVR with a mechanical valve in patients with a mean age ≥18 and ≤55 years published in English after 1/1/1995 were considered for inclusion. Studies were included if >90% of the cohort received bileaflet prostheses. Studies limited to patients with preexisting comorbidities or patients with a history of previous AVR were excluded. Studies with a study size <20 patients or focusing only on certain prosthetic valve sizes or multiple valve replacement were also excluded.

In case of overlapping study populations, only the most recent or most complete study was included. In case of disagreement between the reviewers, a consensus was negotiated.

In case a full text publication was not available or information was missing the author was contacted by e-mail.

Data Extraction

Microsoft Office Excel (details in Supplement 5) was used for data extraction. The same pair of reviewers (NMK, JRGE) extracted the data independently. After data extraction, each reviewer verified the other reviewer's data entries. Recorded study characteristics, baseline patient and operative characteristics and outcome events are listed in Supplement 5. Morbidity and mortality were documented according to the guidelines [4]. Early outcome events were defined as occurring within the first 30 postoperative days, regardless of the patient's location, and late outcome events were defined as occurring after the first 30 postoperative days. If the total follow-up was not reported, it was calculated by multiplying the number of patients with the mean follow-up duration of that study.

Meta-analysis

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as counts and percentages. Linearized event occurrence rates are presented as percentages per year.

Pooled baseline patient characteristics were calculated with the use of sample size weighting. Early mortality risk and linearized occurrence rates of late mortality, reoperations and complications after AVR were calculated and pooled with the use of inverse variance weighting on a logarithmic scale, as the Shapiro-Wilk test revealed a significantly skewed distribution among the included studies in the majority of outcome measures. Inverse variance weighting was conducted according to the number of patients for early mortality and according to the number of patient-years

of follow-up for late events. In case a particular event was reported not to occur in an individual study, then for the purpose of inverse variance weighting it was assumed that 0.5 patient experienced that event. A random-effects model was used to estimate pooled effects.

The Cochran Q statistic and the I2 test were used to assess heterogeneity. Potential causes of heterogeneity were explored by investigating the effect of year of first inclusion, mean follow-up duration, case mix and study design (retrospective versus prospective/randomized controlled trial) by means of univariable random-effects meta-regression. Funnel plots were used to investigate publication bias. To investigate the potential influence of publication bias on pooled outcome, sensitivity analyses were conducted by temporarily excluding the smallest quartile (by sample size) of included studies. Statistical analyses were performed in Microsoft Office Excel, IBM SPSS Statistics and R (software details are listed in Supplement 5).

Microsimulation

A microsimulation model based on the pooled outcome estimates of our meta-analysis was used to calculate age-specific life expectancy and lifetime risk of valve-related morbidity [5,6]. The microsimulation model iteratively simulates individual patient lives after surgery, taking into account the morbidity and mortality events that the patient may experience. The simulated individual patient life histories are then aggregated to obtain estimates of population level outcome. The mortality of a patient is composed of the background mortality of the general population, operative mortality, mortality due to valve-related events and an additional excess mortality component that is not a direct result of valve-related events, but is associated with underlying valve pathology, left ventricular function and other associated pathology.

The operative mortality risk, the occurrence rate of each valve-related event and the risk of mortality and reintervention as a direct result of each of these valve-related events were obtained from our meta-analysis. The occurrence rates of all events were assumed to be linear and non-age-dependent. The hazard ratios of the additional excess mortality not directly resulting from valve-related events have been previously estimated [6]. For patients aged 25, 35, 45 and 55, these hazard ratios were 5.5, 4.4, 2.9 and 1.8 for males and 7.0, 7.0, 4.2 and 2.8 for females, respectively. The background mortality of the general population was obtained from the 1996 United States Life Tables, as 1996 was the pooled median year of intervention (assuming a constant incidence rate over time in each study) and the majority of the included study population originated from, or was comparable to the United States population [7].

To obtain age-specific estimates of life expectancy and lifetime risk of valve-related morbidity, the microsimulation model was run for the ages 25, 35, 45 and 55 years for 10,000 iterations each and separately for males and females. The age-specific outcomes of both genders were then pooled at the male/female ratio obtained from our meta-analysis (72.0% male).

For the purposes of internal validation, the model was additionally run for 10,000 iterations at the pooled mean age (48 years) and pooled male/female ratio of the included studies (72.0% male). The actuarial survival curve obtained from this model was then plotted against the pooled overall mortality observed in our meta-analysis.

RESULTS

The systematic literature search identified 3100 publications, of which 29 were included in the meta-analysis, encompassing a total of 5728 patients with 32515 patient-years of follow-up (pooled mean follow-up: 5.7 years) (Figure 1). Supplement 2 represents the characteristics of the included studies (references listed in Supplement 6). Pooled baseline patient characteristics are shown in Table 1.

Pooled risks of early mortality and early complications and pooled linearized occurrence rates of late mortality and late morbid events are presented in Table 2 (individual study estimates are presented in Supplement 3). Microsimulation-based age-specific estimates of (event-free) life expectancy and lifetime risk of valve-related morbidity are shown in Figure 2.

The microsimulation model calibrated well with the pooled mortality observed in our meta-analysis over the first postoperative decade (Supplement 7). For a 45-year-old, for example, microsimulation-based estimated life expectancy was 19 years (general population: 34 years) and lifetime risks of thrombo-embolism, bleeding and reintervention were 18%, 15% and 10%, respectively.

The funnel plots showed evidence of possible publication bias in early mortality, late mortality, thromboembolism, and bleeding (Supplement 8). Sensitivity analyses showed that this potential publication bias did not substantially influence our pooled outcomes, as pooled outcomes remained largely unchanged after temporary exclusion of the smallest quartile of studies (before vs. after exclusion: early mortality [3.15% vs. 3.03%], late mortality [1.55%/year vs. 1.55%/year], thromboembolism [0.90%/year vs. 0.88%/year], bleeding rates [0.85%/year vs. 0.87%/year]).

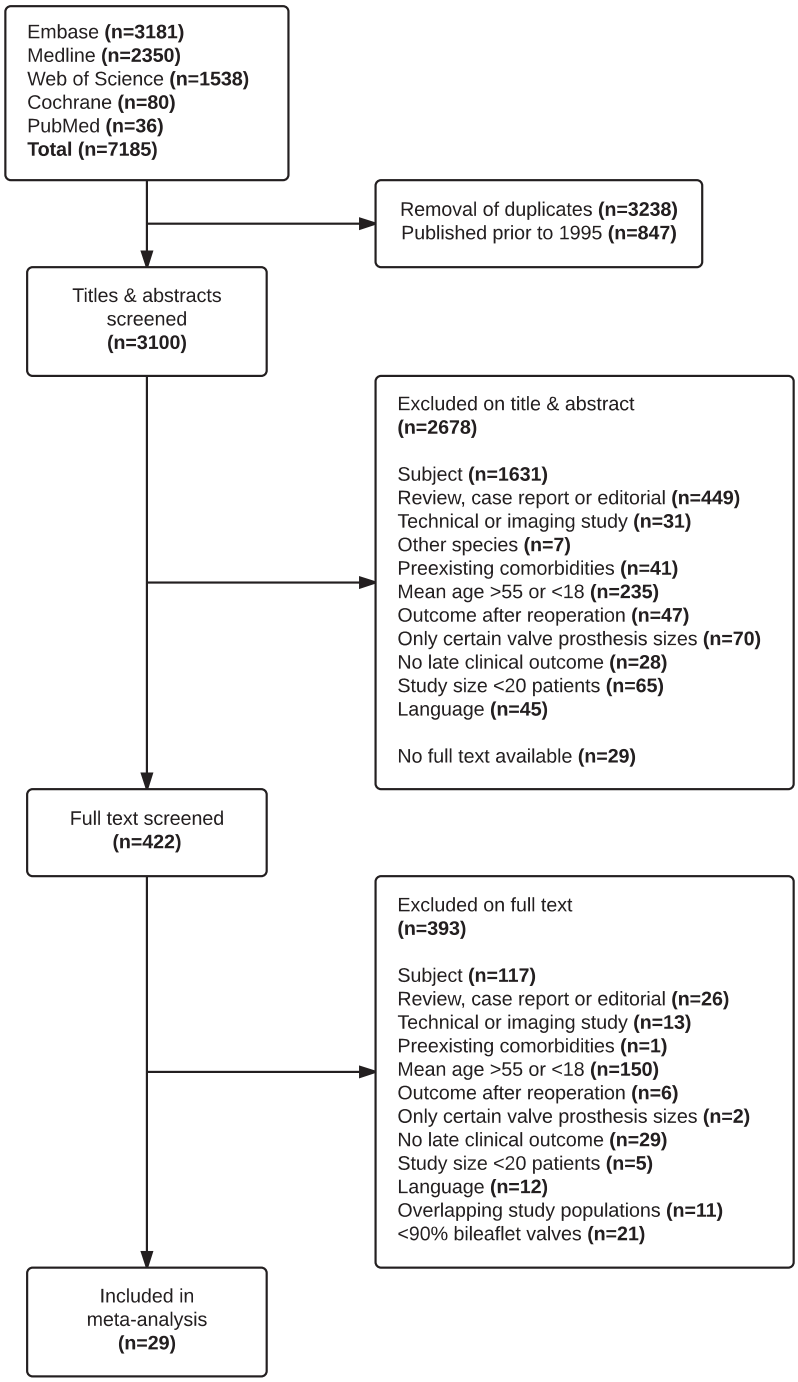

FIGURE 1. Flowchart of systematic literature search.

TABLE 1. Pooled pre-operative and peri-operative characteristics.

Variable	Pooled data	Range	Included studies (N)
Total number of patients	5728	20–865	29
Mean age (years)	48.0	33.0–54.9	29
Gender			
Male	72.0%	50.0–91.0%	23
Etiology			
Degenerative	21.5%	0.0–78.0%	12
Endocarditis	10.0%	0.0–100%	19
Rheumatic	36.4%	0.0–77.8%	12
Congenital	16.5%	0.0–57.0%	10
Prosthetic valve dysfunction	3.8%	0.0–22.0%	14
Other/unknown	11.7%	0.0–66.0%	13
Aortic valve hemodynamics			
Stenosis	43.5%	0.0–100%	13
Regurgitation	40.4%	0.0–70.0%	13
Combined	16.2%	0.0–30.0%	12
Bicuspid aortic valve	24.5%	1.4–100%	4
Previous cardiac intervention	8.4%	0.0–26.0%	13
Emergency surgery	3.4%	0.0–35.0%	10
Prosthetic valve type			
Bileaflet	99.9%	96.5–100%	29
Tilting-disc	0.1%	0.0–3.5%	29
Caged-ball	0.0%	0.0–0.0%	29
Concomitant procedures	22.2%	0.0–52.2%	11
CABG	7.1%	0.0–17.5%	21
Aortic surgery	8.6%	0.0–33.0%	11
Multiple valve replacement	2.6%	0.0–24.6%	17

CABG=coronary artery bypass grafting.

TABLE 2. Pooled risk of early outcome events and linearized occurrence rates of late outcome events obtained from the meta-analysis.

Outcome events	Pooled estimate	Heterogeneity*	Included studies (N)
Early(<30 days)			
Early mortality(%)	3.15(2.37-4.21)	I^2=70%(p<0.001)	25
Re-exploration for bleeding(%)	5.15(2.57-11.81)	I^2=87%(p<0.001)	7
Pacemaker implantation(%)	3.53(2.47-5.05)	I^2=20%(p=0.289)	4
Deep sternal infection/ mediastinitis(%)	2.48(1.56-3.94)	I^2=0%(p=0.409)	5
Endocarditis(%)	0.43(0.16-1.13)	I^2=0%(p=0.853)	7
Stroke(%)	1.55(0.98-2.46)	I^2=15%(p=0.312)	8
Transient ischemic attack(%)	0.81(0.38-1.72)	I^2=1%(p=0.400)	5
Myocardial infarction(%)	0.87(0.40-1.87)	I^2=0%(p=0.687)	5
Valve thrombosis(%)	0.30(0.09-1.05)	I^2=0%(p=0.782)	5
Peripheral bleeding(%)	0.41(0.15-1.09)	I^2=0%(p=0.756)	7
Late(>30 days)			
Late mortality(%/year)	1.55(1.25-1.92)~	I^2=83%(p<0.001)	29
Cardiac death(%/year)	0.95(0.71-1.27)	I^2=70%(p<0.001)	22
Valve-related death(%/year)	0.60(0.44-0.81)	I^2=64%(p<0.001)	24
SUD(%/year)	0.37(0.26-0.54)	I^2=47%(p=0.011)	19
Reintervention(%/year)	0.51(0.37-0.71)	I^2=47%(p=0.011)	20
Thromboembolism(%/year)	0.90(0.68-1.21)#	I^2=79%(p<0.001)	25
Valve thrombosis(%/year)	0.14(0.08-0.25)	I^2=62%(p<0.001)	18
Bleeding(%/year)	0.85(0.65-1.12)#	I^2=67%(p<0.001)	26
SVD(%/year)	0.00†	-	15
NSVD(%/year)	0.39(0.21-0.76)	I^2=83%(p<0.001)	17
Endocarditis(%/year)	0.41(0.29-0.57)	I^2=34%(p=0.072)	19

*The reported p-values are the p-values of Cochran's Q test for heterogeneity. †There were zero events of SVD in the 15 studies that reported this outcome. The background mortality rate in the age- and gender-matched United States general population for the pooled year of surgery and length of follow-up of our cohort was 0.55%/year. #The background rates of thromboembolism and bleeding events in the age- and gender-matched general population were 0.12%/year and 0.03%/year, respectively (based on the Oxford Vascular Study) [28]. Pooled estimates presented as "percentage (95% confidence interval)". SUD=sudden, unexplained death;SVD=structural valve deterioration;NSVD=nonstructural valve dysfunction.

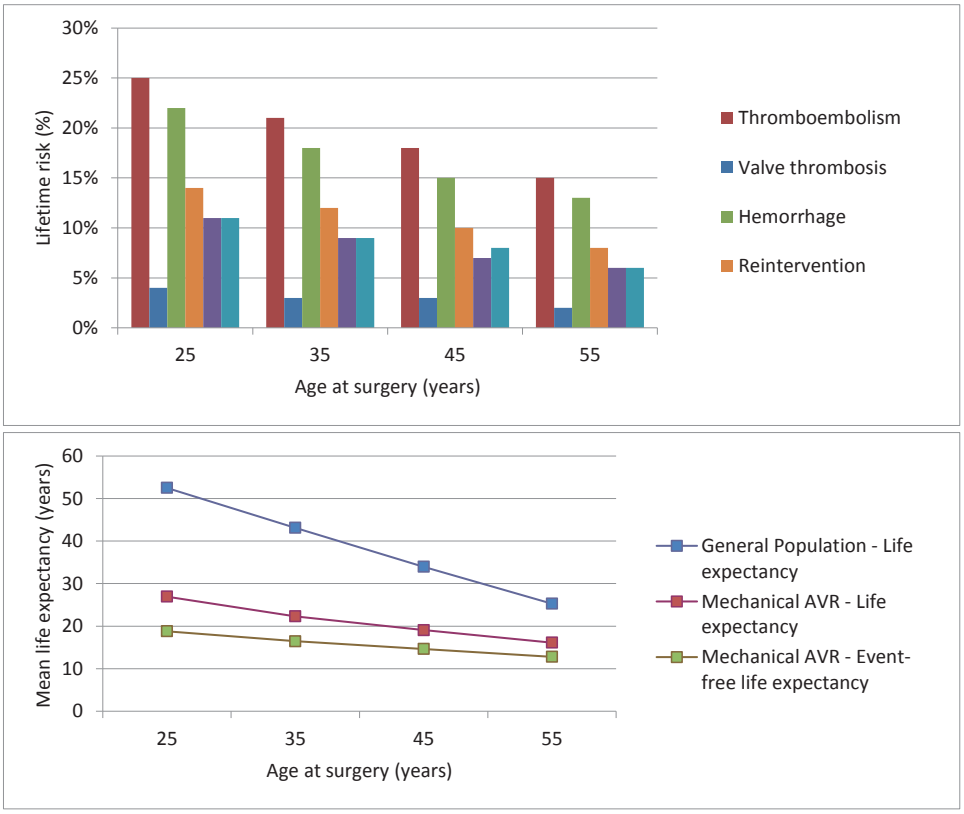

FIGURE 2. Microsimulation-based age-specific life expectancy and lifetime risk of valve-related morbidity. AVR=aortic valve replacement.

Heterogeneity

There was substantial heterogeneity in early mortality, re-exploration for bleeding and all late outcome measures with the exception of structural valve deterioration (SVD) and endocarditis. Univariable random-effects meta-regression (Supplement 4) showed that studies with a longer mean follow-up reported lower early mortality ($p<0.001$), lower reintervention rates ($p=0.010$) and lower bleeding rates ($p=0.042$), although follow-up duration was moderately negatively correlated with concomitant CABG ($r=-0.37$) and earlier year of first inclusion ($r=-0.31$).

Etiology was another important factor associated with heterogeneity as a higher proportion of preoperative endocarditis appeared to be correlated with higher rates of late mortality ($p=0.008$) and NSVD ($p=0.002$), while a higher proportion of rheumatic

etiology was associated with lower rates of NSVD (p=0.004). Bleeding and nonstructural valve dysfunction (NSVD) rates were higher in cohorts with a higher proportion of aortic stenosis (bleeding p=0.026; NSVD p<0.001) and, consequently, a lower proportion of aortic regurgitation (bleeding p=0.003; NSVD p<0.001), although there was a moderate-to-strong negative correlation between preoperative aortic valve stenosis (as opposed to regurgitation) and etiology (endocarditis r=-0.71; rheumatic r=-0.37). Lastly, higher proportions of emergency surgeries (p=0.007) and concomitant CABG (p=0.046) were associated with higher rates of NSVD and a higher proportion of concomitant procedures was associated with higher reported early mortality risk (p=0.045). We were unable to find any explanatory variables for the heterogeneity in thromboembolism and valve thrombosis rates. Differences in study design, year of first inclusion and previous cardiac interventions were not associated with heterogeneity in any of the outcome measures. Meta-regression was not conducted for re-exploration for bleeding due to limited sample size.

DISCUSSION

This study offers an overview of reported mortality and morbidity after mechanical AVR in non-elderly adult patients and microsimulation-based age-specific estimates of expected lifetime outcome. It confirms the excellent long-term durability of mechanical valves in these patients, but also underlines the substantial late cardiovascular death and anticoagulation-related complication hazards after mechanical AVR. Although no cases of SVD were observed after contemporary AVR with currently available mechanical valves, microsimulation revealed a considerable lifetime risk of reintervention in this subgroup that ranged from 15% for patients aged 25 years at surgery to 8% for 55-year-olds, mostly due to NSVD and endocarditis. Most notably however, the combined lifetime risk of thromboembolism, valve thrombosis and bleeding ranged from 53% for patients aged 25 years at surgery to 30% for 55-year-olds. Life expectancy is substantially impaired in these patients compared with the general population and about 40% of deaths are valve-related.

Mortality

Elective, isolated mechanical AVR has been previously shown to be associated with significant excess mortality when compared with the general age-matched population [8]. In our meta-analysis we found a 3.15% early mortality risk and a substantial late mortality rate of 1.55%/year in patients with a pooled mean age of 48.0 years at the time of surgery. Microsimulation-based mean life expectancy after contemporary mechanical AVR ranged from 28 years for patients aged 25 years at surgery to 16 years for 55-year-

olds, which is little over half the life expectancy of the age-matched general population. When taking the absent risk of SVD and subsequent reintervention associated with contemporary mechanical AVR into account, this mortality rate appears to be relatively high in comparison with other valve substitutes in non-elderly adults, such as the Ross procedure, which has been reported to be associated with lower late mortality in non-elderly adults compared with our pooled results after contemporary mechanical AVR (0.64%/year vs. 1.55%/year), while early mortality risk was comparable (3.24% vs. 3.15%) [9]. Prosthetic valve-associated hemodynamic factors, such as prosthesis-patient mismatch, may play a role in this observed excess mortality [10,11]. Furthermore, the higher mortality after mechanical AVR may be attributable in part to the required anticoagulation treatment. In this regard, optimization of the anticoagulation therapy after mechanical AVR may offer a survival benefit in these patients. This is supported by a recent study by Mokhles et al., which found that, with optimal self-management anticoagulation, mechanical AVR offers excellent late survival, comparable to the general age-matched population and also to patients undergoing the Ross procedure [12].

The survival differences between mechanical valves and other valve substitutes may be further explained by possible differences in patient characteristics, surgical technique and concomitant procedures performed at the time of AVR. Rheumatic valve disease being the most common etiology in present study (34% of our patients) may represent evidence of this possible selection bias.

Thromboembolism and bleeding

Present study underlines the burden of thromboembolism and bleeding after mechanical AVR in non-elderly patients as approximately half of patients aged 25 and 1 out of 3 patients aged 55 at the time of surgery are estimated to experience thromboembolism, valve thrombosis or bleeding events during their lifetime. This is most likely an underestimate as the included studies were largely retrospective in design, which may have given rise to recall bias. Anticoagulation-related complications remain an important limitation of mechanical valve prostheses, especially in the young patients in which they are generally used, as there are serious implications for life-, career- and pregnancy-planning in these patients. However, optimizations of the required anticoagulation therapy such as self-management and lower dosing may be promising methods of reducing complication rates after mechanical AVR. There is increasing evidence that patients with contemporary mechanical valves and no comorbidities may be safely managed at a lower INR than currently recommended, subsequently reducing bleeding complications without increasing the risk of thromboembolic events [13-15]. Furthermore, advances in the design of mechanical valves may lead to

reduced thrombogenicity. Mechanical valves specifically designed with this in mind have emerged, one of which has recently received FDA-approval for anticoagulation management at a lower INR than recommended by the guidelines [15]. Nevertheless, we did not find any evidence in this systematic review that thromboembolism and bleeding hazard has decreased in more recent years.

Pharmacological advances that provide more stable INR management may further reduce complication rates as studies have shown that, in patients treated with currently available anticoagulants, 25% of periodically measured INR values lie outside of the target range [13].

Reintervention, (N)SVD and Endocarditis

Our results underline excellent long-term durability as the main advantage of mechanical valves, with negligible SVD rates. Although SVD remains a rare complication in mechanical valve recipients, depending on age at surgery, approximately 8%-15% of patients require reintervention during their lifetime, mostly due to NSVD (pannus formation, paravalvular leakage, etc.), valve thrombosis or prosthetic valve endocarditis. Although this risk of reintervention is very low compared with other valve substitutes in non-elderly adults, it is not absent and should always be taken into consideration and discussed with the patient when prosthetic valve selection is addressed.

Prosthetic valve selection

In prosthetic valve selection, mechanical valve-associated thromboembolism and bleeding risk is generally weighed against the risk of SVD and subsequent reintervention associated with biological valve substitutes. In non-elderly patients a mechanical valve is often recommended due to the limited durability of biological alternatives. However, the durability of modern bioprostheses is improving. These improvements as well as improved outcomes in reoperative aortic valve surgery and the prospect of transcatheter valve-in-valve replacement of failing bioprostheses has led to an increase in their use in younger patients [16-21]. Additionally, the Ross procedure represents another valuable option in these patients that avoids the need for long-term anticoagulation and provides superior long-term survival, excellent hemodynamic performance and a low risk of endocarditis in selected patients when performed in centers of expertise. Due to the continued improvements in bioprosthetic AVR and the option of the Ross procedure, the substantial risk of mechanical valve-related complications, as delineated by our results, will become more prominent in the process of prosthetic valve selection. Furthermore, although the risk of reintervention after mechanical AVR is low, it is certainly not absent and should also be taken into consideration in the process of prosthetic

valve selection. This also applies to the risk of thromboembolism and bleeding after AVR with biological alternatives. Besides clinical factors, the benefits and limitations of each option have substantial implications for life-, career- and pregnancy planning in these patients. Therefore, conveyance of patient-tailored evidence-based risks and benefits of both mechanical and biological valve options in a shared decision-making process is of great importance [2,22]. Innovative solutions such as patient information portals and decision aids may prove useful in this setting [23].

Heterogeneity

Although heterogeneity was considerable in our meta-analysis and may have potentially influenced the results, we pursued a thorough examination of possible sources of heterogeneity. Etiology and concomitant procedures appear to be important factors of influence on the reported outcomes, which is in line with expectations based on the literature [24,25]. Furthermore, we found aortic regurgitation vs. stenosis to be associated with more favorable reported outcome with regard to bleeding and NSVD rates, while regurgitation has been previously described to be associated with less favorable outcome [24]. This discrepancy may be explained by the strong correlation we found in our meta-regression between aortic valve hemodynamics and etiology (studies with a higher proportion of stenosis had lower proportions of endocarditis and rheumatic etiology), which may have confounded the results.

Lastly, although there was no consistent evidence thereof in our analyses, the year of operation, ranging from 1977-2014 among the included studies, may still have affected the results, as case-mix may have changed over the years and evolution of operative techniques may have led to lower operative risk.

Although this observed heterogeneity might have introduced uncertainty in our meta-analysis, with the use of a random-effects model, this uncertainty is incorporated in the reported pooled outcome estimates.

Publication bias

The asymmetry we found in our funnel plots may represent evidence of possible publication bias. However, assessment of publication bias in absolute risk outcomes, as were all of our outcomes, is associated with substantial methodological limitations which may in itself give rise to funnel plot asymmetry [26]. Our funnel plots should therefore be interpreted with caution. Although a conclusive investigation of publication bias may not be possible, our sensitivity analyses show that any potential publication bias did not substantially influence our pooled outcomes.

Limitations

The present study is a systematic review and meta-analysis of observational studies, most of which are retrospective in design. As such, the inherent limitations of meta-analyses and combining data from retrospective observational studies should be taken into consideration [27]. Selection bias may have affected the observed outcomes, as unpublished data, abstracts and presentations were not included. Among the included studies, baseline and surgical characteristics were not reported in sufficient detail and consistently enough for us to fully account for all baseline covariates in our meta-analyses. Direct comparisons with alternative valve prostheses are hampered by the lack of published comparative data. Setting a time limit to systematic literature searches may introduce potential bias, but we chose to do so in our aim to provide an overview of contemporary outcome. Finally, there are some limitations to the microsimulation model that should be taken into account. The relationship of the occurrence rates of valve-related events after mechanical AVR with age, follow-up duration and history of previous valve-related events remains poorly defined and could, thus, not be incorporated into our microsimulation model. Uncertainty in the parameters within the model (second order uncertainty) was also not incorporated in our microsimulation model. The model requires assumptions to be made about the evolution of event occurrence rates beyond the observed follow-up period, which may have introduced uncertainty. Our United States general population-based background mortality estimate should be regarded as merely a reference point, as it may not be an ideal reflection of the general population mortality of the different countries that are represented in the individual studies in the review.

Conclusions

This review shows that the use of mechanical valves in non-elderly adult patients is associated with substantial excess mortality over time and considerable lifetime risk of anticoagulation-related complications, but also reoperation. This confirms the fact that non-elderly adult patients who require AVR are facing a difficult choice between mechanical and biological valves and, therefore, conveyance of patient-tailored evidence-based risks and benefits of both mechanical and biological valve options in a shared decision-making process is of great importance in the setting of prosthetic valve selection.

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REFERENCES

1. Aicher D, Holz A, Feldner S, Kollner V, Schafers HJ. Quality of life after aortic valve surgery: replacement versus reconstruction. J Thorac Cardiovasc Surg 2011;142(2):e19-24.
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD, ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(23):e521-643.
3. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine 2009;6(7):e1000097.
4. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW, Councils of the American Association for Thoracic Surgery; Society of Thoracic Surgeons, European Association for Cardio-Thoracic Surgery, Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135(4):732-8.
5. Takkenberg JJ, Puvimanasinghe JP, Grunkemeier GL. Simulation models to predict outcome after aortic valve replacement. Ann Thorac Surg 2003;75(5):1372-6.
6. Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ, Steyerberg EW, van Herwerden LA, Grunkemeier GL, Habbema JD, Bogers AJ. Choice of a mechanical valve or a bioprosthesis for AVR: does CABG matter? Eur J Cardiothorac Surg 2003;23(5):688-95; discussion 695.
7. Anderson RN, National Center for Health Statistics (U.S.). Method for constructing complete annual U.S. life tables. Hyattsville, Md.: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 1999.
8. Bouhout I, Stevens LM, Mazine A, Poirier N, Cartier R, Demers P, El-Hamamsy I. Long-term outcomes after elective isolated mechanical aortic valve replacement in young adults. J Thorac Cardiovasc Surg 2013.
9. Takkenberg JJ, Klieverik LM, Schoof PH, van Suylen RJ, van Herwerden LA, Zondervan PE, Roos-Hesselink JW, Eijkemans MJ, Yacoub MH, Bogers AJ. The Ross procedure: a systematic review and meta-analysis. Circulation 2009;119(2):222-8.
10. Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. J Am Coll Cardiol 2000;36(4):1131-41.
11. Head SJ, Mokhles MM, Osnabrugge RL, Pibarot P, Mack MJ, Takkenberg JJ, Bogers AJ, Kappetein AP. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. Eur Heart J 2012;33(12):1518-29.

12. Mokhles MM, Kortke H, Stierle U, Wagner O, Charitos EI, Bogers AJJC, Gummert J, Sievers HH, Takkenberg JJM. Survival comparison of the ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: Propensity-matched cohort study. Circulation 2011;123(1):31-38.
13. Koertke H, Zittermann A, Tenderich G, Wagner O, El-Arousy M, Krian A, Ennker J, Taborski U, Klovekorn WP, Moosdorf R, Saggau W, Koerfer R. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: Final report from the early self-management anticoagulation trial II. Eur Heart J 2007;28(20):2479-2484.
14. Torella M, Torella D, Chiodini P, Franciulli M, Romano G, De Santo L, De Feo M, Amarelli C, Sasso FC, Salvatore T, Ellison GM, Indolfi C, Cotrufo M, Nappi G. LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: Results from the "lOWERING-IT" Trial. Am Heart J 2010;160(1):171-178.
15. Puskas J, Gerdisch M, Nichols D, Quinn R, Anderson C, Rhenman B, Fermin L, McGrath M, Kong B, Hughes C, Sethi G, Wait M, Martin T, Graeve A. Reduced anticoagulation after mechanical aortic valve replacement: Interim results from the Prospective Randomized On-X Valve Anticoagulation Clinical Trial randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg 2014;147(4):1202-1211.E1202.
16. Ruel M, Chan V, Bedard P, Kulik A, Ressler L, Lam BK, Rubens FD, Goldstein W, Hendry PJ, Masters RG, Mesana TG. Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age. Circulation 2007;116(11 SUPPL. 1):I294-I300.
17. Niclauss L, Von Segesser LK, Ferrari E. Aortic biological valve prosthesis in patients younger than 65 years of age: Transition to a flexible age limit? Interact Cardiovasc Thorac Surg 2013;16(4):501-508.
18. Une D, Ruel M, David TE. Twenty-year durability of the aortic Hancock II bioprosthesis in young patients: is it durable enough? Eur J Cardiothorac Surg 2014;46(5):825-30.
19. Potter DD, Sundt TM, 3rd, Zehr KJ, Dearani JA, Daly RC, Mullany CJ, McGregor CG, Puga FJ, Schaff HV, Orszulak TA. Operative risk of reoperative aortic valve replacement. J Thorac Cardiovasc Surg 2005;129(1):94-103.
20. Davierwala PM, Borger MA, David TE, Rao V, Maganti M, Yau TM. Reoperation is not an independent predictor of mortality during aortic valve surgery. J Thorac Cardiovasc Surg 2006;131(2):329-35.
21. Bourguignon T, El Khoury R, Candolfi P, Loardi C, Mirza A, Boulanger-Lothion J, Bouquiaux-Stablo-Duncan AL, Espitalier F, Marchand M, Aupart M. Very Long-Term Outcomes of the Carpentier-Edwards Perimount Aortic Valve in Patients Aged 60 or Younger. Ann Thorac Surg 2015;100(3):853-9.
22. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk

V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33(19):2451-96.

23. Stacey D, Legare F, Col NF, Bennett CL, Barry MJ, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L, Wu JH. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2014;1:CD001431.
24. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. J Am Coll Cardiol 2000;35(3):747-56.
25. Klieverik LMA, Noorlander M, Takkenberg JJM, Kappentein AP, Bekkers JA, Herwerden LAV, Bogers AJJ. Outcome after aortic valve replacement in young adults: Is patient profile more important than prosthesis type? J Heart Valve Dis 2006;15(4):479-487.
26. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001;54(10):1046-55.
27. Ioannidis JP, Lau J. Pooling research results: benefits and limitations of meta-analysis. The Joint Commission journal on quality improvement 1999;25(9):462-9.
28. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JN, Bull LM, Welch SJ, Cuthbertson FC, Binney LE, Gutnikov SA, Anslow P, Banning AP, Mant D, Mehta Z, Oxford Vascular S. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366(9499):1773-83.

SUPPLEMENT 1. Literature search query

Embase (Embase en Medline): 3181 results

('Aorta valve replacement'/de OR 'Aorta Valve Prosthesis'/exp OR (('Aorta Valve'/de OR 'Aorta Valve Disease'/exp OR ((aortic OR aorta) NEAR/3 (valve OR valvul* OR stenos* OR insufficien* OR regurgitat* OR incompeten*)):ab,ti) AND ('Transplantation'/de OR 'Implantation'/exp OR (replac* OR transplant* OR implant* OR artificial):ab,ti)) OR (AVR AND valve):ab,ti) AND ('Mechanical heart valve'/exp OR (mechanical OR mechano* OR ATS OR 'Bjork Shiley' OR 'Bjoerk Shiley' OR CarboMedic* OR 'Saint Jude' OR 'St Jude' OR 'St. Jude' OR 'Starr Edwards' OR pyrocarbon OR LTIC OR carbon):ab,ti) AND ('Survival'/exp OR 'Mortality'/exp OR 'Prognosis'/de OR 'Treatment outcome'/exp OR 'Evaluation and follow up'/de OR 'Follow up'/de OR 'Hazard Assessment'/de OR (surviv* OR mortalit* OR death* OR prognos* OR outcome* OR 'follow up' OR 'long term' OR hazard*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OVID-SP): 2350 results

((("Aortic Valve"/ OR exp "Aortic Valve Stenosis"/ OR "Aortic Valve Insufficiency"/ OR ((aortic OR aorta) ADJ3 (valve OR valvul* OR stenos* OR insufficien* OR regurgitat* OR incompeten*)).ab,ti.) AND ("Transplantation"/ OR transplantation.xs. OR "Heart Valve Prosthesis Implantation"/ OR (replac* OR transplant* OR implant* OR artifical).ab,ti.)) OR (AVR AND valve).ab,ti.) AND ("Carbon"/ OR (mechanical OR mechano* OR ATS OR "Bjork Shiley" OR "Bjoerk Shiley" OR Carbomedic* OR "Saint Jude" OR "St Jude" OR "St. Jude" OR "Starr Edwards" OR pyrocarbon OR LTIC OR carbon).ab,ti.) AND ("Survival"/ OR exp "Mortality"/ OR mortality.xs. OR "Prognosis"/ OR exp "Treatment outcome"/ OR "Follow-Up Studies"/ OR (surviv* OR mortalit* OR death* OR prognos* OR outcome* OR "follow up" OR "long term" OR hazard*).ab,ti.) NOT (animals NOT humans).sh.

Cochrane Central: 80 results

(((((aortic OR aorta) NEAR/3 (valve OR valvul* OR stenos* OR insufficien* OR regurgitat* OR incompeten*)):ab,ti) AND ((replac* OR transplant* OR implant* OR artificial):ab,ti)) OR (AVR AND valve):ab,ti) AND ((mechanical OR mechano* OR ATS OR 'Bjork Shiley' OR 'Bjoerk Shiley' OR CarboMedic* OR 'Saint Jude' OR 'St Jude' OR 'St. Jude' OR 'Starr Edwards' OR pyrocarbon OR LTIC OR carbon):ab,ti) AND ((surviv* OR mortalit* OR death* OR prognos* OR outcome* OR 'follow up' OR 'long term' OR hazard*):ab,ti)

Web of Science: 1538 results

TS=(((((aortic OR aorta) NEAR/2 (valve OR valvul* OR stenos* OR insufficien* OR regurgitat* OR incompeten*)) AND (replac* OR transplant* OR implant* OR artificial)) OR (AVR AND valve)) AND ((mechanical OR mechano* OR ATS OR "Bjork Shiley" OR "Bjoerk Shiley" OR CarboMedic* OR "Saint Jude" OR "St Jude" OR "St. Jude" OR "Starr Edwards" OR pyrocarbon OR LTIC OR carbon))

AND ((surviv* OR mortalit* OR death* OR prognos* OR outcome* OR "follow up" OR "long term" OR hazard*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR pigs Or swine OR sheep) NOT (human* OR people OR patient*)))

PubMed as supplied by publisher: 36 results

((((aortic[tiab] OR aorta[tiab]) AND (valve[tiab] OR valvul*[tiab] OR stenos*[tiab] OR insufficien*[tiab] OR regurgitat*[tiab] OR incompeten*[tiab])) AND (replac*[tiab] OR transplant*[tiab] OR implant*[tiab] OR artificial[tiab])) OR (AVR[tiab] AND valve[tiab])) AND ((mechanical[tiab] OR mechano*[tiab] OR ATS[tiab] OR Bjork Shiley*[tiab] OR CarboMedic*[tiab] OR Saint Jude*[tiab] OR St Jude*[tiab] OR St. Jude*[tiab] OR Starr Edwards*[tiab] OR pyrocarbon[tiab] OR LTIC[tiab] OR carbon[tiab])) AND ((surviv*[tiab] OR mortalit*[tiab] OR death*[tiab] OR prognos*[tiab] OR outcome*[tiab] OR follow up*[tiab] OR long term*[tiab] OR hazard*[tiab])) NOT ((animal*[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR pigs[tiab] OR swine[tiab] OR sheep[tiab]) NOT (human*[tiab] OR people[tiab] OR patient[tiab] OR patients[tiab])) AND publisher[sb]

SUPPLEMENT 2. Study characteristics

First author	Year of publication	No. of patients	Inclusion period (y)	Study type	Mean follow-up (y)	Mean age (y)	Gender (% male)	Prosthesis model
Nistal	1996	209	1989-1992	Retrospective	2.5	54.1	74.2	Carbomedics
Gaudino	1997	20	1988-1996	Retrospective	2.5	46.5	85.0	Sorin Bicarbon (n=10)/Carbomedics (n=5)/St. Jude (n=3)
Katircioglu	1997	865	1986-1996	Retrospective	3.3	42.9	-	St. Jude
Renzulli	1997	305	1982-1994	Retrospective	3.1	50.4	-	Carbomedics (n=200)/St. Jude (n=82)/Sorin Bicarbon (n=23)
Natsuaki	1998	37	1985-1997	Retrospective	5.3	52.0	78.4	St. Jude
Jamieson	1999	384	1989-1994	Retrospective	2.5	52.3	74.2	St. Jude/Carbomedics (n=NR)
Chang	2001	256	1988-1997	Retrospective	5.3	43.9	-	St. Jude (n=142)/Carbomedics (n=114)
Imanaka	2001	126	1990-1996	Retrospective	6.3	51.2	59.5	Carbomedics
Ozeren	2001	70	1998-2000	Retrospective	1.3	33.8	-	ATS
Kuwaki	2002	69	1990-2000	Retrospective	6.5	48.9	68.1	Carbomedics
Aagaard	2003	55	1987-2000	Retrospective	7.6[a]	33.0[a]	76.4	Carbomedics
Emery	2003	271	1977-1997	Retrospective	7.2	40.0	74.2	St. Jude
Chang	2005	179	1988-1999	Retrospective	7.9	44.4	-	Carbomedics
Concha	2005	62	1997-2003	Prospective	2.5	37.7	75.8	Carbomedics (n=38)/St. Jude (n=24)
Sakamoto	2005	46	1995-2002	Retrospective	6.2	54.0	91.3	St. Jude
Kandemir	2006	174	1992-2004	Retrospective	6.2	47.7	77.6	Carbomedics (n=94)/St. Jude (n=80)
Klieverik	2006	204	1991-2001	Retrospective	6.2	45.0	73.0	St. Jude (n=199)/ATS (n=4)/Björk-Shiley (n=1)
Kilian	2007	147	1990-1998	Retrospective	8.1	54.8	85.0	Sorin Bicarbon
Rodrigues	2009	117	1995-2003	Retrospective	4.0	45.0	69.2	St. Jude

First author	Year of publication	No. of patients	Inclusion period (y)	Study type	Mean follow-up (y)	Mean age (y)	Gender (% male)	Prosthesis model
Torella	2010	396	2001-2005	RCT	5.6[a]	49.7	69.2	Sorin Bicarbon (n=292)/St. Jude (n=92)/ Edwards MIRA(n=7)/ Carbomedics (n=5)
Doss	2011	20	-	RCT	1.0	48.0	55.0	Edwards MIRA
Weber	2012	103	2000-2009	Prospective	2.8	50.0	84.5	St. Jude/ATS (n=NR)
Cohoon	2013	60	1994-2000	Retrospective	6.6	46.0	83.3	St. Jude
Andreas	2014	173	1991-2008	Retrospective	7.9	41.0	75.1	Carbomedics/Medtronic Hall/On-X/ Edwards/St. Jude (n=NR)
McClure	2014	361	1992-2011	Retrospective	6.0[a]	53.2	70.4	St. Jude (n=318)/On-X (n=23)/ Carbomedics (n=19)/Unknown (n=1)
Nazarov	2014	211	2003-2004	Prospective	5.1	52.2	-	Cardiamed
Nishida	2014	220	1990-2012	Retrospective	12.0	54.9	72.7	Carbomedics
Bouhout	2015	450	1997-2006	Prospective	9.1	53.0	67.6	Carbomedics (n=402)/St. Jude (n=35)/ Medtronic Advantage (n=13)
Nishida	2015	157	1981-2014	Retrospective	11.8	50.6	49.7	St. Jude

aMedian.
-, variable not reported; RCT, randomized controlled trial; NR, not reported.

SUPPLEMENT 3. Pooled early mortality risk and linearized occurrence rates of late outcome events (including individual study estimates)

	Early mortality (%)	**Late mortality (%/yr)**	**Cardiac death (%/yr)**	**Valve-related death (%/yr)**	**SUD (%/yr)**	**Reintervention (%/yr)**	
Nistal (1996)	5.26(2.96-9.36)	1.53(0.77-3.05)	1.15(0.52-2.55)	0.96(0.40-2.29)	0.57(0.19-1.78)	0.38(0.10-1.53)	
Gaudino (1997)	2.50(0.16-38.60)	5.90(1.97-17.69)	5.90(1.97-17.69)	1.97(0.28-13.70)	0.98(0.06-15.51)	1.97(0.28-13.70)	
Katircioglu (1997)	5.90(4.52-7.69)	0.71(0.44-1.14)	-	-	-	1.00(0.67-1.49)	
Renzulli (1997)	8.39(5.72-12.31)	0.79(0.38-1.66)	0.57(0.24-1.36)	0.34(0.11-1.05)	0.23(0.06-0.91)	-	
Natsuaki (1998)	-	1.02(0.26-4.05)	0.51(0.07-3.60)	0.25(0.02-4.06)	-	-	
Jamieson (1999)	2.60(1.41-4.80)	1.75(1.09-2.80)	0.72(0.34-1.51)	0.62(0.28-1.37)	0.10(0.01-0.73)	-	
Chang (2001)	4.69(2.70-8.14)	2.06(1.43-2.98)	-	-	-	-	
Imanaka (2001)	6.35(3.25-12.42)	1.26(0.68-2.34)	0.63(0.26-1.52)	0.51(0.19-1.34)	0.25(0.06-1.01)	-	
Ozeren (2001)	1.43(0.20-10.00)	0.58(0.04-9.25)	-	-	-	1.17(0.17-8.19)	
Kuwaki (2002)	5.80(2.24-15.01)	1.11(0.47-2.67)	0.89(0.34-2.37)	0.22(0.03-1.58)	0.22(0.03-1.58)	0.67(0.22-2.07)	
Aagard (2003)	0.91(0.06-14.35)	0.99(0.37-2.63)	0.74(0.24-2.29)	0.12(0.01-1.98)	0.12(0.01-1.98)	0.50(0.12-1.97)	
Emery (2003)	1.11(0.36-3.41)	0.92(0.58-1.46)	-	0.20(0.08-0.54)	-	0.41(0.20-0.82)	
Chang (2005)	1.68(0.55-5.15)	1.34(0.86-2.10)	0.99(0.59-1.67)	0.64(0.33-1.22)	0.14(0.04-0.56)	0.07(0.01-0.50)	
Concha (2005)	6.45(2.50-16.65)	0.32(0.02-5.06)	0.32(0.02-5.06)	0.32(0.02-5.06)	0.32(0.02-5.06)	0.64(0.09-4.48)	
Sakamoto (2005)	2.17(0.31-15.11)	1.05(0.34-3.24)	0.35(0.05-2.48)	0.35(0.05-2.48)	0.18(0.01-2.80)	0.18(0.01-2.80)	
Kandemir (2006)	2.30(0.87-6.06)	1.52(0.93-2.47)	1.33(0.79-2.24)	0.19(0.05-0.76)	0.09(0.01-0.67)	-	
Klieverik (2006)	1.96(0.74-5.17)	1.58(1.02-2.44)	1.10(0.66-1.86)	0.87(0.48-1.56)	0.47(0.21-1.05)	0.79(0.43-1.46)	
Kilian (2007)	4.08(1.86-8.94)	3.52(2.61-4.73)	-	1.34(0.82-2.18)	-	0.50(0.23-1.12)	
Rodrigues (2009)	6.84(3.50-13.35)	1.91(1.00-3.65)	1.49(0.71-3.10)	1.27(0.57-2.82)	0.42(0.11-1.69)	0.21(0.03-1.50)	
Torella (2010)	-	0.09(0.02-0.36)	0.09(0.02-0.36)	0.09(0.02-0.36)	0.02(0.00-0.36)	-	
Doss (2011)	2.50(0.16-38.60)	5.00(0.74-33.78)	2.50(0.16-38.60)	2.50(0.16-38.60)	2.50(0.16-38.60)	2.50(0.16-38.60)	
Weber (2012)	-	0.71(0.18-2.81)	0.35(0.05-2.50)	0.35(0.05-2.50)	0.18(0.01-2.82)	0.71(0.18-2.81)	
Cohoon (2013)	-	1.77(0.85-3.68)	-	-	-	-	
Andreas (2014)	1.16(0.29-4.59)	2.05(1.42-2.96)	1.54(1.01-2.35)	1.39(0.89-2.17)	1.02(0.61-1.72)	0.73(0.39-1.36)	
McClure (2014)	1.39(0.58-3.31)	2.28(1.78-2.92)	0.67(0.42-1.07)	0.19(0.08-0.45)	0.02(0.00-0.30)	0.26(0.12-0.55)	
Nazarov (2014)	3.32(1.60-6.87)	1.94(1.27-2.97)	-	-	-	-	
Nishida (2014)	0.91(0.23-3.61)	2.80(2.24-3.51)	2.30(1.79-2.95)	1.00(0.68-1.46)	-	0.23(0.10-0.51)	
Bouhout (2015)	1.11(0.46-2.66)	1.41(1.10-1.83)	1.00(0.74-1.36)	0.76(0.53-1.07)	0.49(0.32-0.76)	0.63(0.43-0.93)	
Nishida (2015)	1.27(0.32-5.05)	2.50(1.88-3.32)	1.10(0.71-1.69)	0.60(0.33-1.08)	-	0.27(0.11-0.65)	
Pooled	3.15(2.37-4.21)	1.55(1.25-1.92)	0.95(0.71-1.27)	0.60(0.44-0.81)	0.37(0.26-0.54)	0.51(0.37-0.71)	
Heterogeneity[b]	*I^2=70% (p<0.001)*	*I^2=83% (p<0.001)*	*I^2=70% (p<0.001)*	*I^2=64% (p<0.001)*	*I^2=47% (p=0.011)*	*I^2=47% (p=0.011)*	

Pooled estimates presented as "percentage (95% confidence interval)".

-, variable not reported; Yr, year; SUD, sudden, unexplained death; SVD, structural valve deterioration; NSVD, nonstructural valve dysfunction.

In case a particular event was reported not to occur in an individual study, then for the purpose of the analyses it was assumed that 0.5 patient experienced that event.

aThere were zero events of SVD in the 15 studies that reported this outcome.

bThe reported p-values are the p-values of Cochran's Q test for heterogeneity.

	Thrombo-embolism (%/yr)	Valve thrombosis (%/yr)	Bleeding (%/yr)	SVD (%/yr)	NSVD (%/yr)	Endocarditis (%/yr)
	3.07(1.89-4.97)	0.10(0.01-1.53)	1.92(1.04-3.54)	0.10(0.01-1.53)	0.77(0.29-2.03)	0.10(0.01-1.53)
	-	-	-	-	5.90(1.97-17.69)	1.97(0.28-13.70)
	1.50(1.08-2.07)	0.71(0.44-1.14)	1.58(1.15-2.17)	-	0.12(0.04-0.39)	-
	0.23(0.06-0.91)	0.06(0.00-0.91)	0.91(0.46-1.81)	0.06(0.00-0.91)	-	-
	0.25(0.02-4.06)	-	0.51(0.07-3.60)	-	0.25(0.02-4.06)	-
	1.13(0.63-2.04)	0.05(0.00-0.82)	1.54(0.93-2.55)	-	-	-
	-	-	-	0.04(0.00-0.59)	-	-
	0.25(0.06-1.01)	-	0.25(0.06-1.01)	-	0.13(0.02-0.90)	0.13(0.02-0.90)
	-	0.58(0.04-9.25)	0.58(0.04-9.25)	-	1.17(0.17-8.19)	0.58(0.04-9.25)
	1.34(0.60-2.96)	0.22(0.03-1.58)	0.45(0.11-1.78)	0.11(0.01-1.78)	1.11(0.47-2.67)	0.22(0.03-1.58)
	0.25(0.03-1.75)	0.12(0.01-1.98)	0.12(0.01-1.98)	0.12(0.01-1.98)	0.25(0.03-1.75)	0.25(0.03-1.75)
	0.31(0.14-0.68)	0.10(0.03-0.41)	0.31(0.14-0.68)	0.03(0.00-0.41)	0.31(0.14-0.68)	0.15(0.05-0.47)
	1.20(0.75-1.93)	0.07(0.01-0.50)	0.92(0.54-1.58)	0.04(0.00-0.57)	0.07(0.01-0.50)	0.42(0.19-0.94)
	2.54(0.97-6.69)	-	1.27(0.32-5.04)	-	-	1.91(0.62-5.85)
	0.81(0.22-2.93)	-	0.18(0.01-2.80)	-	-	0.70(0.18-2.79)
	0.95(0.51-1.76)	0.09(0.01-0.67)	0.66(0.32-1.39)	0.05(0.00-0.76)	0.09(0.01-0.67)	-
	0.47(0.21-1.05)	0.24(0.08-0.73)	0.87(0.48-1.56)	0.04(0.00-0.63)	0.32(0.12-0.84)	0.47(0.21-1.05)
	1.34(0.82-2.18)	-	1.51(0.95-2.38)	-	-	-
	0.42(0.11-1.69)	0.11(0.01-1.69)	2.33(1.30-4.19)	0.11(0.01-1.69)	-	0.21(0.03-1.50)
	0.18(0.07-0.48)	-	0.14(0.04-0.42)	-	-	-
	2.50(0.16-38.60)	2.50(0.16-38.60)	5.00(0.74-33.78)	2.50(0.16-38.60)	2.50(0.16-38.60)	2.50(0.16-38.60)
	2.12(0.96-4.68)	-	0.35(0.05-2.50)	-	-	0.71(0.18-2.81)
	-	-	-	-	-	-
	1.10(0.66-1.82)	0.07(0.01-0.52)	1.32(0.83-2.08)	-	-	0.66(0.34-1.26)
	0.41(0.23-0.74)	-	0.75(0.48-1.16)	-	-	-
	2.13(1.42-3.19)	0.05(0.00-0.74)	0.55(0.25-1.23)	0.05(0.00-0.74)	0.18(0.05-0.74)	0.28(0.09-0.86)
	0.80(0.52-1.22)	0.04(0.01-0.27)	0.65(0.40-1.04)	0.02(0.00-0.30)	0.27(0.13-0.56)	0.42(0.23-0.75)
	1.00(0.74-1.36)	0.07(0.02-0.23)	0.93(0.68-1.27)	0.01(0.00-0.19)	0.90(0.65-1.24)	0.24(0.13-0.45)
	0.86(0.53-1.40)	0.03(0.00-0.43)	0.65(0.37-1.14)	0.03(0.00-0.43)	0.16(0.05-0.50)	0.16(0.05-0.50)
	0.90(0.68-1.21)	0.14(0.08-0.25)	0.85(0.65-1.12)	0.00[a]	0.39(0.21-0.76)	0.41(0.29-0.57)
	I^2=79% (p<0.001)	I^2=62% (p<0.001)	I^2=67% (p<0.001)	-	I^2=83% (p<0.001)	I^2=34% (p=0.0721)

SUPPLEMENT 4. Random effects meta-regression of natural log-transformed outcome measures

Covariate	**β**	**95%CI-**	**95%CI+**	**SE**	**p-value**
Early mortality					
Year of first inclusion	-0.007	-0.058	0.045	0.026	0.796
Mean FUP (per year)	-0.172	-0.261	-0.082	0.046	<0.001
Concomitant Procedures	2.479	0.057	4.902	1.236	0.045
Concomitant CABG	3.855	-1.350	9.060	2.656	0.147
AS	-1.565	-3.416	0.286	0.945	0.098
AR	1.250	-1.057	3.557	1.177	0.288
Rheumatic	1.250	-0.059	2.560	0.668	0.061
Mean age (per year)	-0.006	-0.061	0.049	0.028	0.829
Endocarditis	0.306	-2.544	3.156	1.454	0.834
Emergency	1.542	-6.225	9.310	3.963	0.697
Prospective/RCT study design	-0.157	-0.964	0.651	0.412	0.704
Previous cardiac intervention	0.655	-4.494	5.804	2.627	0.803
Late Mortality					
Year of first inclusion	-0.002	-0.036	0.032	0.017	0.911
Mean FUP (per year)	0.063	0.000	0.126	0.032	0.052
Concomitant Procedures	-0.154	-1.911	1.602	0.896	0.863
Concomitant CABG	0.293	-3.462	4.047	1.916	0.879
AS	0.989	-0.73	2.708	0.877	0.260
AR	-1.502	-3.377	0.373	0.956	0.116
Rheumatic	-0.552	-1.317	0.214	0.391	0.158
Mean age (per year)	0.035	-0.001	0.071	0.018	0.054
Endocarditis	1.650	0.426	2.874	0.624	0.008
Emergency	2.699	-0.290	5.687	1.525	0.077
Prospective/RCT study design	-0.314	-0.821	0.193	0.259	0.225
Previous cardiac intervention	1.368	-0.991	3.727	1.204	0.256
Reintervention					
Year of first inclusion	0.018	-0.030	0.067	0.025	0.464
Mean FUP (per year)	-0.107	-0.189	-0.026	0.042	0.010
Concomitant Procedures	0.739	-1.542	3.020	1.164	0.526
Concomitant CABG	2.908	-1.772	7.588	2.388	0.223
AS	0.132	-1.087	1.352	0.622	0.831
AR	0.129	-1.637	1.895	0.901	0.886

Covariate	β	95%CI-	95%CI+	SE	p-value
Rheumatic	0.665	-0.038	1.369	0.359	0.064
Mean age (per year)	-0.042	-0.087	0.003	0.023	0.069
Endocarditis	0.635	-1.386	2.657	1.031	0.538
Emergency	2.666	-2.277	7.608	2.522	0.290
Prospective/RCT study design	0.368	-0.359	1.094	0.371	0.321
Previous cardiac intervention	-0.111	-3.504	3.281	1.731	0.949
TE/VT					
Year of first inclusion	0.023	-0.023	0.069	0.023	0.321
Mean FUP (per year)	-0.062	-0.158	0.034	0.049	0.203
Concomitant Procedures	1.342	-0.669	3.353	1.026	0.191
Concomitant CABG	2.949	-1.601	7.499	2.321	0.204
AS	0.920	-1.046	2.886	1.003	0.359
AR	0.576	-1.513	2.665	1.066	0.589
Rheumatic	0.622	-0.950	2.195	0.802	0.438
Mean age (per year)	-0.004	-0.060	0.052	0.029	0.892
Endocarditis	-0.754	-6.126	4.619	2.741	0.783
Emergency	1.922	-5.606	9.449	3.841	0.617
Prospective/RCT study design	0.368	-0.307	1.044	0.345	0.286
Previous cardiac intervention	0.994	-3.053	5.042	2.065	0.630
Bleeding					
Year of first inclusion	0.000	-0.042	0.041	0.021	0.991
Mean FUP (per year)	-0.077	-0.151	-0.003	0.038	0.042
Concomitant Procedures	1.150	-0.092	2.391	0.633	0.070
Concomitant CABG	3.157	-0.696	7.011	1.966	0.108
AS	2.235	0.263	4.206	1.006	0.026
AR	-3.083	-5.150	-1.016	1.054	0.003
Rheumatic	0.690	-0.633	2.014	0.675	0.307
Mean age (per year)	-0.008	-0.057	0.040	0.025	0.742
Endocarditis	0.324	-4.003	4.652	2.208	0.883
Emergency	-1.907	-11.833	8.019	5.064	0.707
Prospective/RCT study design	-0.338	-0.952	0.277	0.313	0.281
Previous cardiac intervention	0.343	-3.076	3.761	1.744	0.844
NSVD					
Year of first inclusion	0.037	-0.049	0.123	0.044	0.401
Mean FUP (per year)	-0.146	-0.309	0.016	0.083	0.078
Concomitant Procedures	1.619	-4.787	8.026	3.269	0.620

Covariate	β	95%CI-	95%CI+	SE	p-value
Concomitant CABG	-7.148	-14.176	-0.119	3.586	0.046
AS	3.128	1.306	4.949	0.929	<0.001
AR	-3.770	-5.945	-1.595	1.110	<0.001
Rheumatic	-3.296	-5.537	-1.055	1.143	0.004
Mean age (per year)	-0.002	-0.108	0.104	0.054	0.970
Endocarditis	2.718	0.978	4.458	0.888	0.002
Emergency	6.612	1.778	11.445	2.466	0.007
Prospective/RCT study design	0.523	-0.922	1.968	0.737	0.478
Previous cardiac intervention	0.367	-6.177	6.911	3.339	0.913

SE, standard error; 95%CI-, 95% confidence interval lower bound; 95%CI+, 95% confidence interval upper bound; FUP, follow-up; CABG, coronary artery bypass grafting; AS, aortic stenosis; AR, aortic regurgitation; RCT, randomized controlled trial; TE, thromboembolism; VT, valve thrombosis; NSVD, nonstructural valve dysfunction.

SUPPLEMENT 5. Methods

List of recorded variables

Study characteristics:

- Study design
- Number of patients included
- Inclusion period
- Total follow-up

Baseline patient and operative characteristics:

- Mean age
- Gender
- Etiology
- Aortic valve hemodynamics
- Aortic valve morphology
- Previous cardiac interventions (any previous surgical or percutaneous intervention on the heart, thoracic aorta and/or pulmonary trunk)
- Urgency of the operation
- Type of mechanical valve (bileaflet, caged-ball or tilting disc)
    - o Prosthesis model
- Concomitant procedures

Outcome events

- Early outcome events (<30 days after surgery)
    - o Early mortality (all-cause mortality within the first 30 postoperative days)
    - o Re-exploration for bleeding
    - o Pacemaker implantation
    - o Deep sternal infection/mediastinitis
    - o Endocarditis
    - o Stroke
    - o Transient ischemic attack
    - o Myocardial infarction
    - o Valve thrombosis
    - o Peripheral bleeding
- Late outcome events (>30 days after surgery)
    - o Late mortality
        - § Cardiac death
        - § Valve related death

    - § Sudden, unexplained death (SUD)
- o Reintervention
- o Thromboembolism
- o Valve thrombosis
- o Bleeding
- o Endocarditis
- o Structural valve deterioration (SVD)
- o Nonstructural valve dysfunction (NSVD)

Statistical software used

Statistical analyses were performed in Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA), IBM SPSS Statistics (version 21.0.0.1. IBM Corp., Armonk, NY, USA) and in the R statistical software (version 3.1.0. R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the metafor package.

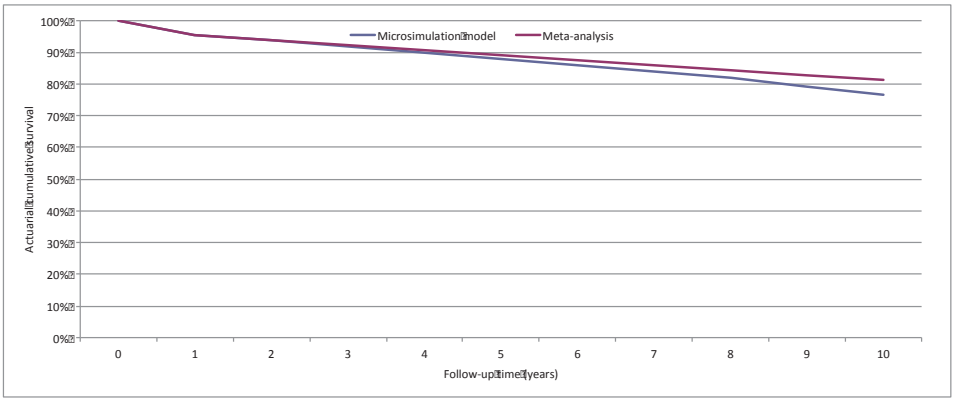
SUPPLEMENT 6. References of studies included in the meta-analysis [14,25,29-55]

14. Torella M, Torella D, Chiodini P, Franciulli M, Romano G, De Santo L, De Feo M, Amarelli C, Sasso FC, Salvatore T, Ellison GM, Indolfi C, Cotrufo M, Nappi G. LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: Results from the "lOWERING-IT" Trial. Am Heart J 2010;160(1):171-178.
25. Klieverik LMA, Noorlander M, Takkenberg JJM, Kappentein AP, Bekkers JA, Herwerden LAV, Bogers AJJ. Outcome after aortic valve replacement in young adults: Is patient profile more important than prosthesis type? J Heart Valve Dis 2006;15(4):479-487.
29. Aagaard J, Tingleff J, Andersen PV, Hansen CN. Fourteen years' experience with the CarboMedics valve in young adults with aortic valve disease. J Heart Valve Dis 2003;12(1):81-86.
30. Andreas M, Wiedemann D, Seebacher G, Rath C, Aref T, Rosenhek R, Heinze G, Eigenbauer E, Simon P, Ruetzler K, Hiesmayr JM, Moritz A, Laufer G, Kocher A. The Ross procedure offers excellent survival compared with mechanical aortic valve replacement in a real-world setting. Eur J Cardiothorac Surg 2014.
31. Bouhout I, Stevens LM, Mazine A, Poirier N, Cartier R, Demers P, El-Hamamsy I. Long-term outcomes after elective isolated mechanical aortic valve replacement in young adults. J Thorac Cardiovasc Surg 2014;148(4):1341-1346.e1341.
32. Chang BC, Lim SH, Kim DK, Seo JY, Cho SY, Shim WH, Chung N, Kim SS, Cho BK. Long-term results with St. Jude Medical and CarboMedics prosthetic heart valves. J Heart Valve Dis 2001;10(2):185-195.
33. Chang HK, Ahn H, Kyung HK, Kim KB. Long-term result of 1144 CarboMedics mechanical valve implantations. Ann Thorac Surg 2005;79(6):1939-1944.
34. Cohoon KP, Foley J, Dieter RS, Bakhos M, Schwartz J. The development of ascending aortic aneurysms after elective aortic valve replacement with St Jude mechanical valve prosthesis in the bicuspid patient: A pilot study. Angiology 2013;64(5):379-384.
35. Concha M, Aranda PJ, Casares J, Merino C, Alados P, Munoz I, Villalba R, Ariza J. Prospective evaluation of aortic valve replacement in young adults and middle-aged patients: Mechanical prosthesis versus pulmonary autograft. J Heart Valve Dis 2005;14(1):40-46.
36. Doss M, Wood JP, Kiessling AH, Moritz A. Comparative evaluation of left ventricular mass regression after aortic valve replacement: a prospective randomized analysis. J Cardiothorac Surg 2011;6:136.
37. Emery RW, Erickson CA, Arom KV, Northrup Iii WF, Kersten TE, Von Rueden TJ, Lillehei TJ, Nicoloff DM. Replacement of the aortic valve in patients under 50 years of age: Long-term follow-up of the St. Jude Medical prosthesis. Ann Thorac Surg 2003;75(6):1815-1819.
38. Gaudino M, De Filippo C, Pennestri F, Possati G. The use of mechanical prostheses in native aortic valve endocarditis. J HEART VALVE DIS 1997;6(1):79-83.
39. Imanaka K, Takamoto S, Furuse A. Favorable results in patients with small size CarboMedics heart valves in the aortic position. Ann Thorac Cardiovasc Surg 2001;7(3):150-154.

40. Jamieson WRE, Miyagishima RT, Grunkemeier GL, Germann E, Henderson C, Lichtenstein SV, Ling H, Munro AI. Bileaflet mechanical prostheses for aortic valve replacement in patients younger than 65 years and 65 years of age or older: Major thromboembolic and hemorrhagic complications. Can J Surg 1999;42(1):27-36.
41. Kandemir O, Tokmakoglu H, Yildiz U, Tezcaner T, Yorgancioglu AC, Gunay I, Suzer K, Zorlutuna Y. St. jude medical and carboMedics mechanical heart valves in the aortic position comparison of long-term results. Texas Heart Institute Journal 2006;33(2):154-159.
42. Katircioglu SF, Yamak B, Ulus AT, Iscan HZ, Mavitas B, Tasdemir O. Aortic valve replacement with the St. Juode Medical prosthesis and fixed dose anticoagulation. J Card Surg 1997;12(6):363-371.
43. Kilian E, Oberhoffer M, Kaczmarek I, Bauerfeind D, Kreuzer E, Reichart B. Outcome after aortic valve replacement: Comparison of homografts with mechanical prostheses. J Heart Valve Dis 2007;16(4):404-409.
44. Kuwaki K, Tsukamoto M, Komatsu K, Sakata J, Abe T. Ten year clinical experience with the CarboMedics heart valve implants. Artif Organs 2002;26(8):695-702.
45. McClure RS, McGurk S, Cevasco M, Maloney A, Gosev I, Wiegerinck EM, Salvio G, Tokmaji G, Borstlap W, Nauta F, Cohn LH. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: A propensity-matched analysis. J Thorac Cardiovasc Surg 2014;148(5):1931-1939.
46. Natsuaki M, Itoh T, Okazaki Y, Ohtubo S, Rikitake K, Naitoh K. Systemic hypertension as a risk factor for complications with an aortic mechanical valve. ASAIO J 1998;44(5):M486-M490.
47. Nazarov VM, Zheleznev SI, Bogachev-Prokophiev AV, Afanasyev AV, Nemchenko EV, Jeltovskiy YV, Lavinyukov SO. CardiaMed mechanical valve: Mid-term results of a multicenter clinical trial. Asian Cardiovasc Thorac Ann 2014;22(1):9-17.
48. Nishida T, Sonoda H, Oishi Y, Tanoue Y, Nakashima A, Shiokawa Y, Tominaga R. Single-institution, 22-year follow-up of 786 CarboMedics mechanical valves used for both primary surgery and reoperation. J Thorac Cardiovasc Surg 2014;147(5):1493-1498.
49. Nishida T, Sonoda H, Oishi Y, Tanoue Y, Tatewaki H, Shiokawa Y, Tominaga R. Long-term comparison of three types of aortic St. Jude medical mechanical prosthesis in Japanese patients. Circ J 2015;79(10):2193-2200.
50. Nistal JF, Hurle A, Revuelta JM, Gandarillas M. Clinical experience with the carbomedics valve: Early results with a new bileaflet mechanical prosthesis. J THORAC CARDIOVASC SURG 1996;112(1):59-68.
51. Ozeren M, Dogan OV, Dolgun A, Kocyldirim E, Karapinar K, Yucel E. Clinical results of the ATS prosthetic valve in 240 implants and review of the literature. J Heart Valve Dis 2001;10(5):628-635.
52. Renzulli A, Ismeno G, Bellitti R, Casale D, Festa M, Nappi GA, Cotrufo M. Long-term results of heart valve replacement with bileaflet prostheses. J CARDIOVASC SURG 1997;38(3):241-247.
53. Rodrigues AJ, Evora PRB, Bassetto S, Alves Jr L, Scorzoni Filho A, Vicente WVA. Isolated mitral and aortic valve replacement with the St. Jude Medical valve: A midterm follow-up. Arq Bras Cardiol 2009;93(3):268-276+282-290+290-298.

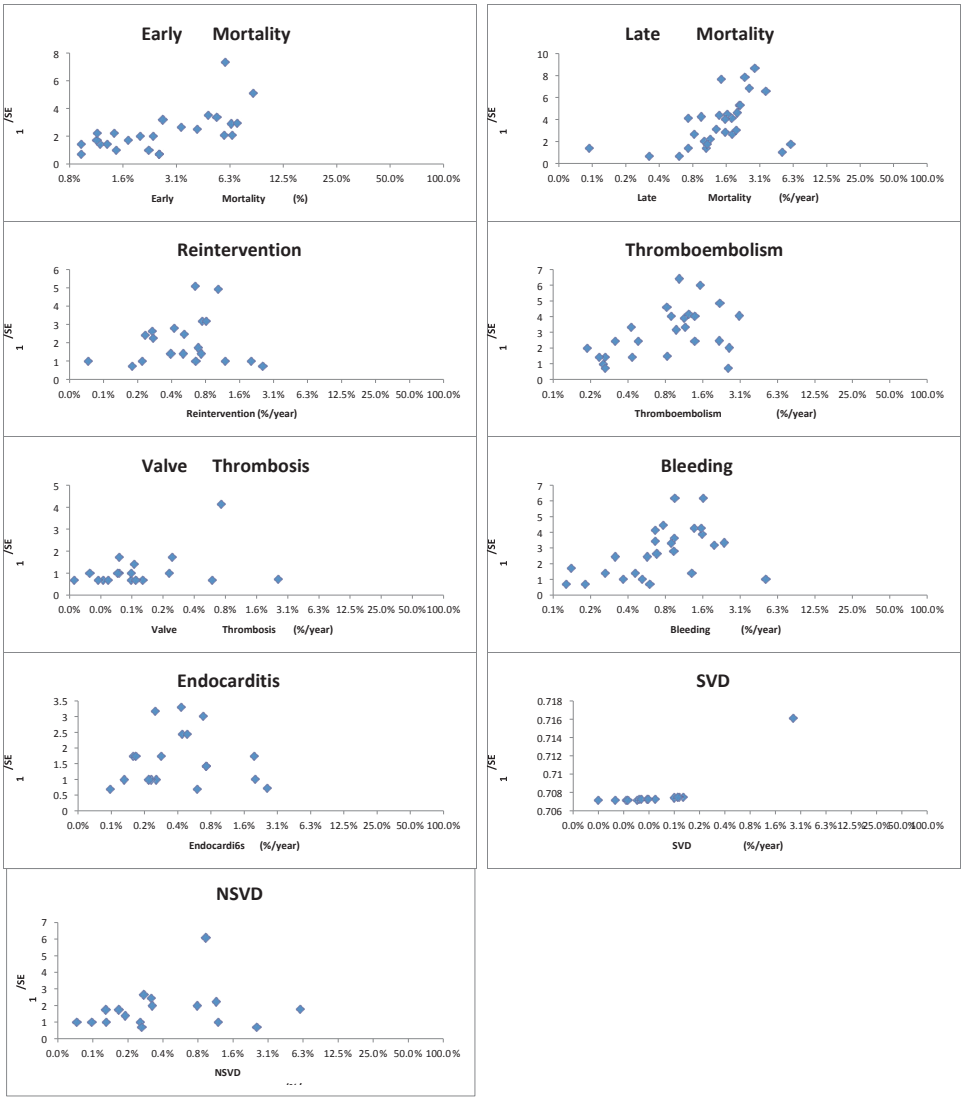
54. Sakamoto Y, Hashimoto K, Okuyama H, Ishii S, Inoue T, Kinouchi K, Abe T. Carpentier-Edwards pericardial aortic valve in middle-aged patients: Comparison with the St. Jude Medical valve. Jpn J Thorac Cardiovasc Surg 2005;53(9):465-469.
55. Weber A, Noureddine H, Englberger L, Dick F, Gahl B, Aymard T, Czerny M, Tevaearai H, Stalder M, Carrel TP. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. J Thorac Cardiovasc Surg 2012;144(5):1075-1083.

SUPPLEMENT 7. Microsimulation model calibration plot



Legend: the actuarial survival curve obtained from the microsimulation model run for 10,000 iterations at the pooled mean age (48 years) and male/female ratio (72.0% male) of the included studies compared to the pooled overall mortality observed in our meta-analysis.

SUPPLEMENT 8. Funnel plots



Legend: Funnel plots on a natural log x-axis. SE = standard error; SVD = structural valve deterioration; NSVD = nonstructural valve dysfunction.

"It's not hard to make decisions when you know what your values are"

Roy Disney

3.

Bentall Procedure: a Systematic Review and Meta-Analysis

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ABSTRACT

Background. The Bentall procedure is considered the gold standard in treatment of patients requiring aortic root replacement. An up-to-date overview of outcome following the Bentall procedure is lacking.

Methods. We conducted a systematic review and meta-analysis of characteristics of and long-term outcome after the Bentall procedure with a mechanical valve prosthesis. Pooling was performed using the inverse variance method within a random-effect model. Outcome events are reported as linearized occurrence rates (percentage per patient year) with 95% confidence intervals.

Results. In total, 46 studies with 7629 patients (mean age 50 years, 76% males) were selected. Pooled early mortality was 6% (422 patients). During a mean follow-up of 6 years (49,175 patient years), the annual linearized occurrence rate for late mortality was 2.02% (1.77% - 2.31%; 892 patients), for aortic root reoperation 0.46% (0.36% - 0.59%), for hemorrhage 0.64% (0.47% - 0.87%), for thromboemboli 0.77% (0.60% - 1.00%), for endocarditis 0.39% (0.33% - 0.46%) and for major adverse valve-related events 2.66% (2.17% - 3.24%). Operations performed in more recent years were associated with lower rates of aortic root reoperation (beta = -0.452, P=0.015).

Conclusion. This systematic review illustrates that rates of aortic root reoperation after the Bentall procedure have decreased over the years. However, late mortality, major bleeding and thromboembolic complications remain a concern. This report may be used to benchmark the potential therapeutic benefit of novel surgical approaches, such as valve-sparing aortic root replacement.

INTRODUCTION

The Bentall procedure is considered the gold standard in treatment of patients requiring aortic root replacement. Since its introduction, novel surgical techniques and approaches have changed the Bentall procedure considerably [1]. While the original procedure was associated with a high incidence of coronary button complications, several modifications have been proposed to tackle this problem [2, 3]. The vast majority of Bentall procedures concerns replacement of the aortic root with a mechanical valved conduit. The use of a mechanical valve provides a durable solution, but requires life-long anticoagulation associated with increased bleeding risk.

Surprisingly, an up-to-date overview of outcome following the Bentall procedure is lacking, as most reports are single center and usually concern limited numbers of patients. Pooling data from the literature will allow individual centers or surgeons to benchmark their experience. More importantly, it is key to allow for assessment of the potential therapeutic benefit of novel techniques such as valve-sparing aortic root replacement [4]. This study comprises a systematic review and meta-analysis of published evidence on characteristics of and outcome after the Bentall procedure using a mechanical valve prosthesis.

METHODS

Search Strategy

On July 20th 2015, a systematic literature search was conducted in Embase, MEDLINE, The Cochrane Collaboration and Web of Science (Appendix 1). All studies published from January 1998 onwards were screened by two independent reviewers (AM and NMK) using the following inclusion criteria: morbidity and mortality after the Bentall procedure with a mechanical valve prosthesis, cohorts ≥ 30 patients and mean age ≥ 18 years. Exclusion criteria were: studies limited to patients with acute type A aortic dissection, studies limited to reoperations or to patients receiving a biological valve prosthesis, studies with mean follow-up less than 4 years and studies reporting state of the art, case reports, experimental studies and reviews. In case of multiple publications on the same patient cohort, the most recent and complete study was selected. All selected studies were cross-referenced to identify additional publications. In case of disagreement between the reviewers about inclusion of a publication, consensus was reached.

Data Extraction

Data extraction was performed in duplicate with Microsoft Excel (Microsoft Office 2010, Microsoft, Redmond, WA, USA) by two of the authors (AM and NMK) according to the guidelines for reporting mortality and morbidity after cardiac valve interventions [5]. Events were not included in our database when adherence to the reporting guidelines could not be ascertained. For each article with missing information on important variables, the corresponding author was requested to provide the missing data. An overview of extracted variables is presented in Appendix 2.

Data Analysis

Data analysis was performed with Microsoft Excel (Microsoft Office 2010, Microsoft, Redmond, WA, USA) and IBM SPSS version 21.0 (IBM, Somers, NY, USA). Reported study characteristics are quoted as mean ± standard deviation for continuous variables and percentages for discrete variables. To study the association between surgical period and outcome after the Bentall procedure, the continuous variable "surgical period" was defined as the year of first patient inclusion in each cohort.

Outcome events are reported as linearized occurrence rates (percentage per patient year). The rate for each event, calculated by dividing the number of events by the total follow-up in patient years, was calculated for each individual study and then pooled on a logarithmic scale using the inverse variance method within a random-effect model. When a certain event did not occur in an individual study, we set the number of events to 0.5 to allow for inclusion of the study in pooling of the linearized occurrence rate for that particular event. When a certain event was not reported according to the guidelines for reporting mortality and morbidity after cardiac valve interventions [5] in an individual study, this study was excluded from the analysis of that particular event.

To assess the association of five variables (age, surgical period, proportion of patients with Marfan's disease, proportion of patients with acute type A aortic dissection, proportion of patients receiving a mechanical valve prosthesis with the Bentall procedure) with four important outcome events (late mortality, reoperation, major bleeding, major adverse valve-related events), linear regression was performed with correction for age as a possible confounder. Regression analysis was weighted by study size according to the inverse variance method. To better characterize the patient population with Marfan's disease or other connective tissue disorders, Pearson's correlation coefficient was calculated to analyze whether the proportion of patients with connective tissue

disorder was correlated to age, proportion of patients with acute type A aortic dissection or proportion of patients receiving a mechanical valve prosthesis with the Bentall procedure.

Statistical heterogeneity between studies was assessed for each outcome event using the I^2 test. Publication bias was assessed for each outcome event by inspection of Funnel plots.

RESULTS

The systematic literature search identified 1,403 articles. Figure 1 illustrates the selection process that resulted in the inclusion of 46 articles in the systematic review and meta-analysis. Missing data was provided by the authors of the article by Van Duffel *et al* [6]. Characteristics of the included studies are summarized in Appendix 3 [2, 6-50].

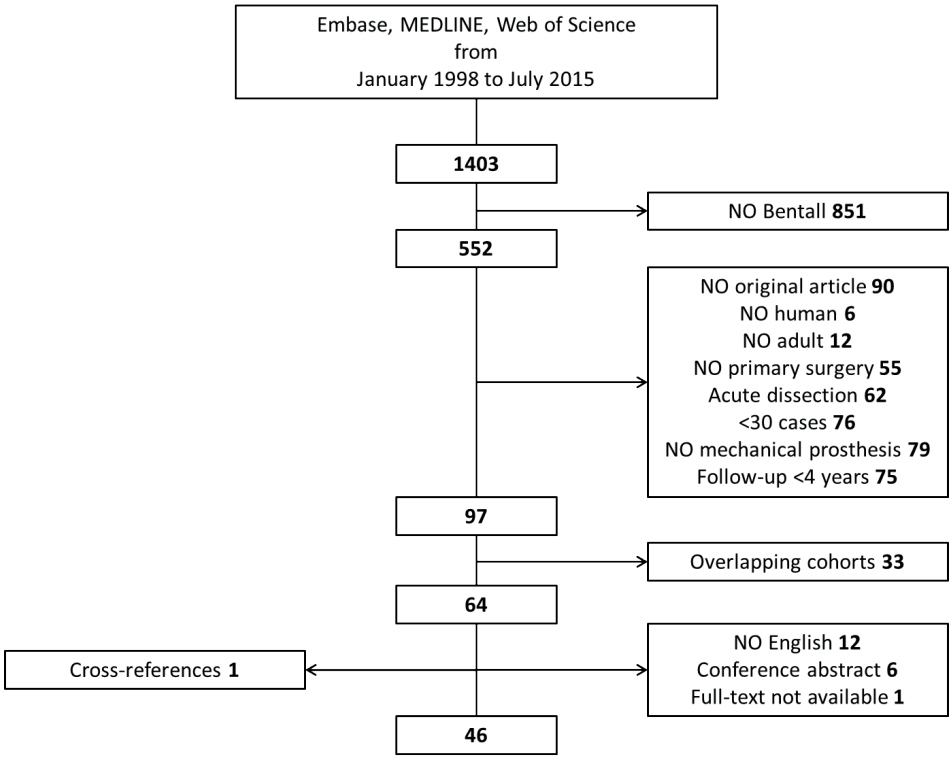

FIGURE 1. Flowchart of systematic literature search.

TABLE 1. Pooled pre-operative and peri-operative characteristics

Variable		Pooled data	Range	Included studies (N)
Total patient number		7629	40 - 675	46
Surgical period		1968 - 2012		45
Mean age		49.8 years	29 – 65 years	44
Gender	Male	76.3%	55 – 91%	45
Comorbidity	Connective tissue disease	22.6%	0 – 100%	38
	Bicuspid aortic valve	24.9%	4 – 100%	17
Prior surgery	Cardiac	16.2%	1 – 37%	22
	Aortic valve	11.8%	0 – 30%	14
Other indications *	Acute type A dissection	15.3%	0 – 39%	43
	Active endocarditis	2.0%	0 – 15%	25
Emergency surgery		15.8%	0 – 43%	35
Other surgery types †	Homograft	0.4%	0 – 5%	43
	Valve-sparing	2.2%	0 – 27%	45
	Other	0.9%	0 – 41%	45
Valve type	Mechanical	93.2%	43 – 100%	40
	Biological	6.8%	0 – 57%	40
Reexploration for bleeding		6.7%	0 – 23%	28
Concomitant	Aortic hemiarch repair	11.6%	0 – 39%	28
	Aortic arch repair	5.9%	0 – 18%	26
	CABG	11.9%	0 – 31%	36
	Mitral valve surgery	6.1%	0 – 18%	36
Early mortality		5.6%	1 – 20%	46
Causes of early mortality ‡	*Low cardiac output*	29.4%		
	Hemorrhage	8.5%		
	Multiorgan failure	7.8%		
	Myocardial infarction	5.9%		
	Cardiac arrhythmias	5.7%		
	Unknown / unreported	20.4%		

CABG indicates coronary artery bypass grafting. * majority of patients underwent Bentall procedure for aortic root aneurysm with or without aortic valve insufficiency; † majority of patients received Bentall procedure; ‡ major causes of early mortality.

Pooled pre-operative and peri-operative characteristics are displayed in Table 1. Early mortality occurred in 422 patients (pooled early mortality 5.6%); there was no trend toward reduced operative mortality in more recent years. The article by Milano *et al*. was not included in this analysis because it only concerned hospital survivors [30].

Mean follow-up after the Bentall procedure was 6.4 years (range 3.0 – 10.4 years) resulting in a total of 49,175 patient years. From four articles, it proved impossible to ascertain the exact number of late deaths [8, 20, 36, 45]. Although unknown or unreported in 47.9% of cases, the main causes of late mortality were low cardiac output (9.9%), distal aortic dissection or rupture (8.9%), hemorrhage (4.1%), stroke (3.8%), endocarditis (3.7%), cardiac arrhythmias (3.3%), other cardiac-related deaths (9.6%) and other non cardiac-related deaths (8.9%). The linearized occurrence rates of late mortality, reoperation on the aortic root, hemorrhage, thromboembolism, endocarditis and major adverse valve-related events are presented along with a measure of statistical heterogeneity in Table 2 and Appendix 4.

TABLE 2. Linearized occurrence rates of late outcome events

Pooled late outcome events	LOR + 95% CI	Heterogeneity (I^2)	Included studies (N)	Events (N)	Patient years (N)
Late mortality *	2.02 (1.77 – 2.31)	70.60	42	892	41803
Valve-related mortality	0.46 (0.36 – 0.59)	49.49	43	172	42845
Root reoperation †	0.46 (0.36 – 0.59)	50.79	40	161	37231
Valve reoperation	0.30 (0.22 – 0.41)	37.27	35	87	32423
Hemorrhage	0.64 (0.47 – 0.87)	67.91	31	174	29234
Thromboembolism	0.77 (0.60 – 1.00)	72.08	30	291	36318
Endocarditis	0.39 (0.33 – 0.46)	0.00	31	125	35638
MAVRE	2.66 (2.17 – 3.24)	79.35	20	531	19839

*Including valve-related mortality. † Including valve reoperation. LOR indicates linearized occurrence rates; CI, confidence interval; MAVRE, major adverse valve-related events.

The proportion of patients with a connective tissue disorder was correlated with age (coefficient -0.671, P<0.001), proportion of patients with a bicuspid aortic valve (coefficient -0.482, P=0.069) and proportion of patients with acute aortic dissection (coefficient 0.370, P=0.024).

A more recent surgical period was associated with a decreased hazard of reoperation on the aortic root (beta = -0.452, P=0.015). Use of a mechanical valve prosthesis was also associated with a decreased hazard of reoperation on the aortic root (beta = -0.425, P=0.011). The other analyses did not show significant associations.

Inspection of funnel plots revealed asymmetry, with smaller studies showing consistently lower event rates than studies with large patient numbers.

COMMENT

This systematic review offers cardiologists and cardiac surgeons a unique and up-to-date overview of long-term outcome following the Bentall procedure. We have shown that surgical centers worldwide have performed the Bentall procedure in a highly heterogeneous patient population with respect to patient age, indication for surgery, comorbidities and concomitant procedures. This is corroborated by the demonstration of substantial statistical heterogeneity.

The findings of the systematic review and meta-analysis, which represent the real-world experience with the Bentall procedure, may be used by individual surgeons or surgical centers to benchmark their experience with the procedure. In addition, the meta-analysis will allow comparison of the gold standard in aortic root aneurysm surgery with novel therapeutic approaches such as valve-sparing aortic root replacement and personalized external aortic root support (PEARS) [51].

In the Society of Thoracic Surgeons database, early mortality in adult patients receiving root reconstruction with a valved conduit, including patients with acute endocarditis and those operated non-electively, operated between 2000 and 2011 was 8.9% [52]. Therefore, our finding of pooled early mortality of 5.6% appears excellent, especially when taking into account that many of our patients were operated several decades ago. However, while the Society of Thoracic Surgeons database represents daily clinical practice, our finding of pooled early mortality may have been influenced by publication bias and/or selective outcome reporting.

Given the mean age and comorbidities of the patient population, pooled late mortality is acceptable. The reported incidence of both major bleeding and thromboembolic complications is substantial accounting for a combined cumulative incidence of 14.1% at ten years. The reported low incidence of prosthetic valve endocarditis following the Bentall procedure is encouraging. However, major adverse valve-related events are common after the Bentall procedure with a cumulative incidence of 26.6% at ten years. Despite the lower linearized occurrence rates of reoperation in patients operated in more recent years, no such trend is apparent for late mortality, major bleeding, thromboembolic complications and endocarditis. Major bleeding and thromboembolic complications are strongly correlated with use of oral anticoagulation and mechanical valve implantation, respectively. Therefore, it may prudent to advise a different surgical approach in selected patients.

In this systematic review and meta-analysis, patients with Marfan's disease or other connective tissue disorders were on average younger and more often presented with acute aortic dissection. Interestingly, hazards of late mortality, reoperation, major bleeding and major adverse valve-related events were not associated with the presence of connective tissue disease. Five studies in this systematic review focused specifically on aortic root surgery in patients with connective tissue disease [7, 10, 15, 20, 53]. The pooled linearized occurrence event rates from these studies were comparable to the rates reported in Table 2, except for reoperation (1.01% versus 0.46% per year). In contrast, in a meta-analysis from Benedetto *et al*. focusing on Marfan's disease, the linearized occurrence rate for reoperation after the Bentall procedure is reported as 0,3% per year [54]. Our reported high reoperation rate in the studies focused on connective tissue disease can be attributed to poor results from one study with an estimated freedom from reoperation of only 67.1% at ten years. This study was not included in the meta-analysis from Benedetto *et al*. [15].

According to the recent American Heart Association/American College of Cardiology valvular heart disease guidelines, a mechanical valve prosthesis is not recommended in patients in whom use of oral anticoagulation is either contraindicated or not desired [55]. For instance, use of oral anticoagulation may not be desired in women who may wish to become pregnant in the future or in high performance athletes. In this meta-analysis, no association was shown between implantation of a mechanical valve prosthesis and occurrence of major valve-related events, including major bleeding and thromboembolic complications. Implantation of a mechanical valve prosthesis was associated with lower hazard of reoperation. In one study included in this meta-analysis with 57% of patients receiving a biological valve substitute, the authors described a higher freedom from thromboembolic complications at ten years in these patients [40].

Interestingly, the majority of manuscripts included in this meta-analysis that reported on a substantial proportion of patients (>10%) receiving a biological valve substitute did not analyze the association between the choice of valve substitute and outcome measures. The only other study to do so, showed similar late survival in both groups [6].

The guidelines also state that choice of both valve intervention and prosthesis type should be an informed, shared decision. This is especially important in aortic valve disease, as the choice between available options is often highly value-sensitive. Therefore, patients and surgeons should discuss and explore all available options, including implantation of a bioprosthesis, valve-sparing aortic root replacement and perhaps even considering novel therapeutic approaches in selected patients such as PEARS [51].

In this light, we compared our findings to those from a systematic review and meta-analysis on outcome after valve-sparing aortic root replacement published by Arabkhani et al. [56]. Pooled data from 4,777 patients with a follow-up of 21,716 patient years show that reinterventions are more common after valve-sparing aortic root replacement than after the Bentall procedure. Interestingly, rates of early and late mortality as well as late hemorrhage and thromboembolic complications were substantially lower after valve-sparing aortic root replacement. Patient characteristics, such as age at the time of operation, proportion of patients with connective tissue disease and aortic arch repair were similar between the two studies. However, differences in surgical era between the studies may explain why differences in early and late mortality were so striking. Nonetheless, the comparison clearly illustrates that valve-sparing aortic root replacement offers a great promise for the future.

To improve decision making, detailed and up-to-date information on long-term outcome of the available techniques is required. In this light, we strongly support projects such as the recently initiated AVIATOR registry; a prospective international registry of patients undergoing surgery, including the Bentall procedure and valve-sparing root replacement, for ascending aorta aneurysm and/or isolated aortic regurgitation.

Limitations

Statistical heterogeneity limits application of our findings for use in individual patients and precluded use of meta-regression. Heterogeneity is likely the result of large diversity in patient characteristics as well as the large time period in which surgery was performed.

When interpreting the findings, it is important to realize that the presented pooled outcome measures may underestimate the actual occurrence of late mortality

and morbidity following the Bentall procedure as most included studies were of a retrospective nature. In addition, publication bias may have contributed to lower mean linearized occurrence rates.

Several studies included in the systematic review did not adhere to the available guidelines on reporting after heart valve interventions [5]. Therefore, it was not always possible to extract (reliable) information on the important outcome measures.

Lack of access to individual patient data precluded the use of more robust outcome measures than the linearized occurrence rate. The main concern with linearized occurrence rates is that many biological events occur in a non-linear fashion.

Conclusions

Published experience with the Bentall procedure with a mechanical valve prosthesis is extensive in a diverse patient population. Over the years, rates of aortic root reoperation have decreased. However, rates of late mortality, major bleeding and thromboembolic complications, associated with the use of a mechanical valve prosthesis, remain a concern. In this light, we encourage using this report as a benchmark to assess the potential therapeutic benefit of novel surgical approaches, such as valve-sparing aortic root replacement.

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REFERENCES

1. Bentall H, De Bono A. A technique for complete replacement of the ascending aorta. Thorax. 1968;23(4):338-9.
2. Aomi S, Nakajima M, Nonoyama M, et al. Aortic root replacement using composite valve graft in patients with aortic valve disease and aneurysm of the ascending aorta: Twenty years' experience of late results. Artif Organs. 2002;26(5):467-73.
3. Girardi LN. Composite Root Replacement with a Mechanical Conduit. Oper Tech Thorac Cardiovasc Surg. 2008;13(3):148-60.
4. David TE, Armstrong S, Manlhiot C, McCrindle BW, Feindel CM. Long-term results of aortic root repair using the reimplantation technique. J Thorac Cardiovasc Surg. 2013;145(3 Suppl):S22-5.
5. Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg. 2008;85(4):1490-5.
6. Van Duffel DV, Van Gemert RV, Starinieri P, et al. Elective reconstruction of the ascending aorta for aneurismal disease restores normal life expectancy. An analysis of risk factors for early and late mortality. Acta Cardiol. 2013;68(4):349-53.
7. Alexiou C, Langley SM, Charlesworth P, Haw MP, Livesey SA, Monro JL. Aortic root replacement in patients with Marfan's syndrome: The Southampton experience. Ann Thorac Surg. 2001;72(5):1502-7.
8. Brandt M, Abdelkerim S, Clemm S, Boning A, Cremer J. Composite valve graft versus separate aortic valve and ascending aortic replacement. Cardiology. 2004;102(3):156-9.
9. Byrne JG, Gudbjartsson T, Karavas AN, et al. Biological vs. mechanical aortic root replacement. European Journal of Cardiothoracic Surgery. 2003;23(3):305-10.
10. Carrel T, Beyeler L, Schnyder A, et al. Reoperations and late adverse outcome in Marfan patients following cardiovascular surgery. European Journal of Cardiothoracic Surgery. 2004;25(5):671-5.
11. Caynak B, Sagbas E, Onan B, et al. Comparison of three different surgical methods in aortic root aneurysms: Long-term results. J Card Surg. 2009;24(6):710-5.
12. Dunne B, Marr T, Andrews D, Larbalestier R, Edwards M, Merry C. Aortic root replacement for ascending aortic disease: A 10 year review. Heart Lung Circul. 2013;22(2):81-7.
13. Etz CD, Bischoff MS, Bodian C, et al. The Bentall procedure: Is it the gold standard? A series of 597 consecutive cases. J Thorac Cardiovasc Surg. 2010;140(6 SUPPL.):S64-S70.
14. Etz CD, Girrbach FF, von Aspern K, et al. Longevity after aortic root replacement: is the mechanically valved conduit really the gold standard for quinquagenarians? Circulation. 2013;128(11 Suppl 1):S253-62.
15. Gao L, Zhou X, Zhang L, et al. Factors influencing prognosis in patients with Marfan syndrome after aortic surgery. J Cardiothorac Vasc Anesth. 2011;25(4):625-31.
16. Gelsomino S, Masullo G, Morocutti G, et al. Sixteen-year results of composite aortic root replacement for non-dissecting chronic aortic aneurysms. Ital Heart J. 2003;4(7):454-9.

17. Girdauskas E, Rouman M, Borger MA, Kuntze T. Comparison of aortic media changes in patients with bicuspid aortic valve stenosis versus bicuspid valve insufficiency and proximal aortic aneurysm. Interact Cardiovasc Thorac Surg. 2013;17(6):931-6.
18. Gott VL, Greene PS, Alejo DE, et al. Replacement of the aortic root in patients with Marfan's syndrome. N Engl J Med. 1999;340(17):1307-13.
19. Joo HC, Chang BC, Youn YN, Yoo KJ, Lee S. Clinical experience with the Bentall procedure: 28 years. Yonsei Med J. 2012;53(5):915-23.
20. Karck M, Kallenbach K, Hagl C, et al. Aortic root surgery in Marfan syndrome: Comparison of aortic valve-sparing reimplantation versus composite grafting. J Thorac Cardiovasc Surg. 2004;127(2):391-8.
21. Kim TS, Na CY, Oh SS, Kim JH. Long-term mortality and morbidity after button bentall operation. J Card Surg. 2013;28(3):280-4.
22. Kindo M, Billaud P, Gerelli S, Levy F, Mazzucotelli JP, Eisenmann B. Twenty-seven-year experience with composite valve graft replacement of the aortic root. J Heart Valve Dis. 2007;16(4):370-7.
23. Lim JY, Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW. Surgical Management of Aortic Root Dilatation with Advanced Aortic Regurgitation: Bentall Operation versus Valve-sparing Procedure. Korean j thorac cardiovasc surg. 2012;45(3):141-7.
24. Luciani GB, Casali G, Barozzi L, Mazzucco A. Aortic root replacement with the carboseal composite graft: 7-year experience with the first 100 implants. Annals of Thoracic Surgery. 1999;68(6):2258-62.
25. Malashenkov AI, Rusanov NI, Muratov RM, et al. Eight years clinical experience with the replacement of the ascending aorta using composite xenopericardial conduit. Eur J Cardiothorac Surg. 2000;18(2):168-73.
26. Mataraci I, Polat A, Kiran B, et al. Long-Term Results of Aortic Root Replacement: 15 Years' Experience. Ann Thorac Surg. 2009;87(6):1783-8.
27. Maureira P, Vanhuyse F, Martin C, et al. Modified bentall procedure using two short grafts for coronary reimplantation: Long-term results. Ann Thorac Surg. 2012;93(2):443-9.
28. Mazzola A, Di Mauro M, Pellone F, et al. Freestyle aortic root bioprosthesis is a suitable alternative for aortic root replacement in elderly patients: a propensity score study. Ann Thorac Surg. 2012;94(4):1185-90.
29. Meharwal ZS, Khanna SN, Choudhary A, Misha M, Mehta Y, Trehan N. Ascending aortic aneurysm resection: 15 year's experience. Asian Cardiovasc Thorac Ann. 2006;14(4):300-5.
30. Milano AD, Pratali S, Mecozzi G, et al. Fate of coronary ostial anastomoses after the modified Bentall procedure. The Annals of thoracic surgery. 2003;75(6):1797-801.
31. Mingke D, Dresler C, Stone CD, Borst HG. Composite graft replacement of the aortic root in 335 patients with aneurysm or dissection. Thoracic and Cardiovascular Surgeon. 1998;46(1):12-9.
32. Nakahira A, Shibata T, Sasaki Y, et al. Outcome After the Modified Bentall Technique With a Long Interposed Graft to the Left Coronary Artery. Ann Thorac Surg. 2009;87(1):109-15.

33. Nardi P, Pellegrino A, Russo M, Saitto G, Bertoldo F, Chiariello L. Midterm results of different surgical techniques to replace dilated ascending aorta associated with bicuspid aortic valve disease. Ann Thorac Surg. 2013;96(5):1648-54.
34. Pacini D, Pantaleo A, Berretta P, et al. Long term results of aortic valve and root replacement in 1045 patients over thirty-three years. A single-centre experience. Circulation. 2011;124(21).
35. Panos A, Amahzoune B, Robin J, Champsaur G, Ninet J. Influence of technique of coronary artery implantation on long-term results in composite aortic root replacement. Ann Thorac Surg. 2001;72(5):1497-501.
36. Prifti E, Bonacchi M, Frati G, et al. Early and long-term outcome in patients undergoing aortic root replacement with composite graft according to the Bentall's technique. Eur J Cardiothorac Surg. 2002;21(1):15-21.
37. Radu NC, Kirsch EWM, Hillion ML, Lagneou F, Drouet L, Loisance D. Embolic and bleeding events after modified Bentall procedure in selected patients. Heart. 2007;93(1):107-12.
38. Ruvolo G, Fattouch K, Sinatra R, et al. Factors influencing immediate and long-term results after button's technique. J Cardiovasc Surg. 2002;43(3):337-43.
39. Schachner T, Vertacnik K, Nagiller J, Laufer G, Bonatti J. Factors associated with mortality and long time survival in patients undergoing modified Bentall operations. J Cardiovasc Surg. 2005;46(5):449-55.
40. Sioris T, David TE, Ivanov J, Armstrong S, Feindel CM. Clinical outcomes after separate and composite replacement of the aortic valve and ascending aorta. J Thorac Cardiovasc Surg. 2004;128(2):260-5.
41. Sokullu O, Sanioglu S, Orhan G, et al. New use of Teflon to reduce bleeding: In modified Bentall operation. Tex Heart Inst J. 2008;35(2):147-51.
42. Tabayashi K, Fukujyu T, Turu Y, et al. Replacement of the ascending aorta and aortic valve with a composite graft: operative and long-term results. Tohoku J Exp Med. 1998;184(4):257-66.
43. Tamura K, Arai H, Kawaguchi S, et al. Long-term results of modified bentall procedure using flanged composite aortic prosthesis. Ann Thorac Cardiovasc Surg. 2013;19(2):126-30.
44. Tsunekawa T, Ogino H, Matsuda H, et al. Composite Valve Graft Replacement of the Aortic Root: Twenty-Seven Years of Experience at One Japanese Center. Ann Thorac Surg. 2008;86(5):1510-7.
45. van Putte BP, Ozturk S, Siddiqi S, Schepens MA, Heijmen RH, Morshuis WJ. Early and late outcome after aortic root replacement with a mechanical valve prosthesis in a series of 528 patients. Ann Thorac Surg. 2012;93(2):503-9.
46. Zafar MA, Farkas EA, Javier A, Anderson M, Gilani O, Elefteriades JA. Are Thromboembolic and Bleeding Complications a Drawback for Composite Aortic Root Replacement? Annals of Thoracic Surgery. 2012;94(3):737-43.
47. Zehr KJ, Orszulak TA, Mullany CJ, et al. Surgery for aneurysms of the aortic root - A 30-year experience. Circulation. 2004;110(11):1364-71.

48. Nishida T, Sonoda H, Oishi Y, et al. More than 20-year experience of Bentall operation with mechanical prostheses for chronic aortic root aneurysm. Gen Thorac Cardiovasc Surg. 2014;63(2):78-85.
49. Varrica A, Satriano A, de Vincentiis C, et al. Bentall operation in 375 patients: long-term results and predictors of death. J Heart Valve Dis. 2014;23(1):127-34.
50. Vendramin I, Meneguzzi M, Sponga S, et al. Bicuspid aortic valve disease and ascending aortic aneurysm: should an aortic root replacement be mandatory?dagger. Eur J Cardiothorac Surg. 2015.
51. Treasure T, Takkenberg JJ, Golesworthy T, et al. Personalised external aortic root support (PEARS) in Marfan syndrome: analysis of 1-9 year outcomes by intention-to-treat in a cohort of the first 30 consecutive patients to receive a novel tissue and valve-conserving procedure, compared with the published results of aortic root replacement. Heart. 2014;100(12):969-75.
52. Caceres M, Ma Y, Rankin JS, et al. Evolving Practice Trends of Aortic Root Surgery in North America. Ann Thorac Surg. 2014.
53. Mingke D, Dresler C, Pethig K, Heinemann M, Borst HG. Surgical treatment of Marfan patients with aneurysms and dissection of the proximal aorta. J Cardiovasc Surg. 1998;39(1):65-74.
54. Benedetto U, Melina G, Takkenberg JJ, Roscitano A, Angeloni E, Sinatra R. Surgical management of aortic root disease in Marfan syndrome: a systematic review and meta-analysis. Heart. 2011;97(12):955-8.
55. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(23):2440-92.
56. Arabkhani B, Mookhoek A, Di Centa I, et al. Reported Outcome After Valve-Sparing Aortic Root Replacement for Aortic Root Aneurysm: A Systematic Review and Meta-Analysis. Ann Thorac Surg. 2015.

APPENDIX 1

Embase

(bentall:ab,ti OR ((('aorta valve'/de OR 'aorta valve replacement'/de OR 'aorta valve prosthesis'/de OR 'aorta valve disease'/exp OR (aort* NEAR/3 valv*):ab,ti) AND ('aorta root'/de OR 'aortic root surgery'/de OR (aort* NEAR/3 root*):ab,ti) AND ('ascending aorta'/de OR 'ascending aorta surgery'/de OR (ascend* NEAR/3 aort*):ab,ti)) AND (surgery/exp OR surgery:lnk OR (surg* OR graft* OR homograft* OR replace* OR composit* OR operat* OR postoperat*):ab,ti))) AND (survival/exp OR mortality/exp OR (surviv* OR mortal* OR 'death rate'):ab,ti) NOT ('case report'/de OR ('case report'):ab,ti)

MEDLINE

(bentall.ab,ti. OR ((("aortic valve"/ OR (aort* ADJ3 valv*).ab,ti.) AND ((aort* ADJ3 root*).ab,ti.) AND ((ascend* ADJ3 aort*).ab,ti.)) AND ("Surgical Procedures, Operative"/ OR surgery.xs. OR (surg* OR graft* OR homograft* OR replace* OR composit* OR operat* OR postoperat*).ab,ti.))) AND (survival/ OR exp mortality/ OR mortality.xs. OR (surviv* OR mortal* OR "death rate").ab,ti.) NOT ("case reports".pt. OR ("case report").ab,ti.)

PubMed as supplied by publisher

(bentall[tiab] OR ((((aort*[tiab] AND valv*[tiab])) AND ((aort*[tiab] AND root*[tiab])) AND ((ascend*[tiab] AND aort*[tiab])))) AND ((surg*[tiab] OR graft*[tiab] OR homograft*[tiab] OR replace*[tiab] OR composit*[tiab] OR operat*[tiab] OR postoperat*[tiab]))))) AND ((surviv*[tiab] OR mortal*[tiab] OR death rate*[tiab])) NOT (case reports[pt] OR (case report[tiab])) AND publisher[sb]

The Cochrane Collaboration

(bentall:ab,ti OR ((((aort* NEAR/3 valv*):ab,ti) AND ((aort* NEAR/3 root*):ab,ti) AND ((ascend* NEAR/3 aort*):ab,ti)) AND ((surg* OR graft* OR homograft* OR replace* OR composit* OR operat* OR postoperat*):ab,ti))) AND ((surviv* OR mortal* OR 'death rate'):ab,ti) NOT (('case report'):ab,ti)

Web of Science

TS=((bentall OR ((((aort* NEAR/3 valv*)) AND ((aort* NEAR/3 root*)) AND ((ascend* NEAR/3 aort*))) AND ((surg* OR graft* OR homograft* OR replace* OR composit* OR operat* OR postoperat*)))) AND ((surviv* OR mortal* OR "death rate")) NOT (("case report")))

APPENDIX 2

Variables	Description
First author	
Publication Year	
Journal	
Country	Country where patients were operated in
Operative period	
Patient Number	
Follow-up	Mean in years; calculated from median and interquartile range when mean was not given
Age	Mean in years; calculated from median and interquartile range when mean was not given
Sex	
CTD	
BAV	
Prior cardiac surgery	
Prior aortic valve surgery	
Acute type A dissection	As indication for Bentall procedure
Acute infective endocarditis	As indication for Bentall procedure
Emergency surgery	Within 24 hours after diagnosis
Homograft surgery	Patients with non-Bentall procedures
Valve-sparing surgery	Patients with non-Bentall procedures
Other surgery	Patients with non-Bentall procedures
Mechanical prosthesis	Valve choice for Bentall procedure
Bioprosthesis	Valve choice for Bentall procedure
Aortic hemiarch repair	
Aortic arch repair	
CABG	
Mitral valve surgery	
Reexploration for bleeding	In-hospital or within 30 days post-operatively
Early mortality	In-hospital mortality and 30 days mortality
Late mortality	According to guidelines (5)
Root reoperation	According to guidelines (5)
Hemorrhage	According to guidelines (5)
Thromboembolism	According to guidelines (5)
Endocarditis	According to guidelines (5)
MAVRE	Composite of late valve-related mortality, reoperation, hemorrhage, thromboembolism and endocarditis

CTD indicates connective disease; BAV, bicuspid aortic valve; CABG, coronary artery bypass grafting; MAVRE, major adverse valve-related events.

APPENDIX 3

First author	Publication year	Country	Operative period	Patients (N)	Mean age (years)	Sex (% female)	Mean follow-up (years)
Mingke	1998	Germany	1979-1996	79	33,8	30%	5,7
Tabayashi	1998	Japan	1974-1995	49	48,1		5,6
Gott	1999	United States	1968-1996	675	34	30%	6,7
Luciani	1999	Italy		190	54,5	22%	5,5
Malashenkov	2000	Russia	1989-1999	144	38,7	27%	4,3
Alexiou	2001	United Kingdom	1972-1998	65	41,7	37%	8
Panos	2001	France	1985-1999	150	55	21%	5,9
Aomi	2002	Japan	1980-1999	193	43,2	34%	5,8
Prifti	2002	Italy	1989-2000	212	56	26%	4,9
Ruvolo	2002	Italy	1989-1999	105	55,1	21%	4,3
Byrne	2003	United States	1992-2001	85		21%	4
Gelsomino	2003	Italy	1986-2002	45	58,7	16%	7,3
Milano*	2003	Italy	1993-1999	71	63	18%	4,1
Pacini	2003	Italy	1978-2001	274	53,5	20%	5,2
Brandt	2004	Germany	1981-2000	84	52,2	20%	10,4
Carrel	2004	Switzerland	1990-2003	71	29	45%	5,2
Karck	2004	Germany	1979-2012	74	35	34%	9,5
Sioris	2004	Canada	1990-2001	452	52,2	23%	4,4
Zehr	2004	United States	1971-2000	203	53	25%	7,3
Schachner	2005	Austria	1986-2002	74	48	18%	4,1
Meharwal	2006	India	1989-2004	148	46,2	12%	8,5
Kindo	2007	France	1975-2002	162	51,3	19%	6,1
Radu	2007	France	1993-2003	100	51	13%	4,4
Sokullu	2008	Turkey	2000-2006	44	53,4	16%	4,8

First author	Publication year	Country	Operative period	Patients (N)	Mean age (years)	Sex (% female)	Mean follow-up (years)
Tsunekawa	2008	Japan	1978-2005	273	47,5	34%	8,8
Caynak	2009	Turkey	1997-2007	54	57,9	11%	5
Mataraci	2009	Turkey	1993-2008	254	48,3	19%	6,3
Nakahira	2009	Japan	1992-2007	40	54,7	20%	5,7
Etz	2010	United States	1995-2008	290	51,3	20%	8,2
Gao	2011	China	1984-2008	125		25%	4
Joo	2012	Korea	1982-2010	218	44,4	31%	9
Lim	2012	Korea	1999-2009	72	49	38%	4,9
Maureira	2012	France	1995-2009	153	57	14%	5,8
Mazzola	2012	Italy	2001-2010	106	56	12%	4,5
Van Putte	2012	The Netherlands	1974-2008	528	53,8	24%	9
Zafar	2012	United States	1995-2011	242	52,8	19%	4,7
Dunne	2013	Australia	1999-2009	89	54	21%	5,6
Etz	2013	United States	1998-2011	448	52,8	21%	5,8
Girdauskas	2013	Germany	1995-2005	79	52,3	19%	9,1
Kim	2013	Korea	1997-2010	195	50,5	29%	
Nardi	2013	Italy	2005-2011	46	51	11%	4,2
Tamura	2013	Japan	1984-2010	73	52,7	34%	7
Van Duffel	2013	Belgium	1988-2012	72	64,8	36%	5,4
Varrica	2014	Italy	90-07	375	57,2	21%	8,2
Nishida	2015	Japan	75-13	71	50,1	18%	9,4
Vendramin	2015	Italy	94-10	77	55,7	9%	8,8

* Not included in analysis of early mortality, only patients who survived to discharge from hospital were included.

APPENDIX 4

First author	Publication year	Late mortality % / year	Root reoperation % / year	Hemorrhage % / year	Thromboembolism % / year	Endocarditis % / year	MAVRE % / year
Mingke	1998	2,23	0,89	0,45		0,45	
Tabayashi	1998	2,19			2,55		
Gott	1999	2,52			0,60	0,53	
Luciani	1999	0,94	0,31	0,31	0,16	0,16	0,63
Malashenkov	2000	1,96	0,49				
Alexiou	2001	2,89	0,39	0,96	0,96	0,19	2,89
Panos	2001	1,13	0,57				
Aomi	2002	2,31	0,35		1,42		
Prifti	2002					0,48	
Ruvolo	2002	2,72	1,02	0,34	0,34	0,68	3,06
Byrne	2003	2,94	0,59	0,59	0,59	0,59	2,35
Gelsomino	2003	1,30	0,22	0,11		0,43	
Milano	2003	1,72	0,17				
Pacini	2003	3,98	0,42	0,91	0,63	0,35	3,84
Brandt	2004		0,06				
Carrel	2004	0,81	0,81				
Karck	2004		0,85	1,71	0,71		
Sioris	2004	2,26	0,55	1,01	1,26	0,40	3,82
Zehr	2004	2,36	1,21	0,27	0,54	0,13	2,90
Schachner	2005	1,85	0,37	0,18	0,18	0,37	0,74
Meharwal	2006	1,43	0,24				
Kindo	2007	4,47	0,51	1,32	1,02	0,30	4,37
Radu	2007	2,75	0,11	2,29	3,21	0,11	5,95

First author	Publication year	Late mortality % / year	Root reoperation % / year	Hemorrhage % / year	Thromboembolism % / year	Endocarditis % / year	MAVRE % / year
Sokullu	2008	0,47	0,24				
Tsunekawa	2008	1,87	1,00	0,58	0,33	0,41	2,90
Caynak	2009	1,12	0,37			0,37	
Mataraci	2009	0,44	0,03	0,13	0,03	0,19	0,50
Nakahira	2009	2,19		0,44		1,32	
Etz	2010	2,12	0,09				
Gao	2011	2,03	2,03	0,20		0,20	
Joo	2012	2,19	0,10	0,41		0,15	
Lim	2012	1,42	0,28	1,13	0,14	0,14	1,70
Maureira	2012	2,43	0,21	1,27	0,42	0,21	3,07
Mazzola	2012	1,66	0,10	0,10	0,62		
Van Putte	2012				1,62	0,42	
Zafar	2012	1,69		0,89	1,07	0,27	
Dunne	2013	1,01	0,10			0,40	
Etz	2013	3,62	0,54	0,19	0,77		
Girdauskas	2013	1,74	0,58	0,14	0,87	0,58	3,19
Kim	2013	1,27	0,17	1,87	0,59	0,25	3,23
Nardi	2013	1,57	0,26	0,52	0,52	0,52	1,57
Tamura	2013	2,36	0,20	0,10	0,10		
Van Duffel	2013	1,80	0,13	0,52	0,26		
Varrica	2014	3,30	0,15	1,20	0,75	0,30	3,15
Nishida	2015	2,23	0,15	0,07	0,07	0,15	1,04
Vendramin	2015	1,04	0,42	0,02	0,59	0,29	1,56

Linearized occurrence rates of late outcome events. MAVRE indicates major adverse valve-related events.

“It does not take much strength
to do things, but it requires
a great deal of strength
to decide what to do”

Elbert Hubbard

4.

Quality of life and prosthetic aortic valve selection in non-elderly adult patients

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ABSTRACT

Objectives. This study assesses quality of life in relation to prosthetic aortic valve selection and preferences for shared decision-making among non-elderly adult patients after aortic valve replacement (AVR).

Methods. A single-center consecutive cohort of 497 AVR patients who underwent AVR between the age of 18 and 60 years was cross-sectionally surveyed 1-10 years after AVR. Health-related quality of life (SF-36), valve-specific quality of life, patient experience with and preferences for involvement and final decision in prosthetic valve selection were investigated.

Results. Two-hundred and forty patients (48%) responded. Median age was 57 years (range 26-70). Compared to the general age-matched Dutch population, AVR patients reported a worse physical health, but better mental health. Biological valve recipients reported a lower general health than mechanical valve recipients. Mechanical valve recipients had more doubts about the decision to undergo surgery, were more bothered by valve sound, the frequency of doctor visits and blood tests, and possible bleeding, but were less afraid of a possible reoperation. Eighty-nine percent were of the opinion that it is important to be involved in prosthetic valve selection, whereas 64% agreed they actually had been involved. A better patient experience with involvement in prosthetic valve selection was associated with better mental health (p=0.036).

Conclusions. Given the observed suboptimal patient involvement in prosthetic valve selection, the broad patient support for shared decision-making, and the positive association between patient involvement in prosthetic valve selection and mental health, tools to support shared decision-making would be useful in the setting of heart valve replacement.

INTRODUCTION

For non-elderly adult patients who require aortic valve replacement (AVR), 2 types of valve substitutes are available: mechanical and biological valves. Mechanical valves are designed to last a lifetime but require lifelong anticoagulation due to their increased thrombogenicity, resulting in an increased bleeding risk and increased risk of complications during pregnancy. Additionally, patients may notice the typical mechanical valve closing sound. Biological valves do not require long-term anticoagulation, unless another indication is present. However, they are subject to valve deterioration over time, and in particular younger patients may require one or more reoperations later in life.

Additionally, valve repair is now becoming available for younger patients with aortic regurgitation, and is currently being evaluated [1]. Aortic valve repair is showing promise for use in younger patients, but more long-term information is needed.

Several factors play a role in the selection of a prosthetic valve type for AVR, such as patient age, life expectancy, valve durability, hemodynamic properties, surgical risk and (contra) indications for anticoagulation use. Furthermore, for non-elderly adult patients factors like an active lifestyle or a pregnancy wish should be taken into consideration. Given the different nature of mechanical versus biological prosthetic valve-related risks and benefits, the 2014 ACC/AHA Valvular Heart Disease Guidelines state that the choice of a prosthetic valve type should be a shared decision process, while the 2012 ESC/EACTS guidelines highlight the importance of considering informed patient preferences in prosthetic valve selection (Class 1 indication) [2, 3].

Particularly younger patients who require AVR are facing a difficult choice given their long life expectancy and active lifestyle. Prosthetic valve type may influence quality of life of patients, although there is no consensus in the literature [4-7]. In this light we cross-sectionally investigated quality of life in patients after AVR, who were between the age of 18 and 60 years at the time of AVR in our institution. Since it has been shown in cancer decision-making research that patient participation in clinical decision-making may improve quality of life [8], we additionally investigated patient experience with involvement in prosthetic valve selection and preferences for involvement and final decision in prosthetic valve selection in relation to observed quality of life.

MATERIALS AND METHODS

This study was approved by the institutional review board (Erasmus MC MEC nr. 2012-163) and written informed consent was obtained from all participants. Between 1 January 2001 and 3 December 2011 a total of 583 consecutive patients between the age of 18 and 60 underwent AVR in our institution. The civil status of all patients was checked through the civil registry. Patients who were alive at the time of the study with an available postal address (N=497; 85%) were approached by mail and requested to complete and return a postal questionnaire.

Information on patient characteristics, perioperative clinical and procedural characteristics, and events during follow-up (gender, date of birth, preoperative NYHA class, date of surgery, urgency of surgery, concomitant procedures, reoperation, and valve-related events (structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, endocarditis)) was collected from hospital records.

The questionnaire consisted of questions about educational level, NYHA class, health-related quality of life, valve-specific quality of life, patient experience with involvement in prosthetic valve selection, and preferences for involvement and final decision in prosthetic valve selection. Educational level and NYHA class were assessed with multiple choice questions.

Health-related quality of life was assessed with the Dutch version of the Short Form Health Survey (SF-36) [9, 10]. This questionnaire consists of 36 health-related questions, grouped into eight domains: physical functioning, role limitations because of physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations because of emotional problems, and general mental health. The Physical Component Scale (PCS) is a summary scale consisting of the physical functioning, physical role functioning, bodily pain and general health scales. The Mental Component Scale (MCS) is a summary scale composed of vitality, social functioning, emotional role functioning, and mental health indexes. Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores and then transforming the scores to a scale from 0 to 100. The mean score of the PCS and MCS is 50 with a standard deviation of 10. A higher score represents a better health status [11].To compare quality of life between the study patients and the general Dutch population the results of the MORGEN Study were used [12]. Valve-specific quality of life was assessed with 7 valve-specific questions [5].

Patient experience with involvement in prosthetic valve selection and their preferences for involvement and final decision in prosthetic valve selection were assessed with multiple choice questions and a Control Preferences scale [13, 14]. For a detailed description, see Appendix 1.

Statistical methods

Continuous variables were displayed by the mean and standard deviation if normally distributed and by the median and range if there was no normal distribution. The distribution of the continuous variables was tested using the Kolmogorov-Smirnov test. Group comparison was done using the unpaired t-test or the Mann-Whitney U-test in case of ordinal data or no normal distribution.

Categorical variables were displayed as counts and percentages. Group comparison was done using the Chi-Square test or the Fisher Exact test where appropriate.

The one-sample t-test was used to compare health-related quality of life between the study population and the general Dutch population mean.

A general linear model (GLM) with bootstrap method was used to assess the association between time since surgery and: (1) health-related quality of life, (2) patient experience with involvement in prosthetic valve selection, and (3) their preferences for involvement and final decision in prosthetic valve selection.

The same method (GLM with bootstrap) was used to assess the association between health-related quality of life and: (1) patient experience with involvement in prosthetic valve selection, and (2) their preferences for involvement and final decision in prosthetic valve selection [15].

All tests were 2-sided, and a p-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using IBM-SPSS 20 (IBM Corp., Armonk, NY).

RESULTS

In total, 240 patients (48%) returned the questionnaire. These patients received the following types of aortic valves prostheses: 190 mechanical valves, 26 bioprostheses, 19 allografts and 3 autografts. Two patients underwent an aortic valve repair. Bioprostheses, allografts, autografts, and aortic valve repair were combined to one group called 'biological valves' for further analyses.

Perioperative clinical and procedural characteristics are presented in Table 1. Patient characteristics at the time of the questionnaire are presented in Table 2.

TABLE 1. Perioperative clinical and procedural characteristics

	All (n=240)	**Mechanical (n=190)**	**Biological (n=50)**
Preoperative NYHA class, n (%)[a]			
I	70 (30)	54 (30)	16 (32)
II	94 (41)	73 (40)	21 (42)
III	52 (23)	41 (23)	11 (22)
IV	15 (7)	13 (7)	2 (4)
Emergency surgery, n(%)			
Yes	34 (14)	27 (14)	7 (14)
No	206 (86)	163 (86)	43 (86)
Concomitant procedures, n(%)[b]			
Yes	109 (45)	79 (42)	30 (60)
No	131 (55)	111 (58)	20 (40)

[a]n=231. [b]p<0.05 mechanical valves versus biological valves.

TABLE 2. Patient characteristics at the time of the questionnaire

	All (n=240)	**Mechanical (n=190)**	**Biological (n=50)**
Males, n (%)	177 (73)	141 (73)	36 (72)
Age (years)[a]	57 (26-70)	57 (26-70)	58 (27-69)
Educational level, n (%)[b, c]			
< High school	41 (17)	37 (20)	4 (8)
High school graduate	112 (48)	91 (49)	21 (44)
College graduate	69 (29)	48 (26)	21 (44)
Other	13 (6)	11 (6)	2 (4)
Time since surgery (years)[a, c]	7 (0-11)	6 (0-11)	10 (0-11)
NYHA class, n (%)[d]			
I	145 (61)	117 (63)	28 (57)
II	66 (28)	53 (28)	13 (27)
III	21 (9)	14 (7)	7 (14)
IV	4 (2)	3 (2)	1 (2)

[a]Values are median (range). [b]n=235. [c]p<0.05 mechanical valves versus biological valves. [d]n=236.

For a detailed description of the patient characteristics by biological valve type, see Appendix 2. The 240 patients who returned the questionnaire were older compared to non-responding patients (median age: 57 (range 26-70) versus 54 years (range 19-71) respectively; p=0.003) and more often males (73% versus 62% respectively; p=0.005). Five percent of the participating patients underwent a reoperation after their primary AVR, and 6% experienced a valve-related event (2 paravalvular leak, 2 embolism, 4 bleeding and 6 endocarditis), with no difference between mechanical and biological valve recipients.

Health-related quality of life is presented in Table 3.

TABLE 3. Health-related quality of life (SF-36)a

	All (n=240)	**Mechanical (n=190)**	**Biological (n=50)**
Physical Functioning	49 ± 10	49 ± 10	49 ± 11
Role-Physical	47 ± 15	47 ± 15	43 ± 16
Bodily Pain	54 ± 10	54 ± 9	54 ± 10
General health[b]	47 ± 11	48 ± 11	44 ± 12
Vitality	54 ± 10	55 ± 10	53 ± 10
Social functioning	50 ± 10	51 ± 9	48 ± 11
Role-Emotional	49 ± 15	49 ± 14	48 ± 15
Mental health	53 ± 10	53 ± 10	52 ± 10
PCS	48 ± 10	48 ± 9	46 ± 12
MCS	53 ± 10	53 ± 10	52 ± 10

aValues are mean ± SD.
bp<0.05 mechanical valves versus biological valves.
MCS = Mental Component Scale. PCS = Physical Component Scale.

Compared to the general age-matched Dutch population, AVR patients scored lower on the PCS (p<0.001), but higher on the MCS (p<0.001). A longer time since surgery was associated with a higher MCS (p=0.037). Other patient characteristics, perioperative clinical and procedural characteristics, and follow-up events were not associated with quality of life. The results of the valve-specific questionnaire are presented in Table 4.

Patient experience with involvement in prosthetic valve selection is presented in Table 5.

TABLE 4. Valve-specific quality of life

	All (n=240)	**Mechanical (n=190)**	**Biological (n=50)**
If I had to do it over again, would I make the same decision to have surgery?[a]			
Yes	71%	67%	84%
Probably	20%	23%	8%
I don't know	6%	8%	2%
Probably not	1%	1%	2%
No	2%	2%	4%
Is there a valve sound that bothers me?[a]			
Never	44%	35%	80%
Rarely	18%	21%	8%
Occasionally	26%	30%	8%
Frequently	6%	6%	2%
Always	7%	8%	2%
Following my valve surgery, the frequency of doctor visits and blood tests bothers me.[a]			
Never	49%	46%	61%
Rarely	16%	15%	18%
Occasionally	27%	30%	12%
Frequently	4%	5%	
Always	4%	3%	8%
The possibility of complications due to my implanted valve concerns me.			
Never	43%	44%	39%
Rarely	28%	29%	25%
Occasionally	24%	21%	35%
Frequently	3%	3%	2%
Always	3%	3%	-
I am concerned about possible bleeding caused by my anticoagulant medication.[a]			
Never	39%	31%	67%
Rarely	25%	27%	14%
Occasionally	28%	31%	16%
Frequently	6%	7%	-
Always	3%	3%	2%
I am afraid that my valve may fail.			
Never	57%	59%	49%
Rarely	23%	22%	27%
Occasionally	17%	15%	25%
Frequently	2%	2%	-
Always	1%	2%	-
I am afraid that I may need another valve operation.[a]			
Never	45%	48%	33%
Rarely	27%	28%	23%

TABLE 4. (continued)

	All (n=240)	Mechanical (n=190)	Biological (n=50)
Occasionally	22%	21%	27%
Frequently	3%	2%	6%
Always	4%	2%	10%

[a]p<0.05 mechanical valves versus biological valves.

TABLE 5. Patient experience with involvement in prosthetic valve selection

	All (n=240)	Mechanical (n=190)	Biological (n=50)
Do you know there are different prosthetic valve types?			
Yes	93%	92%	96%
No	7%	8%	4%
The doctor has involved me in prosthetic valve selection.			
(Totally) agree	64%	62%	74%
Not agree/disagree	8%	9%	4%
(Totally) disagree	21%	23%	14%
Not applicable	17%	7%	8%
I know the risks and benefits of different prosthetic valve types.			
(Totally) agree	73%	70%	82%
Not agree/disagree	8%	8%	4%
(Totally) disagree	16%	18%	10%
Not applicable	4%	4%	4%
I have received enough information to make a deliberate choice.			
(Totally) agree	60%	59%	62%
Not agree/disagree	11%	11%	12%
(Totally) disagree	21%	22%	16%
Not applicable	9%	9%	10%
I think it is important to be involved in prosthetic valve selection.[a]			
(Totally) agree	89%	87%	96%
Not agree/disagree	9%	10%	4%
(Totally) disagree	2%	3%	-
I am satisfied with my prosthetic aortic valve.			
(Totally) agree	89%	89%	92%
Not agree/disagree	8%	9%	6%
(Totally) disagree	3%	3%	2%

[a]p<0.01 mechanical valves versus biological valves.

There was no association between time since surgery and patient experience with involvement in prosthetic valve selection.

Patient preference for final decision in prosthetic aortic valve selection is presented in Figure 1.

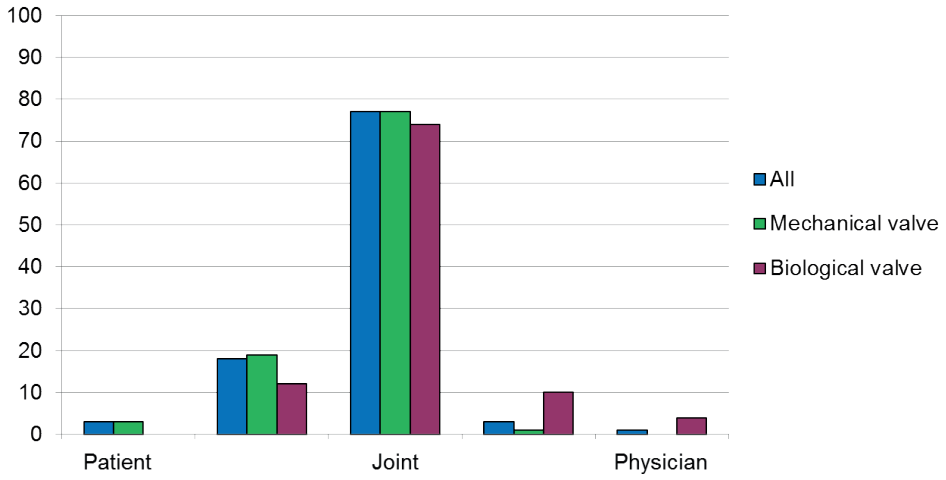

FIGURE 1. Displays patient preference for final decision in prosthetic aortic valve choice. Difference between mechanical and biological valves: $p<0.01$.

There was no association between time since surgery and patient preferences for involvement and final decision in prosthetic valve selection.

A better patient experience with involvement in prosthetic valve selection was associated with a higher MCS ($p=0.036$). Patient preferences for involvement and final decision in prosthetic valve selection were not associated with health-related quality of life.

DISCUSSION

Non-elderly adult patients who require AVR are facing a complex choice with regard to type of valve prosthesis. Factors such as potential desire to become pregnant, lifestyle and occupation, cultural and social factors, other cardiac issues, or multiple prior operations need consideration in the selection of a prosthetic valve [16]. Because

prosthetic valve selection is a value-sensitive decision that may have a great impact on quality of life, informed patient preferences should be carefully considered in a shared decision making process [2, 3].

This cross-sectional study shows that in particular mental health is good in non-elderly adult AVR patients, while physical health is worse compared to the general Dutch population. As expected, valve-specific quality of life differs considerably between mechanical and biological valve recipients, and is driven by valve type specific limitations.

This study also highlights that there is ample room for improvement in the quality of decision making in the setting of prosthetic aortic valve selection: 9 out of 10 patients find it important to be involved in prosthetic valve selection but only two-third of patients actually feels involved, only 40% of patients feel that they received insufficient information, and importantly: patient involvement is associated with a better mental health.

The present study shows that non-elderly adult AVR patients have a good perceived quality of life. This is consistent with previous studies in young adults after valve replacement [17] and surgical correction for congenital heart disease [18, 19]. Compared to the general Dutch population, non-elderly adult AVR patients experience a worse physical health, but a better mental health. One might hypothesize that AVR patients experience a better mental health than the general Dutch population due to the phenomenon of response shift: patients have different internal standards and values after a life-threatening experience, such as cardiac surgery [18, 20]. The results of this study show that a longer time since surgery seems to be associated with better mental health. This may be due to the fact that patients get used to their life with a prosthetic valve, and accept the limitations. In the literature there is no consensus about whether prosthetic valve type influences quality of life [4-7]. In our study biological valve recipients have more impairments in subjective general health than mechanical valve recipients. The reason for this difference remains to be elucidated. It may be that the observed longer time since surgery and the increased anxiety regarding the prospect of another valve operation among biological valve recipients play a role.

The valve-specific questionnaire reveals that patients with a mechanical valve have in retrospect more doubts about the decision to undergo surgery, are more disturbed by valve sound and the frequency of doctor visits and blood tests, and more concerned about bleeding. These differences can be explained by the different nature of mechanical versus biological prosthetic valve-related risks and benefits. Surprisingly, 12% of

biological valve recipients are disturbed by valve sound. A previous study, reporting that 8% (n=125) of patients with an aortic valve repair or autograft implantation were bothered by valve sound, hypothesizes that patients possibly exhibit a high degree of attention to their heart function [5]. In our study 19% percent of mechanical valve recipients are afraid of valve failure and as much as 25% are afraid that they may need another valve operation. Mechanical valves are designed to last a lifetime and the risk of a reoperation after mechanical valve implantation is much lower but not absent compared to biological valves, so it is remarkable that a considerable amount of mechanical valve patients is afraid that their valve might fail. Maybe this fear is due to a lack of information or the inability to comprehend the information that was provided at the time of surgery.

In this study almost one-third of patients are of the opinion that they did not receive enough information to contribute to a deliberate choice. This confirms observations in other studies: patients are often not well informed about the risks and benefits associated with treatments [21, 22]. Well-informed patients are essential for engagement in shared decision making. Only when patients understand the risks and benefits associated with the different treatment options they can weigh these risks and benefits in their own context and contribute to a deliberate choice between treatment options. In this respect there seems to be room for improvement in the information transfer to patients who face AVR. It is known that shared decision making improves patient understanding of the available treatment options, increases the proportion of patients with realistic expectations of risks and benefits, stimulates patient involvement in decision making, and improves agreement between patient values and treatment choices (23). In the field of heart valve disease, current clinical practice guidelines advocate shared decision making in prosthetic valve selection (2, 3). Despite that, the application of shared decision making still remains a challenge. The vast majority of patients in the current study are of the opinion that it is important to be involved in prosthetic valve selection, whereas one-third of patients do not feel involved in the decision making process. This finding is in line with previous research, showing that shared decision making is not often applied in daily clinical practice in a variety of medical conditions (21, 22), and calls for tools for clinicians and patients to engage in shared decision making in their routine practice. The use of a decision aid to support shared decision making may be particularly useful in this setting. A decision aid improves the decision making process by increasing knowledge, improving risk communication, reducing decisional conflict, increasing participation, and increasing the chance that a patient receives care that is in line with their personal values (23). Perhaps frequently, a clinician will bias the presentation of the treatment options according to his or her opinion or 'favorite' procedure. A decision aid encourages a clinician to present a scientifically unbiased presentation.

Of course, preferences for involvement in prosthetic valve selection may vary among patients. Biological valve recipients in this study tend towards an active patient role than mechanical valve recipients. This difference may be due to the fact that biological valve recipients in this study are higher educated than mechanical valve recipients, as it is known that more educated patients often prefer a more active patient role than patients with a lower education (24). Even if patients prefer a passive role in decision making, they should at least be informed about the pros and cons of the different treatment options. Providing patients with information, for example through a decision aid, also stimulates them to take a more active role in decision making (23).

Patient participation in cancer decision making may improve quality of life (8), and the present study also shows that perceived involvement in prosthetic valve selection is associated with better mental health. From cancer research it is known that making decisions regarding health care is important for patients and patients prefer to have some control (25). In the setting of prosthetic valve selection a lack of patient involvement may cause uncertainty which may have a negative impact on patient well-being.

In this study, standard aortic valve procedures were primarily investigated because longer follow-up times were available. But of course, other options, such as aortic valve repair, are gaining interest and reportedly have good intermediate-term results, including quality of life outcomes (1, 5).

Study limitations

This is a single center study that represents clinical practice in a university hospital in the Netherlands. Questionnaires were completed 1 to 10 years after AVR. Due to this wide time range, the accuracy and completeness of the answers may have been influenced by recall bias. Also, the wide time range ignores that there may be temporal trends in quality of life –as was found to be significant for MCS– and patient experience with decision making. Selection bias may have occurred, because only 48% of the total population responded and responding patients were older and more often male compared to non-responding patients. With regard to patient experience with involvement in prosthetic valve selection patients had the option to choose 'not applicable' in the questionnaire. This term could be misinterpreted by patients, since several patients chose 'not applicable' because their doctor made the decision with regard to prosthetic valve type. This also applies to the questions about information provision. It is recommended that the option 'not applicable' is not added to future questionnaires. We did not ask mechanical valve recipients about their compliance to anticoagulation therapy. Therefore we were unable to address the possible association between anticoagulation adherence and quality of life and patient experience with

decision making. Due to the observational character of the study, it is possible that other factors may have influenced the association between patient involvement and mental health.

Conclusions

Non-elderly adult patients after AVR experience an impaired physical health but a better mental health compared to the general age-matched population, and valve type-specific risks may influence perceived health. Given the observed suboptimal patient involvement in prosthetic valve selection, the broad support among patients for shared decision making in the setting of prosthetic valve selection, and the positive association between patient involvement and mental health, tools to support shared decision making may be useful to improve the quality of decision making.

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The authors would like to thank all the patients who participated in this study.

REFERENCES

1. de Meester C, Pasquet A, Gerber BL, Vancraeynest D, Noirhomme P, El Khoury G et al. Valve repair improves the outcome of surgery for chronic severe aortic regurgitation: a propensity score analysis. J Thorac Cardiovasc Surg 2014;148:1913-20.
2. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology, European Association for Cardiothoracic Surgery, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451-2496.
3. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-643.
4. Notzold A, Huppe M, Schmidtke C, Blomer P, Uhlig T, Sievers HH. Quality of life in aortic valve replacement: Pulmonary autografts versus mechanical prostheses. J Am Coll Cardiol 2001;37:1963-1966.
5. Aicher D, Holz A, Feldner S, Kollner V, Schafers HJ. Quality of life after aortic valve surgery: Replacement versus reconstruction. J Thorac Cardiovasc Surg 2011;142:e19-24.
6. Sedrakyan A, Hebert P, Vaccarino V, Paltiel AD, Elefteriades JA, Mattera J et al. Quality of life after aortic valve replacement with tissue and mechanical implants. J Thorac Cardiovasc Surg 2004;128:266-272.
7. Perchinsky M, Henderson C, Jamieson WR, Anderson WN Jr, Lamy A, Lowe N et al. Quality of life in patients with bioprostheses and mechanical prostheses. Evaluation of cohorts of patients aged 51 to 65 years at implantation. Circulation 1998;98:II81-86.
8. Atherton PJ, Smith T, Singh JA, Huntington J, Diekmann BB, Huschka M et al. The relation between cancer patient treatment decision making roles and quality of life. Cancer 2013;119:2342-2349.
9. Ware JE, Jr., Sherbourne CD. The mos 36-item short-form health survey (sf-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.
10. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R et al. Translation, validation, and norming of the dutch language version of the sf-36 health survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-1068.
11. Ware JE Jr., Kosinski M, Bjorner JB, Turner DM, Gandek B, Maruish ME. User's Manual for the SF-36v2 TM Health Survey (2nd ed.). Lincoln RI: Quality Metric Incorporated, 2007.
12. Smit HA, Verschuren WMM, Bueno de Mesquita HB, Seidell JC. Monitoring van Risicofactoren en Gezondheid in Nederland (MORGEN-project): Doelstellingen en werkwijze. Bilthoven: RIVM, 1994.
13. Degner LF, Sloan JA, Venkatesh P. The control preferences scale. Can J Nurs Res 1997;29:21-43.

14. Pieterse AH, Baas-Thijssen MC, Marijnen CA, Stiggelbout AM. Clinician and cancer patient views on patient participation in treatment decision making: A quantitative and qualitative exploration. Br J Cancer 2008;99:875-882.
15. Efron B, Tibshirani R. An introduction to the bootstrap. Monographs on statistics and applied probability. New York: Chapman & Hall, 1993.
16. Jaquiss RDB. Bioprosthetic aortic valve replacement in the young: a cautionary tale. Circulation 2014;130:7-9.
17. Ruel M, Kulik A, Lam BK, Rubens FD, Hendry PJ, Masters RG et al. Long-term outcomes of valve replacement with modern prostheses in young adults. Eur J Cardiothorac Surg 2005;27:425-433.
18. Opić P, Roos-Hesselink JW, Cuypers JA, Witsenburg M, van den Bosch A, van Domburg RT et al. Psychosocial functioning of adults with congenital heart disease: Outcomes of a 30-43 year longitudinal follow-up. Clin Res Cardiol 2015;104:388-400
19. Mokhles MM, van de Woestijne PC, de Jong PL, Witsenburg M, Roos-Hesselink JW, Takkenberg JJ et al. Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit. Eur J Cardiothorac Surg 2011;40:571-578.
20. Moons P. Quality of life in adults with congenital heart disease: Beyond the quantity of life. Leuven: P. Moons, 2004.
21. Hauptman PJ, Chibnall JT, Guild C, Armbrecht ES. Patient perceptions, physician communication, and the implantable cardioverter-defibrillator. JAMA Intern Med 2013;173:571-577.
22. Zikmund-Fisher BJ, Couper MP, Singer E, Ubel PA, Ziniel S, Fowler FJ Jr et al. Deficits and variations in patients' experience with making 9 common medical decisions: The decisions survey. Med Decis Making 2010;30:85S-95S.
23. Stacey D, Légaré F, Col NF, Bennett CL, Barry MJ, Eden KB et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2014;1:CD001431.
24. Levinson W, Kao A, Kuby A, Thisted RA. Not all patients want to participate in decision making. A national study of public preferences. J Gen Intern Med 2005;20:531-535.
25. Hodgkinson K, Butow P, Hunt GE, Pendlebury S, Hobbs KM, Wain G. Breast cancer survivors' supportive care needs 2-10 years after diagnosis. Support Care Cancer 2007;15:515-523.

APPENDIX 1

1. Are you aware that there are different prosthetic valve types?
   - o Yes
   - o No

2. The doctor has involved me in prosthetic valve selection.
   - o Totally agree
   - o Agree
   - o Not agree/not disagree
   - o Disagree
   - o Totally disagree
   - o Not applicable

3. I know the risks and benefits of different prosthetic valve types.
   - o Totally agree
   - o Agree
   - o Not agree/not disagree
   - o Disagree
   - o Totally disagree
   - o Not applicable

4. I have received enough information from my doctor with regard to the different types of aortic valve prostheses to make a deliberate choice.
   - o Totally agree
   - o Agree
   - o Not agree/not disagree
   - o Disagree
   - o Totally disagree
   - o Not applicable

5. I think it is important to be involved in prosthetic valve selection.
   - o Totally agree
   - o Agree
   - o Not agree/not disagree
   - o Disagree
   - o Totally disagree

6. The final decision in prosthetic aortic valve choice should be made by:
    - o The physician
    - o Mainly the physician
    - o The physician and patient together
    - o Mainly the patient
    - o The patient

7. I am satisfied with my prosthetic aortic valve.
    - o Totally agree
    - o Agree
    - o Not agree/not disagree
    - o Disagree
    - o Totally disagree

APPENDIX 2

	All (n=240)	**Mechanical (n=190)**	**Biological (n=26)**	**Allograft (n=19)**	**Autograft (n=3)**	**Repair (n=2)**
Males, n (%)	177 (73)	141 (73)	21 (81)	11 (58)	3 (100)	1 (50)
Age (years)[a]	57 (26-70)	57 (26-70)	57 (27-69)	61 (38-69)	40 (34-67)	49 (40-58)
NYHA class, n (%)[b]						
I	145 (61)	117 (63)	16 (62)	9 (50)	2 (67)	1 (50)
II	66 (28)	53 (28)	6 (23)	6 (33)	1 (33)	-
III	21 (9)	14 (7)	3 (12)	3 (17)	-	1 (50)
IV	4 (2)	3 (2)	1 (4)	-	-	-
Educational level, n (%)[c]						
< High school	41 (17)	37 (20)	1 (4)	3 (16)	-	-
High school graduate	112 (48)	91 (49)	10 (42)	8 (42)	3 (100)	-
College graduate	69 (29)	48 (26)	13 (54)	7 (37)	-	1 (50)
Other	13 (6)	11 (6)	-	1 (5)	-	1 (50)
Time since surgery (years)[a]	7.2 ± 6	6.3 ± 5.4	6.4 ± 5.4	10.6 ± 0.8	11.3	10.7

[a]Values are median (range). [b]n=236. [c]n=235.

“We all make choices,
but in the end our
choices make us”

Ken Levine

5.

A Devilish Dilemma

Korteland NM, Takkenberg JJ, Bogers AJ, Roos-Hesselink JW

Interactive CardioVascular and Thoracic Surgery. 2017 Apr 1;24(4):641-642

CLINICAL PROBLEM

For aortic valve replacement (AVR), two types of valve substitutes are available: mechanical and bioprosthetic valves. Mechanical valves are designed to last a lifetime but require lifelong anticoagulation, resulting in an increased bleeding risk. Bioprostheses do not require long-term anticoagulation, unless another indication is present. However, they are subject to valve deterioration over time, and patients may require one or more reoperations later in life. Given the different nature of these risks and benefits for mechanical and bioprosthetic valves, informed patient preferences deserve consideration in decision making. In some patients the choice is complex.

CASE DESCRIPTION

A 50-year-old patient with proven Marfan syndrome was admitted to the neurology ward of a University Medical Center with complaints of severe headache and vomiting.

His history revealed headache episodes since two months. Six days ago the pain worsened and changed from intermittent to persistent. Patient mentioned that, due to his height, he often hurt his head.

Four years ago patient underwent aortic root replacement with a Vascutek vascular prosthesis and mechanical valve (Bentall procedure) due to ascending aortic aneurysm and aortic regurgitation. A valve-sparing operation was technically not possible at that time.

Current medication included Omeprazol 1 dd 40 mg, acenocoumarol aimed at a therapeutic INR range of 2.0-3.0, Sotalol 3 dd 80 mg, and Pulmicort. Physical and neurological examination showed no abnormalities. Lab results were unremarkable. The INR was 2.2.

A cranial CT scan revealed bilateral subdural hematoma (Figure 1).

Th patient was treated with Dexamethasone. Acenocoumarol was discontinued. During hospitalization an ECG was made which showed new-onset atrial fibrillation. The patient received Digoxine and sinus rhythm was restored. After three days acenocoumarol was restarted.

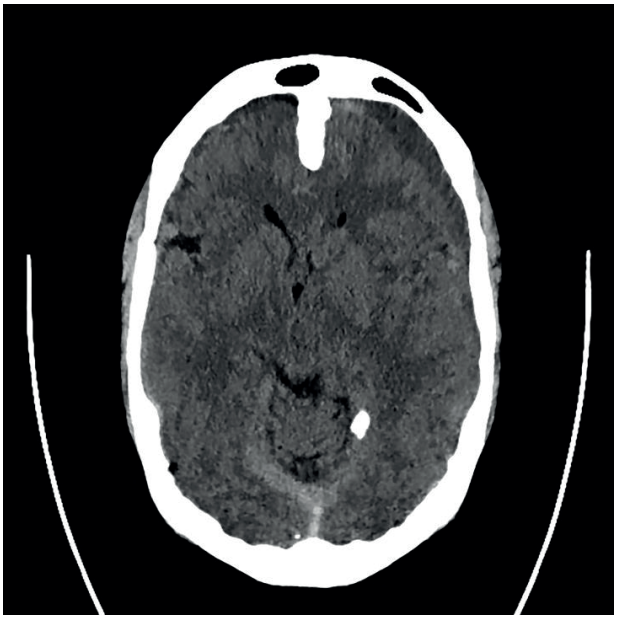

FIGURE 1. Cranial CT scan.

The patient was dismissed from hospital without neurological dysfunction and was treated conservatively for five months. However, the headache and subdural hematoma sustained, although INR was kept around 2.

The patient requested AVR to prevent further need for anticoagulation therapy. This request was quite unusual for the treating physicians and their opinions differed significantly. Most of the time, the mechanical prosthesis is taken as a given and replacing the prosthesis is not even considered. However, the patient was an intelligent man with a clear wish. Therefore, we decided to study the possibilities. First step was to clarify available treatment options and inventorize associated risks and benefits. Since there were several treatment options with considerable risks and benefits, this complex case was discussed within a multidisciplinary team consisting of a cardiologist, a cardiac surgeon and a neurologist.

The subdural hematoma resulted in severe symptoms. There were in our opinion three realistic treatment options to be considered: 1) watchful waiting with Dexamethasone treatment, 2) burr hole trephination, or 3) replacement of the mechanical heart valve by a bioprosthesis. Risks and benefits associated with these available treatment options are demonstrated in Figure 21-5.

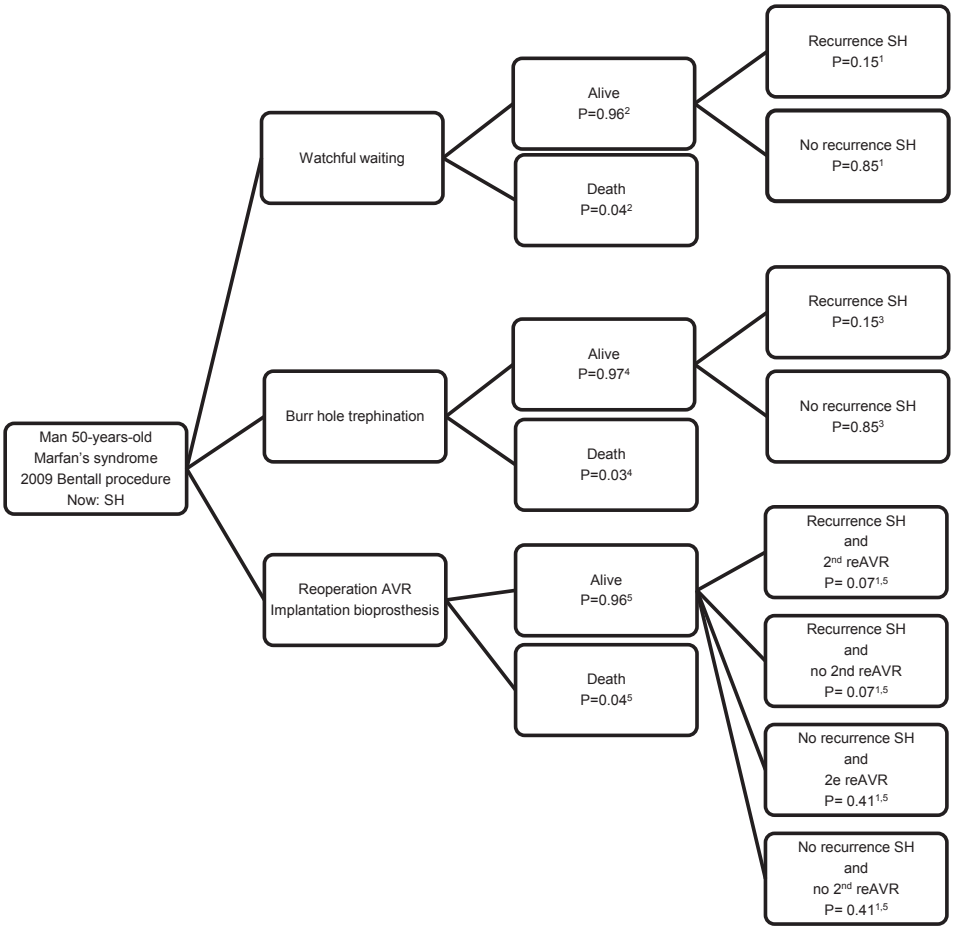

FIGURE 2. Risks and benefits associated with available treatment options. OAC indicates oral anticoagulation, SH indicates subdural hematoma, TE indicates thromboembolic.

Furthermore, to make the discussion even more complex, patient developed new-onset atrial fibrillation. Of course, it is possible that patient will experience another episode of atrial fibrillation after bioprosthesis implantation and despite cardioversion, this may sustain. If so, he still needs oral anticoagulation. In this worst case scenario, the patient would have a risk of bleeding due to oral anticoagulation use and the risk of another operation with considerable risk of reoperation due to bioprosthesis degeneration.

TREATMENT SOLUTION

Patient preference in this case was very clear. He asked for replacement of the mechanical valve by a bioprosthesis, which was driven by symptoms and fear for subdural hematoma persistence or recurrence. After providing detailed information and carefully weighing of the available treatment options, his preference was unchanged and finally accepted by the team. Therefore it was decided to replace the mechanical valve by a bioprosthesis.

Five months after the patient was diagnosed with subdural hematoma he underwent successful surgical replacement of his mechanical valve by a bioprosthesis. He was treated with aspirin for 3 months. Since then, from this moment 5 years ago, he has not experienced subdural hematoma recurrence or episodes of atrial fibrillation.

This case shows that it is possible to apply shared decision making in a very complex clinical decision in which each choice has important consequences. Although not every patient wants to be involved in decision making it is of utmost importance to provide understandable information about the options with their associated risks and benefits, and allow for time and support for the patient to weigh these risks and benefits in his own context. Only then will a patient be empowered to engage in making a deliberate choice that best fits his needs, and become a member of "The Heart team".

REFERENCES

1. Delgado-López PD, Martín-Velasco V, Castilla-Díez JM, Rodríguez-Salazar A, Galacho-Harriero AM, Fernández-Arconada O. Dexamethasone treatment in chronic subdural haematoma. Neurocirugia (Astur). 2009;20:346-59.
2. Sun TF, Boet R, Poon WS. Non-surgical primary treatment of chronic subdural haematoma: Preliminary results of using dexamethasone. Br J Neurosurg. 2005;19:327-33.
3. Kolias AG, Chari A, Santarius T, Hutchinson PJ. Chronic subdural haematoma: modern management and emerging therapies. Nature Reviews Neurology. 2014;10:570–578.
4. Weigel R, Schmiedek P, Krauss JK. Outcome of contemporary surgery for chronic subdural haematoma: evidence based review. J Neurol Neurosurg Psychiatry. 2003;74:937–943.
5. van Geldorp MW, Eric Jamieson WR, Kappetein AP, Ye J, Fradet GJ, Eijkemans MJ, et al. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. J Thorac Cardiovasc Surg. 2009;137:881-886.

“Whatever you decide,
don't let it be because you
don't think you have a choice”

Hannah Harrington

6.

Cardiologist and cardiac surgeon view on decision making in prosthetic aortic valve selection: does profession matter?

Korteland NM, Kluin J, Klautz RJ, Roos-Hesselink JW,
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Netherlands Heart Journal 2014;22:336-343

ABSTRACT

Aims. Assess and compare among Dutch cardiothoracic surgeons and cardiologists: opinion on (1) patient involvement, (2) risk conveyance in aortic valve selection, and (3) aortic valve preferences.

Methods and results. A survey among 117 cardiothoracic surgeons and cardiologists was conducted. Group responses were compared using the Mann-Whitney U-test. Most respondents agreed that patients should be involved in decision making, with surgeons more leaning toward patient involvement (always: 83% versus 50% respectively; $p<0.01$) than cardiologists. Most respondents found that ideally doctors and patients should decide together, with cardiologists more leaning toward taking the lead compared to surgeons ($p<0.01$). Major risks of the therapeutic options were usually discussed with patients, and less common complications to a lesser extent. A wide variation in valve preference was noted with cardiologists more leaning toward mechanical prostheses, while surgeons preferred bioprostheses more often ($p<0.05$).

Conclusion. Patient involvement and risk conveyance in aortic valve selection is considered important by cardiologists and cardiothoracic surgeons. Medical profession influences attitude with regard to aortic valve selection and patient involvement, and preference for a valve substitute. The variation in valve preference suggests that in most patients both valve types are suitable and aortic valve selection may benefit from evidence-based informed shared decision making.

INTRODUCTION

For most patients with severe aortic valve disease, aortic valve replacement is the treatment of choice. For the majority of patients 2 options exist: mechanical or bioprosthetic aortic valve replacement [1]. The decision for a particular prosthetic valve type is ideally driven by scientific evidence on patient outcome after implantation with different valve substitutes, patient's clinical state and circumstances, and informed patient preferences. Each valve type has specific advantages and disadvantages. Mechanical valves are designed to last a lifetime, so a lower re-operation hazard can be anticipated, compared to bioprosthetic valves. However, mechanical valves carry an increased thrombotic risk and therefore require life-long anticoagulation [2]. Clinical characteristics like age, anticipated life expectancy, indication/contraindication for anticoagulation, and comorbidities play an important role in the decision making process [3]. Given the different nature of the pros and cons of different prosthetic valves, informed patient preferences deserve consideration in the decision making. Shared decision making receives more and more attention in healthcare [4]. Using shared decision making, patients are stimulated to think about their treatment, about treatment options and associated benefits and harms so they can place these in their own personal context and discuss their preferences with the physician and next decide with their physician what treatment option is best for them [5].

The 2012 ESC/EACTS Valvular Heart Disease Guidelines state that a mechanical or bioprosthetic valve should be recommended according to the desire of the informed patient [2]. But how do we inform the patient? And how do we assess patient preferences? The opinion of Dutch cardiothoracic surgeons and cardiologists on shared decision making remains yet undefined [6]. To investigate shared decision making in daily cardiovascular practice, we performed this study. The purpose of this study was to assess the expert opinion of the cardiothoracic surgeon and cardiologist on patient involvement and risk conveyance in aortic valve selection, and to assess prosthetic aortic valve preferences of cardiac surgeons and cardiologists.

METHODS

A survey was administered to cardiothoracic surgeons (in training) during the semi-annual meeting of the Netherlands Association for Cardiothoracic Surgery (November 2011) and distributed among cardiothoracic surgeons in several institutions (2012). The same survey was administered to cardiologists (in training) attending the semi-annual meeting of the Netherlands Society of Cardiology (May 2012) and distributed among cardiologists in several institutions (2012).

The questionnaire consisted of five general questions: physician age, specialty (surgeon (in training), cardiologist (in training)), hospital, number of years in practice, and annual number of aortic valve replacements in their institution. The physicians were asked 5 questions to assess their opinion on involvement of patients in decision making using a Control Preference scale [7, 8] and 5 point Likert scales [6, 9]. Physician perspective on discussing risks and benefits of different prosthetic valve types was assessed by rating how often each complication will be discussed using 5 point Likert scales ranging from never to always. Physician opinion on choice of treatment strategies was assessed by 6 hypothetical cases in which the physician rated the likelihood of choosing a particular prosthetic valve type using 7 point Likert scales ranging from 1 (definitely mechanical valve) to 7 (definitely bioprosthetic valve). For a detailed description of the questionnaire, see Appendix 1.

Statistical methods

Continuous variables are displayed as mean, standard deviation and range, discrete variables as counts or proportions. Comparison of group characteristics was done using the unpaired t-test. Group responses are displayed as median, interquartile range, and total range. To compare group responses between surgeons and cardiologists and influence of physician age and cardiac surgery program in the respondent's institution on survey response the Mann-Whitney U-test was used at a probability value of 0.05. All tests were 2-sided, and a p-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using IBM-SPSS 20 (IBM Corp., Armonk, NY).

RESULTS

One-hundred and seventeen Dutch medical specialists from 38 different institutions participated. Mean age was 47±10 years (range 26-67), mean clinical experience 14±9 years (range 0-36). Fifty-four cardiothoracic surgeons (11 in training) represent 38% of the Dutch cardiothoracic surgeon population, 63 cardiologists (7 in training) represent 6% of the Dutch cardiologist population. There were no differences in age and clinical experience between cardiothoracic surgeons and cardiologists.

Physician view on patient participation in decision making

Figure 1 displays physician preference for patient involvement and risk conveyance. Figure 2 displayes physician preferences for final decision making in prosthetic aortic valve choice. Subgroup analysis revealed that physicians above age 50 are more often leaning toward patient involvement in decision making than physicians under age

50. Physicians working in a centre with cardiac surgery were more inclined to decide together with the patient, while physicians working in a centre without a cardiac surgery program more often preferred to take the lead in decision making.

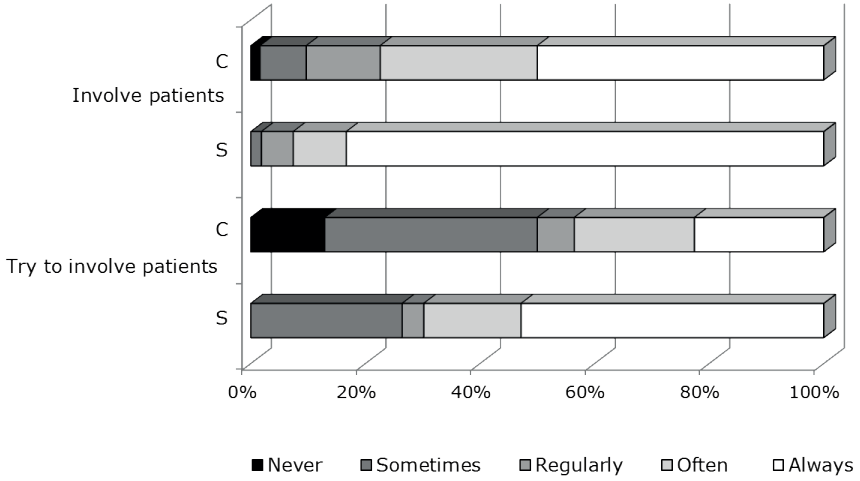

FIGURE 1. Cardiologist (C) and surgeon (S) preference for patient involvement and risk conveyance in aortic valve selection. Total n=117, cardiologists=63 and surgeons=54. Difference between groups: *p<0.01. Pts = patients. QoL = quality of life.

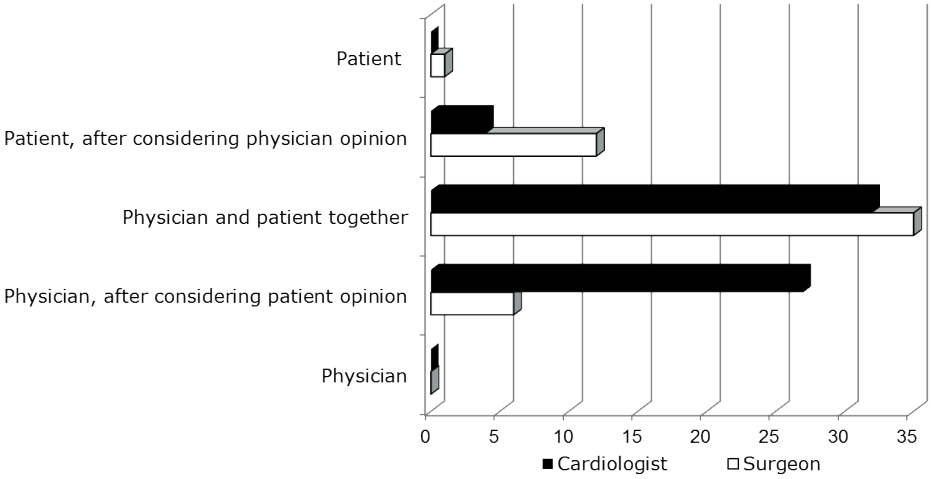

FIGURE 2. Physician preference for final decision in prosthetic aortic valve choice Total n=117, cardiologists=63 and surgeons=54. Difference between cardiologists and surgeons: p<0.01.

Physician view on risk & benefit conveyance

Figures 3 and 4 summarize physician responses regarding risk and benefit conveyance to patients about mechanical valves (Figure 3) and bioprosthetic valves (Figure 4).

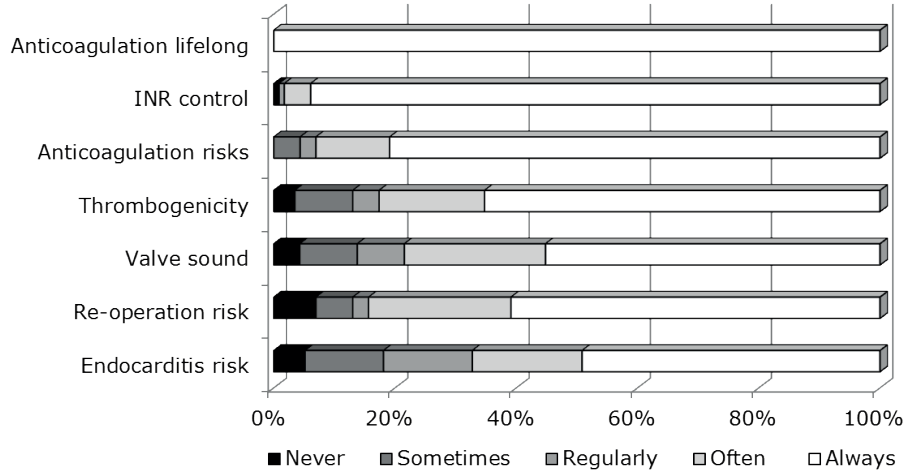

FIGURE 3. Physician responses regarding risk and benefit conveyance to patients about mechanical valves. Total n=117.

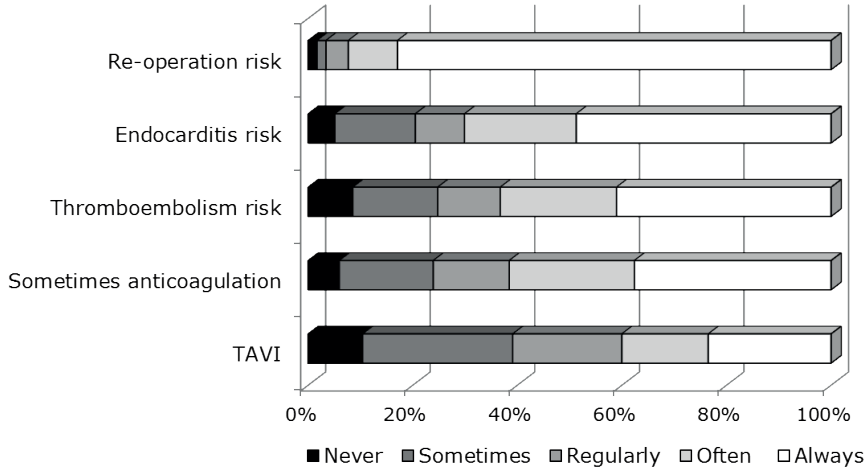

FIGURE 4. Physician responses regarding risk and benefit conveyance to patients about bioprosthetic valves. Total n=117.

There were no differences between surgeons and cardiologists regarding risk and benefit conveyance to patients. Physicians under the age of 50 were more often informing patients regarding anticoagulation risks than physicians older than age 50. Physicians working in a centre with cardiac surgery were more often informing patients about risks and benefits of a mechanical valve compared to those working in a centre without a cardiac surgery program.

Physician prosthetic valve preference

The results of the answers to the 6 hypothetical patient cases are illustrated in the box-and-whisker plot in Figure 5. Physicians above age 50 were leaning more toward mechanical valves compared to physicians under age 50. Presence of a cardiac surgery program in the respondent's institution was not associated with prosthetic valve preference in any of the 6 hypothetical cases.

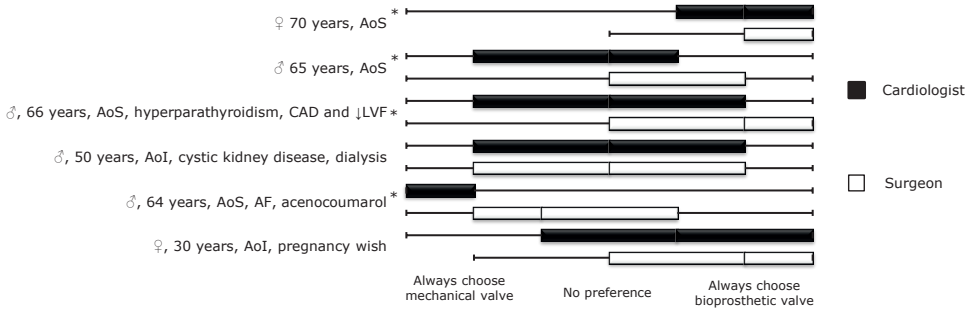

FIGURE 5. Physician preferences for a prosthetic valve type in 6 cases. The box contains 50% of the physician preferences. The vertical line in the box represents the median, and the whiskers illustrate the minimum and maximum value. Total n=117, cardiologists=63 and surgeons=54. Difference between groups: *p<0.05.

DISCUSSION

Prosthetic aortic valve selection is a delicate process. By carefully considering research evidence on outcome after aortic valve replacement with different aortic valve prostheses, clinical characteristics and medical circumstances of the patient, and by taking patient preferences into account, the likelihood of making an optimal choice increases [1]. The results from this survey among Dutch cardiothoracic surgeons and cardiologists suggest that patient involvement in prosthetic aortic valve selection is considered important by most physicians. This finding is in line with previous research

in other medical professions, showing that patients and physicians prefer the decision to be the outcome of a shared decision making process [8, 10]. Dutch cardiothoracic surgeons are more leaning toward patient involvement than cardiologists, who prefer to take the lead in decision making, as are physicians above the age of 50 and physicians who are working in an institution with a cardiac surgery program. These differences could be due to external factors in medical practice, such as differences in consulting time, and cultural differences. Since shared decision making has not yet been standardized in clinical practice, there is probably a wide variation in the application of the concept in current clinical practice. Current practice in one hospital could for example be that the surgeons are mainly discussing the choice for a certain valve type with the patients, while in another clinic cardiologists do so, or both specialties simultaneously. Although the 2012 ESC/EACTS Valvular Heart Disease Guidelines state that a prosthetic valve should be recommended according to the desire of the informed patient [1], the way Dutch hospitals are following these guidelines probably differs a lot. The Netherlands Association for Cardiothoracic Surgery and the Netherlands Society of Cardiology should make their efforts to achieve a more uniform application of the guidelines in Dutch cardiovascular practice.

Most respondents thought that the physician can often decide for patients how risks and benefits should be weighed, and how quality of life should be weighed against life expectancy. It is however doubtful that a physician is actually good at assessing patient preferences in the context of prosthetic aortic valve selection. Physician perception of patient preferences in cardiovascular practice is not yet investigated, but previous studies in the fields of vascular surgery and colorectal cancer screening have shown that physician perception of patient preferences may differ considerably from actual patient preferences [11, 12]. In fact, it was shown that although physicians usually think that they can adequately assess patient preferences, reality shows that they are not. This is regardless of the clinical experience they have: from first year residents to senior registrars, this deficit persists [13]. Because physicians have a major influence on patient decision making, it is important for the physician to realize that their preferences may not be the preferences of the patient.

Patients who require aortic valve replacement need to be informed about the risks and benefits associated with the different prosthetic valve types in order to be able to participate in decision making. The current study shows that in Dutch cardiovascular clinical practice major risks of the different therapeutic options are usually discussed with patients, and less common complications to a lesser extent. The observation that younger physicians are more often reporting to inform the patients regarding anticoagulation risks and that physicians working in an institution with a cardiac surgery

program are more often reporting to inform patients about risks and benefits regarding a mechanical prosthesis, reflects the fact that evaluation of the risks and benefits is a complex process. This complexity is due to uncertainty about the various outcomes, difficulty to evaluate future events and the fact that most patients are unfamiliar with the medical consequences of their decisions [1].

The observation that both patient involvement and information conveyance to the patient are more common in institutions with a cardiac surgery program may be associated with the fact that these institutions have formal heart teams in which the cardiologists and surgeons discuss prosthetic valve selection.

To make patients more familiar with their treatment options it is important to inform patients in a way that they can understand the benefits and risks associated with the different valve types. Well-informed patients are an essential requirement for successful shared decision making. Only then patients can decide what is best for them and this will result in an optimization of valve selection and an improved quality of life [14]. Of course, patients differ in their information needs. Some patients do want to know every detail of their treatment, while other patients do not want to be involved at all. Furthermore, educational level of the patient plays an important role in shared decision making. It is known that incapacity to understand the process of medical-decision making is common [15]. Despite these differences in information needs and educational level, it is important that physicians should at least try to involve the patient. In some patients however, this will require a lot of time and effort from the treating physician. Patient decision aids may be particularly useful in this setting. A decision aid will provide the patient with information about the disease, treatment options and risks and benefits that are associated with the different treatment options. Additionally, a decision aid helps the patient to place the provided information in his or her own context, considering the values and expectations of the patient. It is known that decision aids improve patient knowledge and lower decisional conflict without raising anxiety levels [16]. Only when patients are fully informed about their treatment options they can participate in the decision making process and clarify their preferences to the physician. Although not all patients are willing to participate in decision making, it is known that most patients do want to be informed [17]. Even patients who initially do not want to be involved in decision making, do want to be involved once they are well informed [10, 18].

An important finding of the current study is the observed wide variation in physician preference for a particular valve substitute and the association between medical specialty and prosthetic valve preference. It may be that this variation is caused by differences in clinical practice setting, although we could not detect a difference between practices

with or without an onsite cardiac surgery program. It may also be that physicians feel that in most patients both valve types are suitable. This is supported by the observation that in current practice there appears to be no difference in survival for adult patients with a mechanical or a bioprosthesis [19-22]. If the type of implanted prosthesis is not associated with patient survival, then the choice for a particular aortic valve prosthesis is mainly driven by valve-related event occurrence. Given the completely different nature of valve-related events between mechanical and bioprostheses, and subjective aspects of choosing between the hazards of bleeding due to anticoagulation (mechanical prostheses) and the hazards of re-operation (biological prostheses), informed patient preferences become very important.

In conclusion, this survey among Dutch cardiothoracic surgeons and cardiologists provides important information on current clinical decision making regarding prosthetic aortic valve selection. Dutch cardiovascular professionals are of the opinion that prosthetic aortic valve selection should be done with the patient, and they usually convey most risks and benefits of the different options to the patient. Medical specialty influences both physician attitude with regard to prosthetic aortic valve selection and patient involvement, and preference for a particular valve substitute. The observed wide variation in prosthetic aortic valve preference among Dutch cardiothoracic surgeons and cardiologists suggests that for most patients both mechanical and bioprosthetic valves are suitable, and that formal implementation of the concept of shared decision making including the use of patient decision aids may be helpful for physicians and patients to improve patient information and patient participation in decision making.

REFERENCES

1. Tillquist MN, Maddox TM. Cardiac crossroads: deciding between mechanical or bioprosthetic heart valve replacement. Patient Prefer Adherence. 2011;5:91-9.
2. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardiothoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;42:S1-44.
3. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation. 2009;119:1034-48.
4. Montori VM, Ting HH. Sharing Decision Making About Cardiac Surgery. Circ Cardiovasc Qual Outcomes. 2009;2:519-21.
5. Elwyn G, Laitner S, Coulter A, Walker E, Watson P, Thomson R. Implementing shared decision making in the NHS. BMJ. 2010;341:c5146.
6. Elwyn G, Edwards A, Kinnersley P, Grol R. Shared decision making and the concept of equipoise: the competences of involving patients in healthcare choices. Br J Gen Pract. 2000;50:892-99.
7. Degner LF, Sloan JA, Venkatesh P. The Control Preferences Scale. Can J Nurs Res. 1997;29:21-43.
8. Pieterse AH, Baas-Thijssen MC, Marijnen CA, Stiggelbout AM. Clinician and cancer patient views on patient participation in treatment decision making: a quantitative and qualitative exporation. Br J Cancer. 2008;99:875-82.
9. Elwyn G, Frosch D, Rollnick S. Dual equipoise shared decision making: definitions for decision and behaviour support interventions. Implement Sci. 2009;4:75
10. Janz NK, Wren PA, Copeland LA, Lowery JC, Goldfarb SL, Wilkins EG. Patient-Physician Concordance: Preferences, Perceptions, and Factors Influencing the Breast Cancer Surgical Decision. J Clin Oncol 2004;22:3091-98.
11. Marshall DA, Johnson FR, Kulin NA, Ozdemir S, Walsh JM, Marshall JK, Van Bebber S, Phillips KA. How do physician assessments of patient preferences for colorectal cancer screening tests differ from actual preferences? A comparison in Canada and the United States using a stated-choice survey. Health Econ. 2009;18:1420-39.
12. Brothers TE, Cox MH, Robison JG, Elliott BM, Nietert P. Prospective decision analysis modeling indicates that clinical decisions in vascular surgery often fail to maximize patient expected utility. J Surg Res. 2004;120:278-87
13. Wilson IB, Green ML, Goldman L, Tsevat J, Cook EF, Phillips RS. Is experience a good teacher? How interns and attending physicians understand patients' choices for end-of-life care. SUPPORT Investigators. Study to understand prognoses and preferences for outcomes and risks of treatment. Med Decis Making. 1997;17:217-27.

14. Cher D, Miyamoto J, Lenert L. Incorporating risk attitude into Markov-process decision models: importance for individual decision making. Med Decis Making. 1997;17:340–50.
15. Sessums LL, Zembrzuska H, Jackson JL. Does This Patient Have Medical Decision making Capacity? JAMA. 2011;306:420-27.
16. Knops AM, Legemate DA, Goossens A, Bossuyt PM, Ubbink DT. Decision Aids for Patients Facing a Surgical Treatment Decision: A Systematic Review and Meta-analysis. Ann Surg. 2013;257:860.
17. Manson NC. Why do patients want information if not to take part in decision making? J Med Ethics. 2010;36:834-37.
18. van Til JA, Stiggelbout AM, IJzerman MJ. The effect of information on preferences stated in a choice-based conjoint analysis. Patient Educ Couns. 2009;74:264-71.
19. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol. 2000;36:1152–58.
20. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ, Miller HC. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. Heart 2003;89:715–21.
21. Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, Douglas PS, Peterson ED; DEcIDE AVR (Developing Evidence to Inform Decisions about Effectiveness–Aortic Valve Replacement) Research Team. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the society of thoracic surgeons adult cardiac surgery national database. Circulation. 2013;127:1647-55.
22. Ruel M, Chan V, Bédard P, Kulik A, Ressler L, Lam BK, Rubens FD, Goldstein W, Hendry PJ, Masters RG, Mesana TG. Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age. Circulation. 2007 Sep 11;116(11 Suppl):I294-300.

APPENDIX 1

1. Do you think patients should be involved in choosing an aortic valve?
   Never Sometimes Regularly Often Always I don't know

2. If a patient doesn't want to be involved in choosing an aortic valve, do you think that physicians should try to involve the patient in the decision?
   Never Sometimes Regularly Often Always I don't know

3. The final decision in prosthetic aortic valve choice should be made by:
   - o The patient
   - o The patient, after considering physician opinion
   - o The patient and the physician together
   - o The physician, after considering patient opinion
   - o The physician

4. To choose a prosthetic aortic valve, the advantages and disadvantages of different prosthetic aortic valve types are taken into consideration. Do you think physicians can decide for patients how risks and benefits should be weighed?
   Never Sometimes Regularly Often Always I don't know

5. Do you think that all disadvantages of a prosthetic aortic valve should be discussed with the patient (even if there is a small chance)?
   Never Sometimes Regularly Often Always I don't know

6. How often do you inform the patient about the following issues regarding a mechanical valve?
   - o Anticoagulation lifelong

   Never Sometimes Regularly Often Always I don't know
   - o INR control

   Never Sometimes Regularly Often Always I don't know
   - o Anticoagulation risks

   Never Sometimes Regularly Often Always I don't know
   - o Thrombogenicity

   Never Sometimes Regularly Often Always I don't know
   - o Valve sound

   Never Sometimes Regularly Often Always I don't know

- o Reoperation risk

Never Sometimes Regularly Often Always I don't know

- o Endocarditis risk

Never Sometimes Regularly Often Always I don't know

7. How often do you inform the patient about the following issues regarding a bioprosthetic valve?
   - o Reoperation risk

   Never Sometimes Regularly Often Always I don't know
   - o Endocarditis risk

   Never Sometimes Regularly Often Always I don't know
   - o Thromboembolism risk

   Never Sometimes Regularly Often Always I don't know
   - o Sometimes anticoagulation

   Never Sometimes Regularly Often Always I don't know
   - o TAVI

   Never Sometimes Regularly Often Always I don't know

8. If the decision is between quality of life versus life expectancy with a certain prosthetic aortic valve, do you think that physicians can decide how these options should be weighed?

   Never Sometimes Regularly Often Always I don't know

Case 1

Female, 30 years old. Aortic valve insufficiency, no comorbidity. Patient has a pregnancy wish.

Mechanical valve 1 2 3 4 5 6 7 Bioprosthetic valve

Case 2

Male, 64 years old. Aortic valve stenosis. Atrial fibrillation, patient is using acenocoumarol.

Mechanical valve 1 2 3 4 5 6 7 Bioprosthetic valve

Case 3

Male, 50 years old. Aortic valve insufficiency. Cystic kidney disease and dialysis.

Mechanical valve 1 2 3 4 5 6 7 Bioprosthetic valve

Case 4

Male, 66 years old. Aortic valve stenosis. Hyperparathyroidism, coronary artery disease, impaired left ventricular function.

Mechanical valve	1	2	3	4	5	6	7	Bioprosthetic valve

Case 5

Male, 65 years old. Aortic valve stenosis. No comorbidity.

Mechanical valve	1	2	3	4	5	6	7	Bioprosthetic valve

Case 6

Female, 70 years old. Aortic valve stenosis. No comorbidity.

Mechanical valve	1	2	3	4	5	6	7	Bioprosthetic valve

“You can't make decisions based on fear and the possibility of what might happen”

Michelle Obama

7.

Prosthetic aortic valve selection: current patient experience, preferences and knowledge

Korteland, NM, Bras FJ, van Hout FM, Kluin J, Klautz RJ, Bogers AJ, Takkenberg JJ

Open Heart, 2015. 2(1): p. e000237

ABSTRACT

Objective. Current clinical practice guidelines advocate shared decision making (SDM) in prosthetic valve selection. This study assesses among adult patients accepted for aortic valve replacement (AVR): (1) experience with current clinical decision making regarding prosthetic valve selection, (2) preferences for SDM and risk presentation, and (3) prosthetic valve knowledge and numeracy.

Methods. In a prospective multicentre cohort study AVR patients were surveyed preoperatively and 3 months postoperatively.

Results. Preoperatively 132 patients (89 males/43 females; mean age 67 years (range 23-86)) responded. Decisional conflict was observed in 56% of patients, and in 25% to such extent that it made them feel unsure about the decision. Sixty-eight percent wanted to be involved in decision making, whereas 53% agreed they actually were. Sixty-nine percent were able to answer three basic knowledge questions concerning prosthetic valves correctly. Fifty-six percent were able to answer three basic numeracy questions correctly. Three months post-surgery 90% (n=110) were satisfied with their aortic valve prosthesis, with no difference between mechanical and bioprosthetic valve recipients.

Conclusions. In current clinical practice many AVR patients experience decisional conflict, suboptimal involvement in prosthetic valve selection, and exhibit impaired knowledge concerning prosthetic valves and numeracy. Given the broad support for SDM among AVR patients and obvious need for understandable information, to-be-developed tools to support SDM in the setting of prosthetic valve selection will help to improve quality of decision making, better inform and actively involve patients, and reduce decisional conflict.

INTRODUCTION

For most patients who require aortic valve replacement (AVR) two options exist: mechanical or bioprosthetic valve replacement. Each prosthetic valve has specific risks and benefits. Mechanical valves are thrombogenic and therefore require life-long anticoagulation. Bioprosthetic valves carry a higher risk of reoperation due to valve degeneration [1,2]. There is no apparent difference in survival for adult patients with a mechanical or bioprosthetic valve [3,4]. Therefore, prosthetic valve choice is mainly driven by valve specific risks and benefits. Given the different nature of these risks and benefits for mechanical and bioprosthetic valves, informed patient preferences deserve consideration in decision making.

The 2014 ACC/AHA Valvular Heart Disease Guidelines state that prosthetic valve choice should be a shared decision process [2], while the 2012 ESC/EACTS guidelines highlight the importance of considering informed patient preferences (Class 1 recommendations) [1]. We previously showed that the majority of the Dutch cardiothoracic surgeons and cardiologists are of the opinion that prosthetic aortic valve selection should ideally be done together with the patient and they report to communicate to the patient most important risks of the different prosthetic valve types. Nevertheless, only half of them actively involves patients in prosthetic valve selection [5]. Although the guidelines advocate shared decision making (SDM), clinicians do not have any tools to engage this activity.

In order to engage in SDM both clinician and patient should be able and willing to participate. It is unknown how patients experience decision making in prosthetic aortic valve selection and what their attitude toward SDM is. The purpose of this prospective study was to assess among adult patients accepted for AVR: (1) experience with current clinical decision making regarding prosthetic valve selection, (2) preferences for SDM and risk presentation, and (3) prosthetic valve knowledge and numeracy.

METHODS

This study was approved by the institutional review board of all 3 participating centers (Erasmus MC MEC nr. 12-323). Written informed consent was obtained. Participants were adult patients who were accepted for elective AVR in one of the three hospitals between September 2012 and June 2013. Patients had to be legally capable. Two surveys were conducted, one preoperatively after preoperative outpatient counselling, and another three months postoperatively.

Preoperative survey

Patient experience with prosthetic valve selection

Multiple choice (MC) questions assessed which clinician (surgeon, cardiologist, both or other) performed the preoperative consultation with regard to prosthetic valve choice, if a friend or family member was involved in prosthetic valve choice, patient opinion on the amount of time available for prosthetic valve choice, and how patients valued their participation in prosthetic valve choice.

The Decisional Conflict Scale (DCS) was used to measure degree of uncertainty about which course of action to take and the main modifiable factors contributing to uncertainty. It is a 16 item questionnaire with 5 subscales: uncertainty, informed, values clarity, support and effective decision. Total scores <25 are associated with no decisional conflict and implementation of decision. Scores exceeding 25 are associated with decisional conflict, with higher scores indicating higher decisional conflict. Scores ≥37.5 are associated with decision delay or feeling unsure about implementation [6].

1-5 Likert scales were used to assess how patients value the importance of the different risks and benefits associated with a mechanical and bioprosthetic valve.

Patient preferences for SDM and risk presentation

A 1-5 Likert Scale and Control Preferences Scale were used to assess patient view on participation in decision making [7].

Patient preference for presentation of scientific evidence was assessed by asking patients to rate four graphical formats of scientific evidence: a horizontal bar, pie chart, and two pictographs (a visual presentation of data) [8].

Patient prosthetic valve knowledge and numeracy

Information that patients perceived from the treating physician with regard to prosthetic valve selection and patient knowledge regarding the risks and benefits associated with mechanical and bioprosthetic valves were assessed by MC questions and a 1-5 Likert Scale.

Patient numeracy was assessed using the Numeracy Scale [9].

For a detailed description of the preoperative survey, see Appendix 1.

Postoperative survey

Patient experience with prosthetic valve selection

MC questions and a 1-5 Likert Scale were used to assess patient opinion on the amount of time available for prosthetic valve choice, how patients value their participation in prosthetic valve choice, and patient satisfaction with the type of prosthetic valve they received.

Valve specific quality of life (QoL) was measured with a valve specific questionnaire [10].

Patient preferences for SDM

Patient view on participation in decision making was assessed by 1-5 Likert Scales, and a Control Preferences scale.

Patient prosthetic valve knowledge

Information that patients perceived from the treating physician with regard to prosthetic valve selection was assessed with MC questions and a 1-5 Likert Scale.

For a detailed description of the postoperative survey, see Appendix 2.

Statistical methods

Continuous variables were displayed by the mean, standard deviation and range. Discrete variables were displayed as counts or proportions. Multiple imputations (5 iterations) were used to impute missing DCS values. To compare DCS group responses the Mann-Whitney U-test or Kruskal-Wallis test was used. To compare group responses between patients with a mechanical and bioprosthetic valve the Mann-Whitney U-test or Fisher exact test was used. Patients were allocated to the mechanical or bioprosthetic subgroup according to their survey answer. To compare group responses pre- and post-surgery the Wilcoxon signed-rank test was used. All tests were 2-sided, and a p-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using IBM-SPSS 20 (IBM Corp., Armonk, NY).

RESULTS

Preoperative survey

One hundred thirty-two elective adult patients scheduled for AVR in three academic Dutch hospitals participated. Twenty-nine patients reported that they were to receive a mechanical valve, 74 a bioprosthetic valve, 2 patients a valve repair, and 29

patients did not know which valve they were going to receive. Table 1 displays patient characteristics. Patients with a bioprosthetic valve were significantly older than patients with a mechanical valve (p=0.000).

Patient experience with prosthetic valve selection

The preoperative consult with regard to prosthetic valve choice was performed by the cardiologist (48%), the surgeon (18%), surgeon and cardiologist together (16%) or other, for example a resident or physician assistant (19%). More than half of the patients (57%) involved a friend or family member in prosthetic valve choice. Sixty-four percent of the patients felt they had sufficient time to make a deliberate prosthetic valve choice and 64% felt they had a prosthetic valve choice.

Table 2 displays the results of the Decisional Conflict Scale.

There were no significant differences in total DCS score between patients from the three different hospitals, and between patients with a mechanical versus bioprosthetic valve. The type of medical professional who performed the preoperative consult did not influence patient total DCS score. Patients who involved a friend or family member in prosthetic valve choice experienced significantly less decisional conflict than patients who made the decision alone (p=0.001).

Table 3 displays the patient's valuation of the importance of the different risks and benefits associated with mechanical and bioprosthetic valves.

TABLE 1. Patient characteristics

	n=132
Age, mean (SD), years	66.7 (12.8)
Age, range, years	23-86
Male sex, n (%)	89 (67)
Educational level, n (%) (n=130)	
< High school	45 (35)
High school graduate	55 (42)
College graduate	27 (21)
Other	3 (2)
Hospital, n (%)	
1	57 (43)
2	55 (42)
3	20 (15)
Referral to academic hospital, n (%) (n=129)	
Other hospital	114 (88)
General practitioner	15 (12)

TABLE 2. Preoperative score on Decisional Conflict Scale (DCS)

N (%) with total score on DCS	
< 25	58 (44%)
25 – 37.5	41 (31%)
> 37.5	33 (25%)
Mean (SD) score on DCS subscales:	
Uncertainty	33.6 (24.9)
Informed	22.3 (25.3)
Values clarity	29.3 (23.5)
Support	24.0 (23.5)
Effective decision	13.0 (18.4)

Total score <25: no decisional conflict and implementation of decision.
Total score ≥ 25: decisional conflict.
Total score ≥37.5: decision delay or feeling unsure about implementation.

TABLE 3. Patient's valuation of the importance of the different risks and benefits associated with a mechanical (MP) and bioprosthetic (BP) valve

	Total	**MP**	**BP**
I am concerned about a possible bleeding.			
(Totally) agree	23%	24%	21%
Not agree/disagree	18%	28%	16%
(Totally) disagree	27%	31%	24%
Don't know*	31%	17%	39%
I am afraid of blood clots.			
(Totally) agree	24%	21%	23%
Not agree/disagree	20%	24%	23%
(Totally) disagree	32%	45%	26%
Don't know	24%	10%	29%
I have problems with taking medication.			
(Totally) agree	9%	7%	7%
Not agree/disagree	6%	7%	4%
(Totally) disagree	75%	82%	72%
Don't know	11%	4%	17%
I am afraid that I may need another valve operation.			
(Totally) agree	23%	45%	20%
Not agree/disagree	13%	21%	9%
(Totally) disagree	41%	31%	44%
Don't know*	23%	3%	28%
I am afraid that my valve may fail.			
(Totally) agree	13%	28%	11%
Not agree/disagree	11%	21%	8%
(Totally) disagree	55%	45%	54%
Don't know*	22%	7%	26%
I am afraid that I will be limited by my new heart valve in my daily activities.			
(Totally) agree	12%	24%	6%
Not agree/disagree	10%	14%	6%
(Totally) disagree	58%	52%	64%
Don't know	20%	10%	25%
I am afraid that my new heart valve will negatively influence my social life.			
(Totally) agree	5%	3%	7%
Not agree/disagree	12%	24%	4%
(Totally) disagree	65%	62%	67%
Don't know	18%	10%	22%

TABLE 3. (continued)

	Total	MP	BP
It bothers me that I have to use oral anticoagulation lifelong.			
(Totally) agree	53%	45%	57%
Not agree/disagree	9%	7%	6%
(Totally) disagree	27%	38%	23%
Don't know	12%	10%	14%
I am afraid that the valve sound will bother me.			
(Totally) agree	34%	38%	34%
Not agree/disagree	14%	21%	10%
(Totally) disagree	28%	34%	24%
Don't know*	24%	7%	31%

* p<0.05 proportion of patients answering 'don't know' in mechanical versus bioprosthetic valve groups.

Patient preferences for SDM and risk presentation

Patient preference for final decision in prosthetic valve choice is displayed in Figure 1. Sixty-eight percent of patients wanted to be involved in decision making, whereas 53% agreed that they actually were involved.

The majority of patients (68%) preferred scientific evidence presentation in a pie chart, followed by the horizontal bar, and the two pictographs.

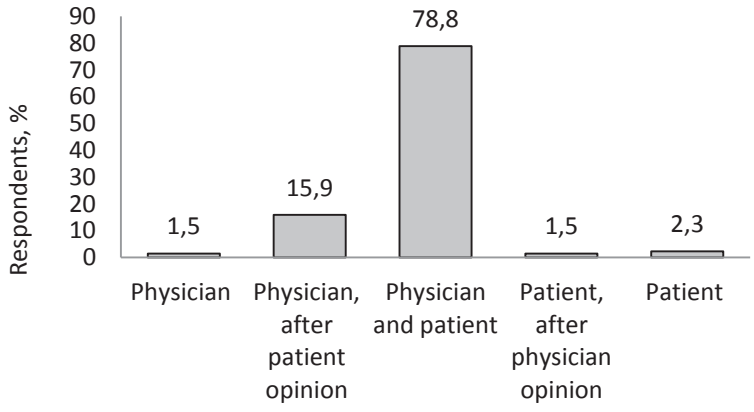

FIGURE 1. Preoperative patient preference for final decision in prosthetic aortic valve choice (n=132).

Patient prosthetic valve knowledge

Ninety-nine percent of patients were aware that there are different types of aortic valve prostheses and 80% reported to know which valve they were going to receive. Fifty-nine percent were of the opinion that they had sufficient knowledge about the different types of aortic valve prostheses.

Table 4 displays patient prosthetic valve knowledge and numeracy.

TABLE 4. Preoperative prosthetic valve knowledge and basic numeracy

	Correct
Prosthetic valve knowledge (n=129)	
1. Which valve type is most durable?	84%
2. Which valve type is associated with increased risk of blood clots?	72%
3. Which valve type requires lifelong anticoagulation?	88%
Basic numeracy questions (n=84)	
1. Convert 1% to 10 in 1000	87%
2. Convert 1 in 1000 to 0.1%	61%
3. How many heads in 1000 coin flips?	89%

Ninety-eight percent of patients (n=129) answered all 3 questions concerning prosthetic valve knowledge. Of these, 5% were not able to answer any of the 3 questions correctly, 9% were able to answer 1 question correctly, and 16% and 69% were able to answer 2 and 3 questions correctly, respectively. There were no significant differences between patients with a mechanical and bioprosthetic valve. Sixty-four percent of patients (n=84) answered all three numeracy questions. Four percent were not able to answer any of the 3 questions correctly, 12% were able to answer 1 question correctly, 29% were able to answer 2 questions correctly and 56% were able to answer 3 questions correctly. There were no significant differences between patients with a mechanical and bioprosthetic valve.

Postoperative survey

One hundred and ten patients responded to the postoperative survey. Reasons for loss to follow up included death (n=4), inability to complete the survey due to morbidity (n=5), cancelled operation due to comorbidity (n=2) or non-response (n=11). At the time of the postoperative survey, 86% of patients (n=95) were in NYHA class I or II, and

14% of patients (n=15) were in NYHA Class III or IV. Twenty-eight patients reported that they received a mechanical valve, 81 a bioprosthetic valve and 1 patient had a valve repair.

Patient experience with prosthetic valve selection

Seventy-seven percent of patients felt they had sufficient time to make a deliberate prosthetic valve choice, which was significantly higher than preoperatively (p=0.001). Seventy-four percent of patients felt they had a prosthetic valve choice (p=NS compared to preoperative).

Ninety percent were satisfied with their valve prosthesis, 7% did not have an opinion and 4% were unsatisfied. There was no difference between patients with a mechanical and bioprosthetic valve.

The results of the valve-specific questionnaire are displayed in Table 5.

Patient preferences for SDM

Eighty-seven percent of patients wanted to be involved in decision making, whereas 74% agreed that they actually were involved. This was significantly higher than preoperatively (68% versus 87%; p=0.000, and 53% versus 74%; p=0.000 respectively). Seventy-nine percent preferred the final prosthetic valve choice to be a shared decision process (p=NS compared to preoperative).

Patient prosthetic valve knowledge

Ninety-nine percent of patients were aware that there are different types of aortic valve prostheses and 100% reported to know which valve they received. Seventy-four percent were of the opinion that they had sufficient knowledge about the different types of aortic valve prostheses (p=NS compared to preoperative).

TABLE 5. Postoperative answers to valve-specific questionnaire. MP = mechanical valve. BP = bioprosthetic valve

	Total	**MP**	**BP**
If I had to do it over again, would I make the same decision to have surgery?			
Yes/probably	85%	85%	85%
I don't know	11%	7%	13%
Probably not/absolutely not	4%	7%	3%
Is there a valve sound that bothers me?*			
Frequently/always	6%	22%	0%
Occasionally	11%	32%	4%
Never/rarely	83%	47%	96%
Following my valve surgery, the frequency of doctor visits and blood tests bothers me.			
Frequently/always	8%	14%	6%
Occasionally	25%	29%	24%
Never/rarely	67%	57%	70%
The possibility of complications due to my implanted valve concerns me.			
Frequently/always	4%	4%	4%
Occasionally	26%	29%	25%
Never/rarely	70%	68%	71%
I am concerned about possible bleeding caused by my anticoagulant medication.			
Frequently/always	7%	11%	5%
Occasionally	25%	32%	23%
Never/rarely	69%	57%	73%
I am afraid that my valve may fail.			
Frequently/always	3%	4%	3%
Occasionally	16%	18%	15%
Never/rarely	82%	79%	83%
I am afraid that I may need another valve operation.			
Frequently/always	5%	4%	5%
Occasionally	22%	7%	27%
Never/rarely	74%	89%	68%

* $p<0.05$ mechanical versus bioprosthetic valve groups.

DISCUSSION

In current Dutch cardiovascular clinical practice patients who require AVR often experience decisional conflict, suboptimal involvement in prosthetic valve selection, and exhibit impaired numeracy. The majority of patients want to be involved in prosthetic valve selection, while only half of the patients actually feels involved. Given the limited patient knowledge of prosthetic valves and numeracy, there is an obvious need for improved information conveyance on prosthetic valve options and their associated risks and benefits.

Patient experience with prosthetic valve selection

The quality of decision making does not appear to be influenced by the physician who discusses prosthetic valve selection, but our study results suggest that it is important for patients to involve a friend or relative, as this will reduce decisional conflict. This is in alignment with the 2014 ACC/AHA Valvular Heart Disease Guidelines that highlight the importance of involving family members in decision making [2].

Preoperatively, one-third of patients in this study felt they did not have sufficient time to make a deliberate prosthetic valve choice, and/or felt like they did not have a choice at all. This observation indicates room for improvement in decision making, allowing for sufficient time and adequate information conveyance. Postoperatively, significantly more patients felt they had sufficient time than preoperatively. It is possible that preoperative stress may have influenced patient perception regarding the amount of time needed for prosthetic valve choice.

More than half of the patients experienced decisional conflict, and 1 in 4 patients to such an extent that it made them feel unsure about the decision. Decisional conflict was most evident in the uncertainty and values clarity subscales, suggesting that particular measures aimed at reducing patient uncertainty and improving value clarification will be effective to improve decision making quality [6]. Patient satisfaction with the selected prosthetic valve did not appear to be affected by the suboptimal decision making. This may be caused by the phenomenon of choice closure: the process by which people come to perceive a decision to be resolved and complete. As choice closure results in greater satisfaction, it can explain at least in part why most patients were satisfied with their prosthetic valve [11].

Preoperatively, the most common patient concerns about complications were related to the use of lifelong oral anticoagulation, the risk of bleeding or blood clot, valve sound and the need for a reoperation. Therefore these topics require particular attention in the

preoperative consultation. Interestingly, patients with a bioprosthetic valve more often answered 'do not know' when they were asked about complications. This may be due to their older age as it is known that older patients usually have a more passive role in decision making and more difficulties understanding medical information [12,13].

Patient preferences for SDM and risk presentation

A common misperception among clinicians is that many patients do not want to be involved in decision making [14]. The current study shows the contrary: most of patients who require AVR do want to be involved. Previous studies in different medical fields also show that patients prefer to be involved in decision making [15,16]. In our study, postoperatively more patients felt involved in decision making than preoperatively. The preoperative survey was conducted after preoperative outpatient counselling, on average two weeks before the operation. It is possible that patients received more information about prosthetic valve selection in the remaining time prior to and following the operation.

SDM receives more and more attention in healthcare. SDM can be described as a meeting of experts, the clinician as an expert on the medical issues and the patient as an expert on their values and preferences [14]. SDM has several advantages, like increased patient knowledge, less patient anxiety, improved health outcomes, reductions in care and cost variation and more alignment of care with patient values [17]. Therefore it is not surprising that the 2014 ACC/AHA Valvular Heart Disease Guidelines and the 2012 ESC/EACTS guidelines state that SDM is a Class I recommendation for prosthetic valve selection [1,2]. Nevertheless, despite the advantages of SDM and the fact that the guidelines advocate SDM, informed SDM is not often applied in daily clinical practice [18, 19]. SDM can be time consuming and requires extra effort, which can be a barrier for cardiovascular professionals. In this respect the use of a decision aid (DA) may be useful to support SDM. It has been shown that patients who use a DA have improved knowledge, more accurate risk perception, reduced decisional conflict, and are more likely to receive care that is in line with their personal values [17]. In the setting of prosthetic valve selection a DA can inform patients about the different prosthetic valves and associated risks and benefits, help them clarify their preferences, and guide them through the decision making.

In order to participate in decision making patients should be able to understand what the available prosthetic valve options and their associated risks and benefits are. The way risks and benefits are presented influences the ability of the patient to understand the given information. Presenting statistical information in a graphical instead of numerical format increases people's understanding and may affect their decision

making [20]. Previous studies show that a pictograph is the preferred option to present probabilistic information to patients [8]. In the current study however, most patients preferred a pie chart. Of note, the present study only investigated patient preference for the presentation of scientific evidence, while previous studies investigated which graph format achieved the best accuracy of risk perception. Therefore, although most patients in our study preferred a pie chart, this does not necessarily imply that it is the most effective way to communicate risks.

Patient prosthetic valve knowledge and numeracy

Almost half of the patients in our study felt that they had insufficient knowledge of prosthetic valves and almost one-third were unable to answer three basic knowledge questions about prosthetic valves correctly. We can only hypothesize that they either were not informed about the different prosthetic valves or received information that they were unable to comprehend. This observation nevertheless calls for the development of information provision on prosthetic valves that is tailored to the needs of patients.

Besides testing patient knowledge, we also deliberately tested numeracy. Since numbers are an inherent part of weighing risks and benefits [9], numeracy is of great influence on the capacity of patients to engage in SDM. One third of the study patients did not answer any basic numeracy question. It could be that the questions were perceived too difficult and patients were afraid to answer them. Additionally, nearly half of the patients who did answer all numeracy questions exhibited impaired numeracy. These observations underline the importance of recognition among physicians that many patients have difficulties understanding numbers and need help in understanding risks and benefits of treatment options [21].

Given their limited basic knowledge regarding prosthetic valves and limited numeracy, many patients will experience difficulties in weighing risks and benefits associated with mechanical and bioprosthetic valves. A DA with plain language, absolute risks presented as frequencies, and pictographs used to communicate risks and benefits [20] may therefore be helpful in the setting of prosthetic valve selection. Building on the current study and a previous survey concerning SDM in prosthetic valve selection among Dutch cardiovascular professionals [5], an information portal and DA for prosthetic valve selection has been developed and is currently tested in a multicentre RCT to assess whether the use of the DA indeed improves quality of decision making and patient outcome in the setting of prosthetic valve selection.

Study limitations

This study population represents Dutch academic cardiovascular clinical practice. A limitation of the study was the relatively small sample size. Furthermore, surveys were completed at home and patients may have been influenced by family members or friends. Finally, it is possible that only more motivated patients have completed the questionnaire, which could introduce selection bias.

In conclusion, this study illustrates that in current Dutch cardiovascular practice patients who require AVR experience suboptimal involvement in prosthetic valve selection, and exhibit impaired knowledge concerning prosthetic valves and numeracy. Given the broad support for SDM among patients and cardiovascular community, and the obvious need for understandable information, implementation in clinical practice of the concept of SDM would be a major step forward in improving clinical decision making in prosthetic valve selection. This will result in better patient involvement in decisions, increased patient knowledge, involvement and satisfaction, and perhaps even a better QoL.

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REFERENCES

1. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardiothoracic S, Vahanian A, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451-96.
2. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-643.
3. Brennan JM, Edwards FH, Zhao Y, et al. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. Circulation 2013;127:1647-55.
4. Ruel M, Chan V, Bedard P, et al. Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age. Circulation 2007;116:I294-300.
5. Korteland NM, Kluin J, Klautz RJ, et al. Cardiologist and cardiac surgeon view on decision making in prosthetic aortic valve selection: does profession matter? Neth Heart J 2014;22:336-43.
6. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making 1995;15:25-30.
7. Degner LF, Sloan JA, Venkatesh P. The Control Preferences Scale. Can J Nurs Res 1997;29:21-43.
8. Hawley ST, Zikmund-Fisher B, Ubel P, et al. The impact of the format of graphical presentation on health-related knowledge and treatment choices. Patient Educ Couns 2008;73:448-55.
9. Lipkus IM, Samsa G, Rimer BK. General performance on a numeracy scale among highly educated samples. Med Decis Making 2001;21:37-44.
10. Aicher D, Holz A, Feldner S, et al. Quality of life after aortic valve surgery: replacement versus reconstruction. J Thorac Cardiovasc Surg 2011;142:e19-24.
11. Gu YJ, Botti S, Faro D. Turning the Page: The Impact of Choice Closure on Satisfaction. J Consum Res 2013;40:268-83.
12. Arora NK, McHorney CA. Patient preferences for medical decision making: who really wants to participate? Med Care 2000;38:335-41.
13. DeVoe JE, Wallace LS, Fryer GE, Jr. Patient age influences perceptions about health care communication. Fam Med 2009;41:126-33.
14. Ting HH, Brito JP, Montori VM. Shared decision making: science and action. Circ Cardiovasc Qual Outcomes 2014;7:323-7.
15. Albrecht KJ, Nashan D, Meiss F, et al. Shared decision making in dermato-oncology: preference for involvement of melanoma patients. Melanoma Res 2014;24:68-74.
16. Uldry E, Schafer M, Saadi A, et al. Patients' preferences on information and involvement in decision making for gastrointestinal surgery. World J Surg 2013;37:2162-71.
17. Lee EO, Emanuel EJ. Shared Decision making to Improve Care and Reduce Costs. New Engl J Med 2013;368:6-8.

18. Hauptman PJ, Chibnall JT, Guild C, et al. Patient perceptions, physician communication, and the implantable cardioverter-defibrillator. JAMA Intern Med 2013;173:571-7.
19. Zikmund-Fisher BJ, Couper MP, Singer E, et al. Deficits and variations in patients' experience with making 9 common medical decisions: the DECISIONS survey. Med Decis Making 2010;30:85S-95S.
20. Fagerlin A, Zikmund-Fisher BJ, Ubel PA. Helping patients decide: ten steps to better risk communication. J Natl Cancer Inst 2011;103:1436-43.
21. Gigerenzer G. Making sense of health statistics. Bull World Health Organ 2009;87:567.

APPENDIX 1

1. Are you aware that there are different types of aortic valve prostheses?
   - o Yes
   - o No

2. Has a decision been made regarding a specific type of aortic valve prosthesis?
   - o Yes
   - o No
   - o I don't know

3. What kind of aortic valve prosthesis will you receive?
   - o Mechanical valve
   - o Biological valve
   - o A different valve prosthesis, namely…
   - o I don't know

4. What type of aortic valve prosthesis is the most durable?
   - o Biological valve
   - o Mechanical valve
   - o I don't know

5. Which type of aortic valve prosthesis has the highest risk of causing blood clots?
   - o Biological valve
   - o Mechanical valve
   - o I don't know

6. With which type of aortic valve prosthesis does one have to use lifelong anticoagulation?
   - o Biological valve
   - o Mechanical valve
   - o I don't know

7. Do you think you possess sufficient knowledge on the risks and benefits that come with the different types of aortic valve prostheses?
   Strongly disagree 1 2 3 4 5 Strongly agree

8. With whom did you have the consultation regarding the choice for a specific type of aortic valve prosthesis?
   - o Cardiologist
   - o Cardiothoracic surgeon
   - o Other

9. Do you feel like you have been given enough time to make a well thought through decision?
   - o Yes
   - o No
   - o I don't know
   - o I did not have to make the decision by myself

10. Has someone else been involved with the decision making for this specific type of aortic valve prosthesis?
   - o Yes, a family member
   - o Yes, a close friend
   - o Yes,…
   - o No

11. The doctor has included me during the decision making process for a specific type of aortic valve prosthesis.
   Strongly disagree 1 2 3 4 5 Strongly agree
   - o I don't know
   - o Inapplicable

12. I think it is important to be included in the decision making process for a specific type of aortic valve prosthesis.
   Strongly disagree 1 2 3 4 5 Strongly agree
   - o I don't know
   - o Inapplicable

13. Do you feel like you had a voice in the decision making process for a specific type of aortic valve prosthesis?
   - o Yes
   - o No
   - o I don't know

14. The final decision in prosthetic aortic valve choice should be made by:
    - o The physician
    - o The physician, after considering the patients opinion
    - o The patient and physician together
    - o The patient, after considering the physicians opinion
    - o The patient

15. This decision was difficult for me to make.
    Strongly disagree 1 2 3 4 5 Strongly agree

16. I was clear about the best choice for me.
    Strongly disagree 1 2 3 4 5 Strongly agree

17. I was not sure about what to choose.
    Strongly disagree 1 2 3 4 5 Strongly agree

18. I was aware of which types of aortic valve prostheses were available to me.
    Strongly disagree 1 2 3 4 5 Strongly agree

19. I was aware of the benefits of each type of aortic valve prosthesis.
    Strongly disagree 1 2 3 4 5 Strongly agree

20. I was aware of the risks and side effects of each type of aortic valve prosthesis.
    Strongly disagree 1 2 3 4 5 Strongly agree

21. I would like to have had more advice and information on the different types of valve prostheses.
    Strongly disagree 1 2 3 4 5 Strongly agree

22. It was clear which benefits of the different types of valve prostheses applied most to me.
    Strongly disagree 1 2 3 4 5 Strongly agree

23. It was clear which risks and side effects of the different types of valve prostheses applied most to me.
    Strongly disagree 1 2 3 4 5 Strongly agree

24. It was difficult for me to decide what was more important to me (the benefits or the risks and side effects).
    Strongly disagree 1 2 3 4 5 Strongly agree

25. I felt pressure from others during the making of this choice.
    Strongly disagree 1 2 3 4 5 Strongly agree

26. I received enough support from others while making a choice.
    Strongly disagree 1 2 3 4 5 Strongly agree

27. I feel I have made an informed choice.
    Strongly disagree 1 2 3 4 5 Strongly agree

28. My decision shows what is important to me.
    Strongly disagree 1 2 3 4 5 Strongly agree

29. I expect to stick with my decision.
    Strongly disagree 1 2 3 4 5 Strongly agree

30. I am satisfied with my decision.
    Strongly disagree 1 2 3 4 5 Strongly agree

31. I am afraid of possible bleeding.
    Strongly disagree 1 2 3 4 5 Strongly agree
    o I don't know

32. I am afraid of getting thrombosis.
    Strongly disagree 1 2 3 4 5 Strongly agree
    o I don't know

33. I have a problem with taking medication.
    Strongly disagree 1 2 3 4 5 Strongly agree
    o I don't know

34. I am afraid of possibly needing another valve operation in the future.
    Strongly disagree 1 2 3 4 5 Strongly agree
    o I don't know

35. I am afraid of the possibility of my valve failing.
    Strongly disagree 1 2 3 4 5 Strongly agree
    o I don't know

36. I am scared that my new heart valve will limit me in my daily activities.
    Strongly disagree 1 2 3 4 5 Strongly agree
    o I don't know

37. I am scared that my new heart valve will influence my social life negatively.
    Strongly disagree 1 2 3 4 5 Strongly agree
    o I don't know

38. It bothers me that I have to use oral anticoagulation for the rest of my life.
    Strongly agree 1 2 3 4 5 Strongly disagree
    o I don't know

39. I am scared that the valve sound might bother me.
    Strongly agree 1 2 3 4 5 Strongly disagree
    o I don't know

40. A person taking Drug A has a 1% chance of having an allergic reaction. If 1,000 people take Drug A, how many would you expect to have an allergic reaction?
    … person(s) out of 1,000

41. A person taking Drug B has a 1 in 1,000 chance of an allergic reaction. What percent of people taking Drug B will have an allergic reaction?
    … %

42. Imagine that I flip a coin 1,000 times. What is your best guess on how many times the coin would come up heads in 1,000 flips?
    … times out of 1,000

43. Imagine the risk of a reoperation after heart valve replacement is 5 percent. This is represented in the following figures. Please order the figures based on how clear they are to you. 1 = most clear, 4 = least clear.
    Figure 1 1 2 3 4
    Figure 2 1 2 3 4
    Figure 3 1 2 3 4
    Figure 4 1 2 3 4

APPENDIX 2

1. Are you aware that there are different types of aortic valve prostheses?
   - o Yes
   - o No

2. What kind of aortic valve prosthesis did you receive?
   - o Mechanical valve
   - o Biological valve
   - o A different type, namely…
   - o I don't know

3. Do you think you possess sufficient knowledge on the risks and benefits that come with the different types of aortic valve prostheses?
   Strongly disagree 1 2 3 4 5 Strongly agree

4. The doctor has included me during the decision making process for a specific type of aortic valve prosthesis.
   Strongly disagree 1 2 3 4 5 Strongly agree

5. I think it is important to be included in the decision making process for a specific type of aortic valve prosthesis.
   Strongly disagree 1 2 3 4 5 Strongly agree
   - o I don't know
   - o Inapplicable

6. Do you feel that you have been given enough time to make a well thought through choice?
   - o Yes
   - o No
   - o I don't know
   - o I did not have to make the decision by myself

7. Do you feel like you had a voice in the decision making process for a specific type of aortic valve prosthesis?
   - o Yes
   - o No
   - o I don't know

8. The final decision in prosthetic aortic valve choice should be made by:
   - o The physician
   - o The physician, after considering the patients opinion
   - o The patient and physician together
   - o The patient, after considering physicians opinion
   - o The patient

9. Do you sometimes experience a shortness of breath?
   - o Yes
   - o No

   If yes,

   - o Do you experience shortness of breath during exercise (more than normal), but not in rest?
   - o Do you experience shortness of breath during minor exercise, but not in rest?
   - o Do you experience shortness of breath in rest?

10. If I had to do it over again, would I make the same decision to have surgery?
    - o Yes, for sure
    - o Yes, probably
    - o I don't know
    - o No, probably not
    - o No, absolutely not

11. Is there a valve sound that bothers me?
    - o Always
    - o Frequently
    - o Occasionally
    - o Rarely
    - o Never

12. Following my valve surgery, the frequency of doctor visits and blood tests bothers me.
    - o Always
    - o Frequently
    - o Occasionally
    - o Rarely
    - o Never

13. The possibility of complications due to my implanted valve concerns me.
    - o Always
    - o Frequently
    - o Occasionally
    - o Rarely
    - o Never

14. I am concerned about possible bleeding caused by my anticoagulant medication.
    - o Always
    - o Frequently
    - o Occasionally
    - o Rarely
    - o Never

15. I am afraid that my valve may fail.
    - o Always
    - o Frequently
    - o Occasionally
    - o Rarely
    - o Never

16. I am afraid that I may need another valve operation.
    - o Always
    - o Frequently
    - o Occasionally
    - o Rarely
    - o Never

17. I am satisfied with my new aortic valve.
    Strongly agree 1 2 3 4 5 Strongly disagree

“It's not about making the right choice. It's about making a choice and making it right”

J.R. Rim

8.

Does the Use of a Decision Aid Improve Decision Making in Prosthetic Heart Valve Selection?

A Multicenter Randomized Trial

Korteland NM, Ahmed Y, Koolbergen DR, Brouwer M, de Heer F, Kluin J, Bruggemans EF, Klautz RJ, Stiggelbout AM, Bucx JJ, Roos-Hesselink JW, Polak P, Markou T, van den Broek I, Ligthart R, Bogers AJ, Takkenberg JJ.

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ABSTRACT

Background. A Dutch online patient decision aid (PDA) to support prosthetic heart valve selection was recently developed. A multicenter randomized controlled trial (RCT) was conducted to assess whether use of the PDA results in optimization of shared decision making (SDM) in prosthetic heart valve selection.

Methods and Results. In a five-center RCT, patients were allocated to receive either standard preoperative care (control group) or additional access to the PDA (intervention group). Legally capable adult patients accepted for elective aortic and/or mitral valve replacement were included. Primary outcome was preoperative decisional conflict (Decisional Conflict Scale (DCS)), secondary outcomes included patient knowledge, involvement in valve selection, anxiety and depression, (valve-specific) quality of life (QoL), and regret.

Out of 306 eligible patients, 155 were randomized (78 control and 77 intervention). Preoperative decisional conflict did not differ between the groups (34% versus 33%; p=0.834). Intervention patients felt better informed (median DCS informed subscore: 8 versus 17; p=0.046) and had a better knowledge of prosthetic valves (85% versus 68%; p=0.004). Intervention patients experienced less anxiety and depression (median HADS score: 6 versus 9; p=0.015) and better mental well-being (mean SF-36 score: 54 versus 50; p=0.032). Three months postoperatively valve-specific QoL and regret did not differ between the groups.

Conclusions. A PDA to support SDM in prosthetic heart valve selection does not lower decisional conflict. It does result in more knowledgeable, better informed and less anxious and depressed patients, with a better mental well-being.

Clinical Trial Registration NTR4350.

http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4350.

The study is reported in accordance with the CONSORT guidelines for cluster-randomised trials.

INTRODUCTION

For heart valve replacement, two types of valve substitutes are available: mechanical and biological valves. Mechanical valves are designed to last a lifetime but require lifelong anticoagulation due to their increased thrombogenicity, resulting in an increased bleeding risk and increased risk of complications during pregnancy. Biological valves do not require long-term anticoagulation, unless another indication is present. However, they are subject to valve deterioration over time, and patients may require one or more reoperations later in life. The ESC Guidelines on the management of cardiovascular diseases during pregnancy state that a desire for pregnancy is considered an indication for a biological valve [1]. Given the different nature of mechanical versus biological prosthetic valve-related risks and benefits, and the fact that the choice for either of the prosthetic heart valves is often highly value-sensitive [2], current clinical practice guidelines recommend shared decision making (SDM) and explicit consideration of patient preferences in prosthetic heart valve selection [3, 4]. In a previous study we have shown that many patients experience decisional conflict and suboptimal involvement in prosthetic valve selection, and have limited knowledge of the advantages and disadvantages of mechanical and biological valves [5].

Since no tools to support SDM are available in this setting, an online patient decision aid (PDA) to support prosthetic heart valve selection was recently developed in the Netherlands. The PDA informs patients about the available treatment options, encourages participation in decision making and helps patients to assess their prosthetic valve preferences in relation to their values and goals in life, so they are optimally prepared to participate in prosthetic valve selection with their treating physician [6].

We tested in a multicenter randomized controlled trial the hypothesis that the use of the PDA results in an improved quality of decision making in prosthetic heart valve selection compared to standard preoperative care in patients accepted for aortic and/or mitral valve replacement. Quality of decision making measures included decisional conflict (primary outcome measure), patient knowledge, patient participation in decision making, anxiety and depression, health-related quality of life (QoL), valve-specific QoL and patient regret.

METHODS

Trial design

A prospective, 1:1 randomized, open, parallel-design clinical trial was conducted in five Dutch hospitals between May 2014 and May 2016.

Participants

Eligible participants were adult patients who were accepted for elective aortic valve replacement (AVR) and/or mitral valve replacement (MVR). Patients who were legally incapable were excluded. Eligible patients were contacted by phone, several weeks prior to their valve replacement surgery, and asked to participate. If a patient was willing to participate he/she received an information letter, and written informed consent was obtained. Participants were recruited from five Dutch hospitals; four academic centers and one non-academic hospital.

The study was approved by the institutional review board of all five participating centers (Erasmus MC MEC nr. 2013-569).

Intervention

The PDA was developed in a Delphi process according to the International Patient Decision Aids Standards (IPDAS) [7]. In October 2012, a steering group, consisting of 2 cardiothoracic surgeons, 2 cardiologists, 2 patient representatives and an epidemiologist, was formed and the scope and purpose of the PDA were determined. Alpha and beta testing were performed to investigate comprehensibility, acceptability and usability of the PDA by patients and clinicians. Based on this information, a draft of the PDA was developed by the steering group. Next the comprehensibility and acceptability of the PDA by patients and clinicians was assessed. After that, the PDA was again reviewed by the steering group and field tests were performed with patients and clinicians to assess usability. The steering group reviewed the test results and the PDA was finalized. For a more detailed description of the development of the PDA, see Appendix 1.

The final PDA is an online tool (www.hartklepkeuze.nl), and contains two sections: an information section on heart function, heart valve disease, available heart valve prostheses, the operation, living with a heart valve prosthesis, and hyperlinks for further information; and the actual PDA, which is made up of seven parts: 1) introduction and personal information (patients may optionally enter age and gender), 2) information on the two options (mechanical or biological valve), 3) a comparison of the options (if patient has entered age and gender, then age- and gender-specific estimates of the

lifetime risk of bleeding with a mechanical prosthesis and reoperation with a biological valve are displayed), 4) exploration of personal feelings regarding the two options, 5) a knowledge quiz, 6) exploration of patient preference, and 8) a summary of the results of the PDA that can be printed or e-mailed for use in the doctor's office [7].

The clinical pathway for patients who are referred for heart valve replacement at the participating centers is as follows: referral letters and required patient information are sent to the secretariat of the department of cardiothoracic surgery. A heart team next discusses each patient and a decision is made whether to pursue surgery or an alternative treatment strategy. After the patient is accepted for surgery, an invitation from the preoperative outpatient clinic is sent to the patient. At this point in time the patient was invited to participate in the trial. Patients in the intervention group received a username and password to gain access to the PDA prior to the preoperative consultation. From that moment on they had free access to the PDA and were able to visit the PDA as often as they preferred. Next, the patient was seen in the preoperative outpatient clinic and the prosthetic valve choice was discussed. Physicians who performed the preoperative consultation were informed about the trial and were able to answer questions of the patient with regard to the PDA. Most often, the patient was seen by the surgeon before surgery and then the definitive choice for a prosthetic valve was made.

Outcomes

Patients completed two questionnaires, one preoperatively after surgical workup (including the preoperative consultation) and one 3 months postoperatively.

Demographic questions included gender, age and education. Highest educational level was assessed with a multiple choice (MC) question, which consisted of the following categories: college graduate or higher, high school graduate, less then high school, and other. Other baseline questions included assessment of which clinician (surgeon, cardiologist, both or other) performed the preoperative consultation, whether a friend or family member was involved in prosthetic valve choice, and patient opinion on the amount of time available for prosthetic valve choice. Three months postoperatively self-reported New York Heart Association (NYHA) Class was assessed through a MC question.

Primary outcome

Decisional conflict

The Decisional Conflict Scale (DCS) was used preoperatively to measure degree of uncertainty about which course of action to take (in this case prosthetic valve selection) and the main modifiable factors contributing to uncertainty. It is a 16 item questionnaire

with 5 subscales: uncertainty, informed, values clarity, support and effective decision. Total scores <25 are associated with no decisional conflict and implementation of decision. Scores exceeding 25 are associated with decisional conflict. Scores ≥37.5 are associated with decision delay or feeling unsure about implementation [8].

Secondary outcomes

Patient knowledge

Preoperatively and 3 months postoperatively basic knowledge concerning prosthetic valves and patient self-perceived sufficiency of knowledge concerning prosthetic heart valves were assessed by MC questions and a 1-5 Likert Scale [9].

Patient (preference for) involvement in prosthetic valve selection

Preoperative and 3 months postoperative patient perceived experience with involvement in prosthetic valve selection and preferences for involvement in prosthetic valve selection and final decision for a prosthetic valve were assessed with MC questions and the Control Preferences Scale [10, 11].

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) was used to assess preoperative and 3 months postoperative symptoms and severity of anxiety and depression [12, 13].

Health-related QoL

Health-related QoL was assessed preoperatively and 3 months postoperatively with the Dutch version of the Short Form Health Survey (SF-36) [14, 15].

Valve-specific QoL

Valve-specific QoL was assessed 3 months postoperatively with 7 valve-specific questions [16, 17].

Patient regret

Patient regret with regard to prosthetic valve selection was assessed 3 months postoperatively with the Decision Regret Scale. A score of 0 means no regret, a score of 100 means high regret [18].

Sample size

The sample size calculation was based on our primary outcome, decisional conflict. In total 140 patients were needed to detect an effect size of 0.35 on the Decisional Conflict Scale (two-tailed, power 80%, alpha 0.025) [19].

Randomization

Patients were randomly assigned (1:1) to standard preoperative care (control group) or standard preoperative care plus additional use of the PDA (intervention group) with permuted block sizes of 10, stratified by center.

The randomisation sequence was generated by an independent statistician using a random number generator. Allocations were placed in serially numbered, opaque, sealed envelopes by 2 independent research assistants. The investigators were unaware of allocation sequence to ensure allocation concealment. They selected the next randomization envelope in sequence and outcome was noted in a randomization and identification log.

Blinding

Due to the nature of the intervention it was not possible to blind investigators and patients to the allocation.

Statistical methods

All outcomes were analyzed according to the intention-to-treat principle [20]. Continuous variables are displayed by the mean and standard deviation if normally distributed and by the median and range if there was no normal distribution. The distribution of the continuous variables was tested using the Kolmogorov-Smirnov test. Categorical variables are displayed as counts and percentages. Group comparison was done using the unpaired t-test for continuous data with a normal distribution. In case of ordinal data or data with no normal distribution we used the Mann-Whitney U-test or the Chi-Square test. To compare preoperative and postoperative group responses the paired t-test or Wilcoxon signed-rank test was used where appropriate. Multiple imputations (5 iterations) were used to impute missing DCS values. For the imputation we used the 16 items of the DCS. In two patients, the DCS was completely missing, so we did not impute these data. In 18 patients one or more items were missing, and in 90% of these cases it concerned 1 question. We performed post hoc sensitivity analyses to assess the potential influence of imbalances in baseline characteristics on the effect of the use of the PDA on the primary outcome DCS by performing ordinal regression analyses. For some of the questions patients had the option to choose 'I don't know' or 'not applicable' as an answer. These two options were omitted from the group comparisons.

All tests were 2-sided, and a p-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using IBM-SPSS 20 (IBM Corp., Armonk, NY).

RESULTS

Between May 2014 and March 2015 306 patients were accepted for elective AVR and/or MVR in one of the five participating centers. The follow-up period lasted until June 2015 and study closure was in May 2016. Of these 306 eligible patients, 155 patients provided written informed consent and were randomized, of whom 78 received standard preoperative care and 77 received standard preoperative care and additional access to the PDA. One hundred and thirty-eight patients (71 allocated to the control group and 67 allocated to the intervention group) completed the preoperative questionnaire (Figure 1).

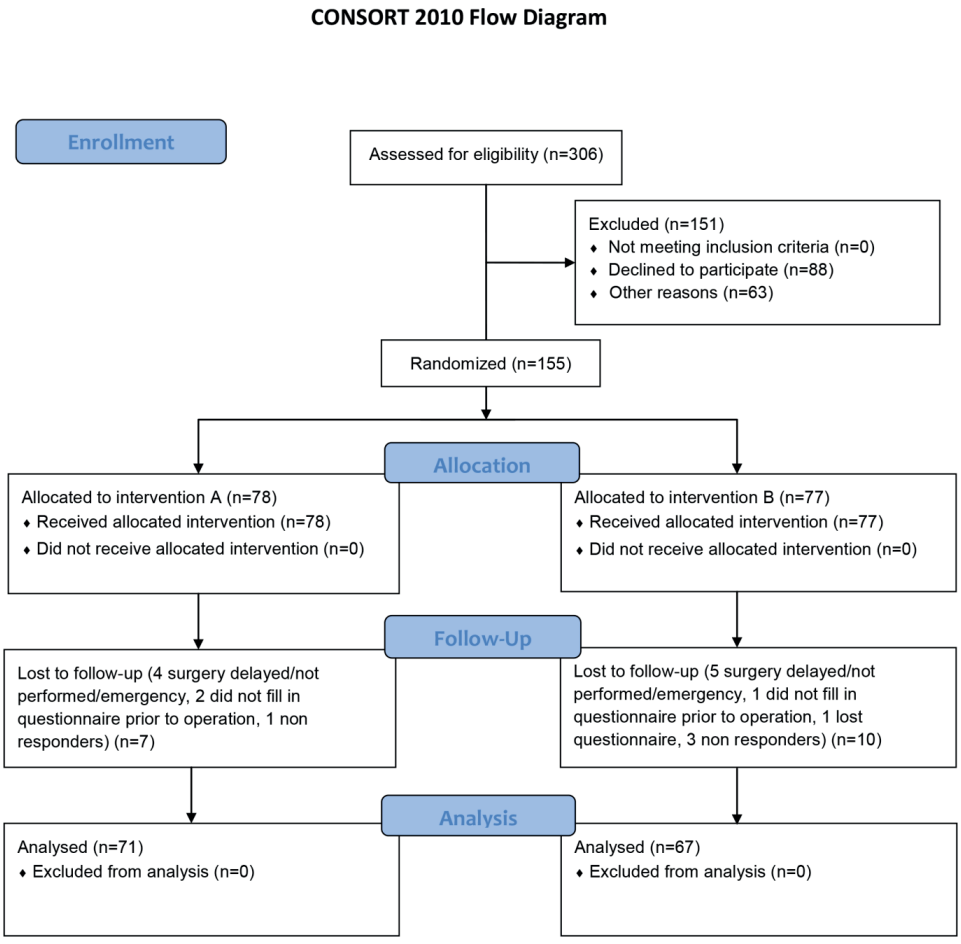

FIGURE 1. Flowchart.

Main reasons for declining informed consent, besides one patient who declined to participate, were the absence of a computer at home, a language barrier, or a postponed operation. Patient characteristics, other baseline data and the patient-reported implanted heart valve type are presented in Table 1.

TABLE 1. Patient characteristics and other baseline data

	Intervention group n=67	**Control group n=71**
Age (years), median (range)	66 (22-82)	68 (31-84)
Male gender, n (%)	51 (76)	53 (75)
Patient-reported educational level, n (%)		
< High school	13 (19)	19 (27)
High school graduate	34 (51)	31 (44)
College graduate	18 (28)	16 (23)
Other	2 (3)	4 (6)
Missing	0	1 (1)
Patient-reported implanted prosthesis type*, n (%)		
Mechanical valve	16 (24)	15 (21)
Biological valve	37 (55)	42 (59)
Other	1 (2)	2 (3)
Don't know	6 (9)	4 (6)
Missing	7 (10)	8 (11)
Preoperative consultation by, n (%)		
Surgeon	27 (40)	20 (28)
Cardiologist	26 (39)	36 (51)
Other	14 (21)	15 (21)
Involved in prosthetic valve choice, n (%)		
Family member	26 (39)	38 (54)
Friend	1 (2)	0
Other	10 (15)	4 (6)
No one else	30 (45)	27 (38)
Missing	0	2 (3)
Enough time available for prosthetic valve choice, n (%)		
Yes	48 (72)	43 (61)
No	2 (3)	3 (4)
I don't know	2 (3)	2 (3)
I did not have to make a decision	15 (22)	20 (29)
Missing	0	3 (4)

*This is the patient-reported prosthesis type that the patient received. It was assessed post operatively.

As there appeared to be potential imbalances in the baseline characteristics 'preoperative consultation' and 'involved in prosthetic valve choice', we first performed an ordinal regression analysis to assess the effect of the use of the DA on the primary outcome DCS without correction for these potential imbalances, and next a multivariable ordinal regression analysis with the 2 baseline characteristics included. There was no influence of the 2 baseline characteristics on the effect of the use of the PDA on the DCS (uncorrected exp beta= 0.90, p=0.38; corrected exp beta = 0.94, p=0.63).

Table 2 presents the results for the primary outcome, preoperative decisional conflict.

TABLE 2. Preoperative decisional conflict

	Intervention group n=66	**Control group n=70**
Decisional conflict, n (%)		
> 25	22 (33)	24 (34)
> 37.5	11 (16)	13 (18)
Total score, median (range)	24 (0-69)	24 (0-72)
Informed subscale*	8 (0-100)	17 (0-100)
Clarity subscale	28 (0-72)	27 (0-93)
Support subscale	25 (0-78)	25 (0-72)
Uncertainty subscale	40 (0-92)	33 (0-100)
Effectiveness subscale	6 (0-100)	6 (0-100)

*p<0.05 intervention versus control group.

Figure 2 presents preoperative (preference for) involvement in prosthetic valve selection.

Postoperatively there were some minor changes in (preference for) involvement in prosthetic valve selection in comparison to the preoperative results: a larger proportion of patients totally agreed that they were involved in prosthetic valve choice (p=0.061); and in the intervention group postoperatively a larger proportion of patients was of the opinion that it is important to be involved in prosthetic valve choice (p=0.066). Table 3 shows preoperative and 3 months postoperative patient knowledge.

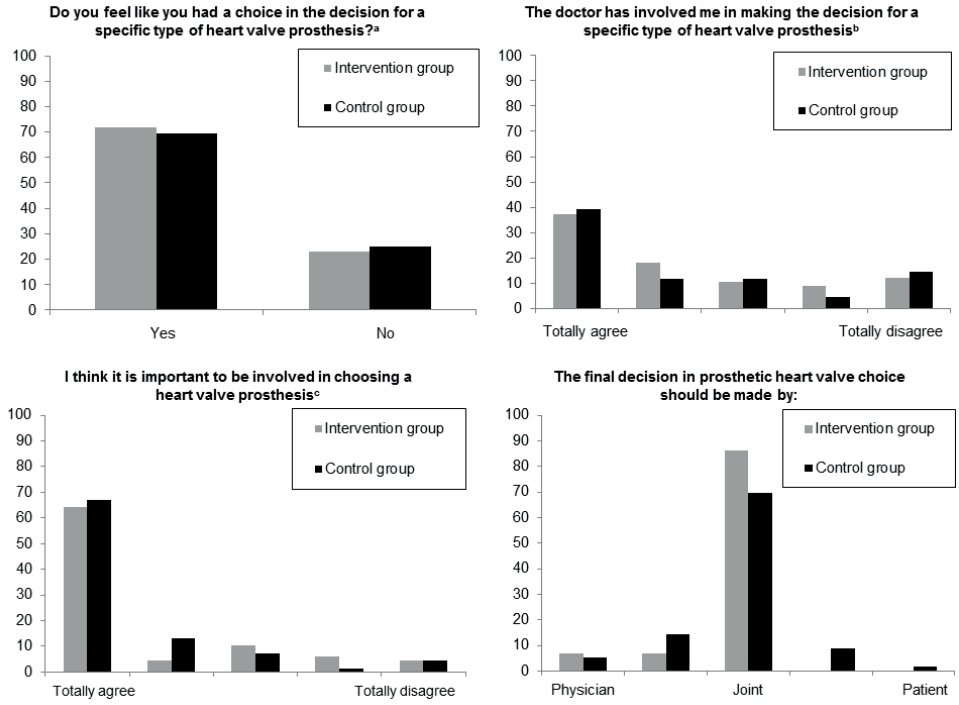

FIGURE 2. Preoperative patient (preference for) involvement in prosthetic valve selection. [a]Percentages of patients in the intervention and control group who answered 'I don't know' (5.3% and 5.4% respectively). [b]Percentages of patients in the intervention and control group who answered 'I don't know' (1.5% and 4.3% respectively) and 'not applicable' (11.9% and 14.5% respectively). [c]Percentages of patients in the intervention and control group who answered 'I don't know' (1.5% and 1.4% respectively) and 'not applicable' (9% and 5.7% respectively).

TABLE 3. Patient knowledge

	Preoperative		Postoperative	
Basic knowledge, n (%)	**Intervention group**	**Control group**	**Intervention group**	**Control group**
What type of aortic valve prosthesis is the most durable?	63 (94)	59 (83)	58 (94)	56 (86)
Which type of aortic valve prosthesis has the highest risk of causing blood clots?*,†	57 (85)	51 (72)	55 (89)	51 (79)
With which type of aortic valve prosthesis does one have to use lifelong anticoagulation?†	61 (91)	58 (82)	57 (92)	55 (85)
All questions correct*	57 (85)	48 (68)	51 (82)	48 (74)
2 questions correct	4 (6)	10 (14)	7 (11)	7 (11)
1 question correct	2 (3)	3 (4)	3 (5)	4 (6)
0 questions correct	3 (5)	9 (13)	1 (2)	5 (8)
Missing	1 (2)	1 (1)	0	1 (2)
Patient self-perceived sufficiency of knowledge	49 (73)	44 (62)	54 (87)	49 (77)

*p<0.05 intervention versus control group preoperative. †p<0.05 intervention versus control group postoperative.

Table 4 presents preoperative and postoperative anxiety and depression (HADS), and health-related QoL (SF-36). Three months postoperatively, 84% of patients were in NYHA class I or II.

Three months postoperative regret with regard to prosthetic valve choice ranged from 0 to 55, with no statistical difference between the intervention and control group. The majority of patients in the intervention and control group did not experience any regret (70% versus 64% respectively; p=0.513). Patients that were more involved in prosthetic valve choice experienced less regret three months postoperative (p=0.001).

Table 5 presents valve-specific QoL 3 months postoperatively.

TABLE 4. HADS and SF-36 outcomes

	Preoperative		Postoperative	
	Intervention group	**Control group**	**Intervention group**	**Control group**
HADS, median (range)*,†	6 (0-33)	9 (0-41)	3 (0-38)	4 (0-21)
Anxiety, n (%)†				
Normal (0-7)	20 (30)	17 (24)	49 (79)	56 (86)
Mild (8-10)	31 (46)	38 (54)	2 (3)	2 (3)
Moderate (11-14)	13 (19)	9 (13)	5 (9)	4 (6)
Severe (15-21)	3 (5)	7 (10)	1 (2)	0
Missing	0	0	5 (8)	3 (5)
Depression, n (%)†				
Normal (0-7)	0	0	49 (79)	60 (92)
Mild (8-10)	16 (24)	16 (23)	5 (8)	2 (3)
Moderate (11-14)	51 (76)	55 (78)	2 (3)	1 (2)
Severe (15-21)	0	0	2 (3)	0
Missing	0	0	4 (7)	2 (3)
Quality of life, mean (SD)				
PCS†	41 (11)	39 (11)	44 (10)	44 (10)
MCS*	54 (9)	50 (11)	54 (10)	53 (10)
Physical Functioning†	63 (24)	57 (26)	74 (23)	75 (22)
Role-Physical*	50 (42)	35 (43)	50 (42)	52 (43)
Bodily Pain	74 (24)	74 (24)	76 (24)	78 (21)
General Health†	61 (20)	56 (22)	68 (20)	68 (19)
Vitality†	58 (22)	56 (22)	67 (24)	66 (20)
Social Functioning*	81 (22)	70 (26)	77 (27)	78 (22)
Role-Emotional*	81 (34)	67 (40)	80 (37)	80 (33)
Mental Health†	80 (16)	73 (21)	82 (17)	81 (16)

*p<0.05 intervention versus control group preoperative.
†p<0.05 preoperative versus postoperative total group.
MCS = Mental Component Scale. PCS = Physical Component Scale.

TABLE 5. Three months postoperative valve-specific QoL

	Intervention group	Control group	P-value
If I had to do it over again, would I make the same decision to have surgery?			
Yes	93%	90%	.717
I don't know	3%	6%	
No	-	2%	
Missing	3%	3%	
Is there a valve sound that bothers me?			
Never/rarely	69%	66%	.487
Occasionally	23%	15%	
Frequently/always	3%	12%	
Missing	5%	6%	
Following my valve surgery, the frequency of doctor visits and blood tests bothers me.			
Never/rarely	71%	72%	.819
Occasionally	21%	19%	
Frequently/always	2%	6%	
Missing	7%	3%	
The possibility of complications due to my implanted valve concerns me.			
Never/rarely	78%	68%	.116
Occasionally	11%	28%	
Frequently/always	6%	2%	
Missing	5%	3%	
I am concerned about possible bleeding caused by my anticoagulant medication.			
Never/rarely	66%	63%	.235
Occasionally	27%	23%	
Frequently/always	2%	11%	
Missing	5%	3%	
I am afraid that my valve may fail.			
Never/rarely	84%	85%	.668
Occasionally	10%	11%	
Frequently/always	2%	2%	
Missing	5%	3%	
I am afraid that I may need another valve operation.			
Never/rarely	77%	80%	.187
Occasionally	18%	17%	
Frequently/always	-	-	
Missing	5%	3%	

DISCUSSION

For most patients, there is no right or wrong choice in prosthetic valve selection. Therefore, for this trial it was decided to evaluate the effect of the PDA on the quality of decision making, patient knowledge, and patient anxiety and QoL, rather than its potential effect on prosthetic valve selection and clinical outcomes. The most important findings of the trial are that, although it fails to show an effect on the primary outcome measure, preoperative decisional conflict, a PDA to support SDM in the setting of prosthetic heart valve selection results prior to surgery in more knowledgeable, better informed and less distressed patients with a better patient mental well-being.

Preoperative decisional conflict was quite common: one-third of patients experienced decisional conflict and 1 out of 6 patients to such an extent that they felt unsure about the prosthetic valve choice. There was relatively no effect of the PDA on preoperative decisional conflict. According to the DCS subscales intervention patients felt more informed. Both groups scored relatively low, indicating that they felt quite good informed. However, the magnitude of the difference between the groups is impressive, namely 9 (intervention group 8 and control group 17). Intervention patients felt more informed but also seemed a bit more uncertain, which may explain why the PDA failed to improve decisional conflict. It appears that the underlying assumption that more knowledge about a topic will automatically lead to more certainty in judgement may not be necessarily true. Also, the quantity of information needed to be comfortable in the decision making process may show strong individual differences. Eventually, it may be that we just have to accept a certain level of decisional conflict and support our patients herein only by recognition of this problem. What remains then is to concentrate on the optimum quantity and quality of information, and maybe personalize this for different types of people [21]. It is also possible that the failure of improving decisional conflict is in part due to the fact that the PDA is not yet implemented into the clinical care path. The PDA helped patients to prepare for choosing a particular valve prosthesis but also the treating physician needs to be prepared to engage into SDM. Participating patients sometimes were informed by a physician who stated that a choice was already made by the heart team or that there was no choice. One can imagine that this will have led to an increase in decisional conflict, in particular more uncertainty. Therefore, besides refinement of the PDA and formal implementation of the PDA in the care path (including a change in health care policy that rewards SDM), education of the treating physicians will be necessary and hopefully this will result in reduction of decisional conflict.

Interestingly, intervention patients did not only feel more informed, but they actually had better preoperative knowledge with regard to prosthetic heart valves. It therefore seems that the PDA is an important source of information for patients who are facing a heart valve replacement. This is in line with a previous systematic review on PDA's in a wide variety of diseases, which showed that PDA's improve patient knowledge [22]. As improved patient knowledge is associated with improved therapy compliance and reduced health care costs, the use of this PDA might also help health care cost containment [23, 24].

This trial also shows that most patients prefer to participate in decision making and indicate that prosthetic heart valve selection should be a joint decision of the patient and the physician. However, about a quarter of the patients felt that they did not have a choice and 20% were of the opinion that one was not involved in prosthetic valve selection. A considerable part of the patients was of the opinion that they did not have to make a decision with regard to prosthetic valve choice. In other words, their doctor made the decision. It is not clear whether prosthetic valve choice was actually not possible or SDM was not applied. We have shown in a previous study that although Dutch cardiologists and cardiothoracic surgeons consider patient involvement in prosthetic valve selection, it seems that there is room for improvement in its practical application [2]. In order to better serve patient needs with regard to participation in decision making, SDM should be implemented in the medical curriculum and tools to support SDM such as information portals and PDA's should be implemented in the care path.

We additionally investigated if use of the PDA reduces anxiety and depression and improves QoL, since it has been shown that patient participation in clinical decision making may improve QoL in a variety of medical conditions [25, 26]. The current trial confirms these observations as intervention patients had a better mental QoL preoperatively compared to control patients. Not surprisingly, use of the PDA has no effect on the physical QoL which is severely influenced by the heart valve disease for which surgical treatment is needed. Furthermore, as can be expected, physical QoL was evidently better 3 months postoperative compared to preoperatively in both the intervention and control group, illustrating the relief of symptoms by the surgical treatment. Intervention patients experienced less preoperative anxiety and depression. It can be debated if anxiety is an appropriate measure to evaluate a PDA, because it is known from the literature that anxiety can be associated with more effective decision making. Furthermore, the heart valve replacement itself can cause a raised level of anxiety [27]. In our randomized trial, the PDA did reduce anxiety. The reason for this remains to be elucidated. This was the first randomized trial that evaluated a PDA in

the field of prosthetic heart valve selection. It is possible that a PDA reduces anxiety in this particular field, also because SDM is not often applied [5]. Additionally, as can be expected, the surgical treatment resulted in a dramatic decrease in anxiety and depression. Of note, in contrast to the preoperative results, there were no differences 3 months postoperatively in anxiety, depression and QoL between intervention and control patients. It therefore appears that a PDA to support prosthetic heart valve selection is particularly effective in preoperative reduction of anxiety and depression and improvement of patient mental well-being. Whether this is clinically meaningful can of course be debated, but given the consistent direction of these differences in favor of the use of the PDA, we think we can state that the use of the PDA has a positive effect on the mental well-being of patients at the time of decision making.

Patients that were more involved in prosthetic valve choice experienced less regret postoperative. It is important to keep in mind that it is possible that patients that were more involved in decision making have different patient characteristics than patients that were less involved, and that this is the reason for the observed difference. Overall regret however, was very low despite the suboptimal decision making in the current trial. It is possible that the phenomenon of choice closure contributed to this. Choice closure is the process by which people come to perceive a decision to be resolved and complete. As choice closure results in less regret, it can explain at least in part why the vast majority of patients did not have any regret with regard to their prosthetic valve choice [28].

Three months postoperative valve-specific QoL did not differ between the groups, and revealed that most common valve-related concerns among patients are valve sound and possible bleeding caused by anticoagulation therapy. It is known that patients sometimes experience fear of rare valve-specific limitations, despite the preoperative information they received [29]. We hypothesized that a PDA provides understandable information which helps patients to clarify valve specific limitations. Our results however, did not endorse this hypothesis.

With regard to future research it would be useful to consider a trial that looks into the effect of the use of a PDA on the prosthetic heart valve choice that is eventually made, now that we know that the quality of decision making is positively influenced by the use of a PDA.

Limitations

This study population represents Dutch cardiovascular clinical practice and may not be generalizable to other countries. Unfortunately, although every effort was made

to recruit all eligible patients, patient recruitment was low (155/306). Main reasons were the absence of a computer at home, a language barrier (the Netherlands has an increasingly diverse population with many nationalities and cultural backgrounds), or a postponed operation. These reasons underline the importance of expanding the delivery modes (also provide a paper version) and language options of the PDA in order to improve uptake. Not all randomized patients completed the preoperative questionnaire which may have resulted in selection bias. Due to privacy law regulations in the Netherlands we are unable to register information of patients who were invited to participate in the trial but who declined to participate or did not fill in the preoperative questionnaire. Therefore we are unable to report any details on those patients or to perform a sensitivity analysis to assess the degree of selection bias introduced by the missing preoperative questionnaires.

The results in this randomized trial are based on self-reported outcomes during a small time window (preoperatively and 3 months postoperatively). The potential longer-term effects of the use of the PDA remain unexplored.

Questionnaires were completed at home and patients may have been influenced by family members or friends.

Patient age ranged from 22 through 84 years, and it may very well be that particular age groups (for example young adult patients) potentially benefit more from the use of a PDA than others. Given the limited sample size of this study, age sub groups were not analyzed but are worthwhile exploring in future studies.

Although the PDA was developed according to the IPDAS in a Delphi process including all stakeholders, it may be that the PDA is not yet optimally tailored to the needs of Dutch patients and the Dutch healthcare system. Continuous maintenance and further improvement of the PDA in a joint effort of all stakeholders is required to ascertain an effective and sustainable tool to support the SDM process in Dutch clinical practice.

With regard to patient experience with involvement in prosthetic valve selection patients had the option to choose 'not applicable' in the questionnaire. This term may have been misinterpreted by patients, since several patients chose 'not applicable' because their doctor made the decision with regard to prosthetic valve type. This also applies to the questions concerning information provision. It is recommended that the option 'not applicable' is not added to future questionnaires.

Conclusions

A PDA in the setting of prosthetic heart valve selection does not reduce decisional conflict. It does improve the quality of decision making by better informing patients, reducing anxiety and depression, and improving mental health prior to the operation. Effective implementation of the PDA in the care path of patients who require aortic and/or mitral valve replacement is the next major step forward in improving clinical decision making, and will hopefully help to lower overall decisional conflict.

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REFERENCES

1. European Society of G, Association for European Paediatric C, German Society for Gender M, Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L and Guidelines ESCCfP. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147-97.
2. Korteland NM, Kluin J, Klautz RJ, Roos-Hesselink JW, Versteegh MI, Bogers AJ and Takkenberg JJ. Cardiologist and cardiac surgeon view on decision making in prosthetic aortic valve selection: does profession matter? Neth Heart J. 2014;22:336-43.
3. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Guidelines ESCCfP, Joint Task Force on the Management of Valvular Heart Disease of the European Society of C and European Association for Cardiothoracic S. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardiothoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;42:S1-44.
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD and Members AATF. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:e521-643.
5. Korteland NM, Bras FJ, van Hout FM, Kluin J, Klautz RJ, Bogers AJ and Takkenberg JJ. Prosthetic aortic valve selection: current patient experience, preferences and knowledge. Open Heart. 2015;2:e000237.
6. Internation Patient Decision Aids Standards Collaboration. Criteria for judging the quality of patient decision aids. 2005. www.ipdas.ohri.ca/IPDAS_checklist.pdf Access date 11 January 2017.
7. Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, Thomson R, Barratt A, Barry M, Bernstein S, Butow P, Clarke A, Entwistle V, Feldman-Stewart D, Holmes-Rovner M, Llewellyn-Thomas H, Moumjid N, Mulley A, Ruland C, Sepucha K, Sykes A, Whelan T and International Patient Decision Aids Standards C. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. BMJ. 2006;333:417.
8. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15:25-30.
9. Healthwise Staff. Heart Valve Problems: Should I Choose a Mechanical Valve or Tissue Valve to Replace My Heart Valve? Healthwise.

https://www.healthwise.net/cochranedecisionaid/Content/StdDocument.aspx?DOCHWID=uf4587 Access date 11 January 2017.
10. Degner LF, Sloan JA and Venkatesh P. The Control Preferences Scale. Can J Nurs Res. 1997;29:21-43.
11. Pieterse AH, Baas-Thijssen MC, Marijnen CA and Stiggelbout AM. Clinician and cancer patient views on patient participation in treatment decision making: a quantitative and qualitative exploration. Br J Cancer. 2008;99:875-82.
12. Zigmond AS and Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361-70.
13. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE and Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27:363-70.
14. Ware JE, Jr. and Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.
15. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A and Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998;51:1055-68.
16. Aicher D, Holz A, Feldner S, Kollner V and Schafers HJ. Quality of life after aortic valve surgery: replacement versus reconstruction. J Thorac Cardiovasc Surg. 2011;142:e19-24.
17. Perchinsky M, Henderson C, Jamieson WR, Anderson WN, Jr., Lamy A, Lowe N and de Guzman S. Quality of life in patients with bioprostheses and mechanical prostheses. Evaluation of cohorts of patients aged 51 to 65 years at implantation. Circulation. 1998;98:II81-6; discussion II86-7.
18. Brehaut JC, O'Connor AM, Wood TJ, Hack TF, Siminoff L, Gordon E and Feldman-Stewart D. Validation of a decision regret scale. Med Decis Making. 2003;23:281-92.
19. O'Connor AM. User Manual - Decisional Conflict Scale. Ottawa Hospital Research Institute. 2017.https://decisionaid.ohri.ca/docs/develop/User_Manuals/UM_Decisional_Conflict.pdf Access date 11 January.
20. Donner A, Klar NS. Design and Analysis of Cluster Randomisation Trials in Health Research. London, Engeland: Hodder Arnold; 2000.
21. Stiggelbout AM, Molewijk AC, Otten W, Van Bockel JH, Bruijninckx CM, Van der Salm I and Kievit J. The impact of individualized evidence-based decision support on aneurysm patients' decision making, ideals of autonomy, and quality of life. Med Decis Making. 2008;28:751-62.
22. Stacey D, Legare F, Col NF, Bennett CL, Barry MJ, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L and Wu JH. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2014;1:CD001431.
23. van der Wal MH, Jaarsma T, Moser DK, Veeger NJ, van Gilst WH and van Veldhuisen DJ. Compliance in heart failure patients: the importance of knowledge and beliefs. Eur Heart J. 2006;27:434-40.

24. Grady KL, Dracup K, Kennedy G, Moser DK, Piano M, Stevenson LW and Young JB. Team management of patients with heart failure: A statement for healthcare professionals from The Cardiovascular Nursing Council of the American Heart Association. Circulation. 2000;102:2443-56.
25. Atherton PJ, Smith T, Singh JA, Huntington J, Diekmann BB, Huschka M and Sloan JA. The relation between cancer patient treatment decision making roles and quality of life. Cancer. 2013;119:2342-9.
26. Meade T, Dowswell E, Manolios N and Sharpe L. The motherhood choices decision aid for women with rheumatoid arthritis increases knowledge and reduces decisional conflict: a randomized controlled trial. BMC Musculoskelet Disord. 2015;16:260.
27. Bekker HL, Legare F, Stacey D, O'Connor A and Lemyre L. Is anxiety a suitable measure of decision aid effectiveness: a systematic review? Patient Educ Couns. 2003;50:255-62.
28. Gu YJ, Botti S, Faro D. Turning the Page: The Impact of Choice Closure on Satisfaction. J Consum Res 2013;40:268-83.
29. Aicher D, Fries R, Rodionycheva S, Schmidt K, Langer F and Schafers HJ. Aortic valve repair leads to a low incidence of valve-related complications. Eur J Cardiothorac Surg. 2010;37:127-32.

APPENDIX 1

The PDA was developed in a Delphi process according to the International Patient Decision Aids Standards (IPDAS) [1].

First, a survey among 117 cardiothoracic surgeons and cardiologists was conducted, to assess and compare their opinion on (1) patient involvement, (2) risk conveyance in aortic valve selection, and (3) aortic valve preferences. Most respondents agreed that patients should be involved in decision making, with surgeons more leaning toward patient involvement (always: 83% versus 50% respectively; $p<0.01$) than cardiologists. Most respondents found that ideally doctors and patients should decide together, with cardiologists more leaning toward taking the lead compared to surgeons ($p<0.01$). Major risks of the therapeutic options were usually discussed with patients, and less common complications to a lesser extent. A wide variation in valve preference was noted with cardiologists more leaning toward mechanical prostheses, while surgeons preferred bioprostheses more often ($p<0.05$). The conclusion of this survey was that patient involvement and risk conveyance in aortic valve selection was considered important by cardiologists and cardiothoracic surgeons. Medical profession influenced attitude with regard to aortic valve selection and patient involvement, and preference for a valve substitute. The variation in valve preference suggested that in most patients both valve types are suitable and aortic valve selection may benefit from evidence-based informed shared decision making [2].

Second, a prospective multicenter cohort study was set up. Aim of the study was to assess among adult patients accepted for aortic valve replacement (AVR): (1) experience with current clinical decision making regarding prosthetic valve selection, (2) preferences for SDM and risk presentation, and (3) prosthetic valve knowledge and numeracy. Patients were surveyed preoperatively and 3 months postoperatively. Preoperatively 132 patients (89 males/43 females; mean age 67 years (range 23-86)) responded. Decisional conflict was observed in 56% of patients, and in 25% to such extent that it made them feel unsure about the decision. Sixty-eight percent wanted to be involved in decision making, whereas 53% agreed they actually were. Sixty-nine percent were able to answer three basic knowledge questions concerning prosthetic valves correctly. Fifty-six percent were able to answer three basic numeracy questions correctly. Three months post-surgery 90% (n=110) were satisfied with their aortic valve prosthesis, with no difference between mechanical and bioprosthetic valve recipients. This cohort study showed that in current clinical practice many AVR patients experience decisional conflict, suboptimal involvement in prosthetic valve selection, and exhibit impaired knowledge concerning prosthetic valves and numeracy. Given the broad support for

SDM among AVR patients and obvious need for understandable information, to-be-developed tools to support SDM in the setting of prosthetic valve selection will help to improve quality of decision making, better inform and actively involve patients, and reduce decisional conflict [3].

In addition to the studies among clinicians and patients, a steering group, consisting of two cardiothoracic surgeons, two cardiologists, two patient representatives and an epidemiologist, was formed.

Based on the information from the clinicians and patients study, the draft of the PDA was developed by the steering group. Next step was to check the comprehensibility and acceptability of the PDA by patients (alpha testing 1) and clinicians (alpha testing 2).

Alpha testing 1 was conducted by means of a focus group. We approached eight patients with a prosthetic heart valve and seven of them participated. Two main subjects were discussed: 1) differences between a mechanical and biological valve that are essential to make a choice, and 2) other information that should be included in the PDA. Any additional information from the focus group meeting was incorporated in the PDA.

Alpha testing 2 was conducted by the steering group. We tried and tested the PDA on different devices. We also looked for errors in the text. After alpha testing 1 and 2, the PDA was again reviewed by the steering group. The PDA was modified according to the decisions from the steering group. After that field tests were performed with patients (beta testing 1) and clinicians (beta testing 2) to assess usability. We contacted eight clinicians (cardiothoracic surgeons and cardiologists) and eleven patients who underwent an aortic valve replacement by e-mail. We sent the clinicians and patients a review form which contained the following questions: 1) what do you think is missing?, 2) what can be improved?, and 3) are there things unclear? Furthermore we asked the clinicians and patient to grade the following things: 1) lay-out, 2) user-friendliness, 3) speed, 4) comprehensibility, and 5) general impression. Seven patients and one clinician responded. After beta testing the steering group reviewed the test results, made changes to the PDA in case this was necessary and the PDA was finalized.

REFERENCES

1. Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, Thomson R, Barratt A, Barry M, Bernstein S, Butow P, Clarke A, Entwistle V, Feldman-Stewart D, Holmes-Rovner M, Llewellyn-Thomas H, Moumjid N, Mulley A, Ruland C, Sepucha K, Sykes A, Whelan T and International Patient Decision Aids Standards C. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. BMJ. 2006;333:417.
2. Korteland NM, Kluin J, Klautz RJ, Roos-Hesselink JW, Versteegh MI, Bogers AJ and Takkenberg JJ. Cardiologist and cardiac surgeon view on decision making in prosthetic aortic valve selection: does profession matter? Neth Heart J. 2014;22:336-43.
3. Korteland NM, Bras FJ, van Hout FM, Kluin J, Klautz RJ, Bogers AJ and Takkenberg JJ. Prosthetic aortic valve selection: current patient experience, preferences and knowledge. Open Heart. 2015;2:e000237.

“Hear them all out
but decide for yourself”

Haresh Sippy

9.

General Discussion

The aim of this thesis was to provide insight in current prosthetic heart valve selection and outcomes in non-elderly adults and to introduce a tool to support shared decision making in this setting.

This chapter places the results of the research presented in this thesis in a broader perspective. Firstly, clinical and quality of life outcomes after aortic valve replacement in non-elderly adults will be discussed in the context of 21st century cardiovascular practice. Secondly, patient and physician attitudes toward shared decision making will be addressed. Thirdly, lessons learned from testing the efficacy of a decision aid for prosthetic heart valve replacement in a randomized controlled trial setting will be presented and the challenges with regard to implementation of the decision aid will be discussed.

Clinical and quality of life outcomes after aortic valve replacement in non-elderly adults

Although clinical and quality of life outcomes have improved markedly since the introduction of aortic valve replacement [1], nowadays concerns remain about prosthetic valve-related complications and their impact on patient life expectancy and quality of life.

Chapters 2 and 3 illustrate that the use of mechanical valve prostheses for aortic valve replacement or aortic root replacement is still associated with suboptimal survival in non-elderly adult patients. Possible underlying factors of this increased late mortality, besides prosthetic valve-related events, are prosthetic valve-associated hemodynamic factors, such as prosthesis-patient mismatch [2, 3], and associated myocardial disease. Furthermore, the required anticoagulation treatment after mechanical aortic valve replacement may be associated with a higher mortality rate due to their associated increased bleeding hazard. This remains a concern after mechanical aortic valve replacement, especially for non-elderly adults, since they usually have an active lifestyle and may have an occupation that is difficult to combine with anticoagulation use, or in case of women of child bearing age, may have the desire to become pregnant.

The main advantage of mechanical valve prostheses is their durability, and this is reflected in a low lifetime risk of reoperation following mechanical aortic valve replacement in comparison with biological aortic valve replacement. Our results in Chapter 2 emphasize that the lifetime risk of a reoperation with a mechanical valve prosthesis is about 8-15% in patients with a mean age between 18 and 55 years. This is based on the observation that the annual linearized occurrence rate of reoperation for mechanical valve prostheses is 0.51%. In Chapter 3 we found a comparable annual

linearized occurrence rate for aortic root reoperation of 0.46% in patients who received a root replacement with a mechanical valve prosthesis conduit (Bentall procedure). Main reasons for reoperation are nonstructural valve dysfunction, valve thrombosis or prosthetic valve endocarditis. One need to realize that reoperation following aortic valve replacement is in fact not a complication, but rather a medical decision following a valve-related complication, and that not all patients who need a reoperation, actually undergo a reoperation. During the last decades the safety of a reoperation has greatly improved as a result of improvements in surgical, medical and perioperative care. With regard to aortic valve replacement in non-elderly adults the alternatives for a mechanical valve prosthesis are a biological valve prosthesis and aortic valve repair. Although anticoagulation therapy is not indicated with biological valve substitutes, there is a substantial risk of structural valve deterioration and therefore a considerable risk of reoperation [4-7].

Structural valve deterioration is rarely a cause of reoperation in mechanical valve prostheses, but again one need to realize that not all patients with structural valve deterioration are re-operated, for example because of comorbidity, heart failure, or (patient) preferences. It also needs to be emphasized that structural valve deterioration is a process that takes place over a number of years, and that during this time there is gradually increasing suboptimal functioning of the biological valve substitute that may increase the hazard of endocarditis and thromboembolism, cause myocardial damage, and thus increase the mortality hazard. Therefore it is important to carefully monitor non-elderly adults with biological valve substitutes over time, in particular in the second postoperative decade when the hazard of structural valve deterioration increases exponentially [8-11].

Besides the influence of prosthetic heart valves on clinical outcomes, the limitations of mechanical and biological valves may have a great impact on quality of life. In Chapter 4 it was shown that the majority of 240 non-elderly adults who underwent aortic valve replacement in our institution experienced a good perceived quality of life 1-10 years after surgery. However, quality of life was influenced by prosthetic valve type: biological valve recipients reported lower general health than mechanical valve recipients while mechanical valve recipients had more doubts about the decision to undergo surgery, were more bothered by valve sound, the frequency of physician visits and blood tests, and possible bleeding, but were less afraid of a possible reoperation. In the literature there is no consensus about whether there is a preferred prosthetic valve type in relation to quality of life. Two studies reported no difference in quality of life between mechanical and biological valve recipients [12, 13]. One study reported a relatively high quality of life in mechanical valve recipients with a mean follow-up of 30 years [14].

Four studies reported a better quality of life in patients who received a biological valve substitute or underwent aortic valve repair in comparison with patients who received a mechanical valve [15-18]. With regard to aortic root surgery, one study reported a better quality of life in patients who underwent aortic valve re-implantation in comparison to patients who underwent an aortic composite replacement [19], while a systematic review reported one study that found no difference in quality of life [20]. With regard to composite graft root replacement, two studies found comparable quality of life in mechanical and tissue (biological valve or Ross procedure) valve recipients [21, 22]. The observation that there seems to be no "best" prosthetic valve type with regard to quality of life, and the observation that the pros and cons of different valve types have a markedly different nature, underlines the importance of discussing both options in detail with the patient, and exploring patient values and goals in life in relation to the advantages and disadvantages of the different valve types. Particularly non-elderly adults have a substantial lifetime risk of valve-related events. Especially the tradeoff between the risk associated with lifelong anticoagulation use and the risk of a reoperation is an important factor in prosthetic valve selection. Patients differ in their attitude with regard to these risks. While one person prefers a low lifetime risk of reoperation, others may prefer a life without the hazards that are associated with lifelong anticoagulation. There is an increasing awareness that informed patient preferences should also be considered in the selection of a prosthetic valve, and the ACC/AHA Valvular Heart Disease Guidelines and ESC/EACTS guidelines recommend shared decision making in prosthetic heart valve selection (Class 1 indications) [23, 24, 25].

In Chapter 4 we used the SF-36 to measure quality of life [26]. Questionnaires were completed 1 to 10 years after aortic valve replacement. Measuring quality of life in retrospect will give insight in patient perceived quality of life at one point, namely at the moment the patient completes the questionnaire. One step further is to measure quality of life prospectively and use these outcomes to improve quality of care for patients [27]. In the field of aortic valve replacement it would be particularly useful to measure quality of life pre- and postoperatively, with a minimal follow-up of one year in order to explore potential longer-term effects of aortic valve replacement on quality of life. To encourage quality of life measurement in the field of aortic valve replacement patients should have the ability to fill in quality of life questionnaires online. In the era of value-based health care and rapidly expanding information technology innovations, serial measurements of quality of life over time after cardiac surgery is at the horizon. These measurements are not only of value for monitoring the quality of cardiovascular care but also have added value for the patient to monitor his or her quality of life in relation to their health [27].

The perfect aortic valve substitute is not yet available. There are two innovations that may become important for non-elderly adults who require aortic valve replacement: tissue engineered valves and transcatheter implantation of aortic valve substitutes. Tissue engineered aortic valves are still in the preclinical phase of development, but may be a solution in the future. Although in vivo and in vitro results are promising, the gap with clinical practice is yet to be closed [28-30]. Currently available valve substitutes have a good performance, so a tissue engineered valve has to be at least as good, with less complications and at a reasonable cost [31]. Transcatheter aortic valve implantation can influence the treatment of non-elderly adults in two ways. Firstly, as a treatment for newly diagnosed aortic valve disease. Secondly, as a reintervention by implanting a prosthesis inside a degenerated biological valve prosthesis. As an option for reintervention, transcatheter aortic valve implantation can influence prosthetic valve choice in newly diagnosed aortic valve disease. A biological valve prosthesis can become more preferable for primary aortic valve replacement in younger patients in comparison to a mechanical valve prosthesis, because transcatheter aortic valve implantation is not possible after primary valve replacement with a mechanical valve prosthesis.

Patient and physician attitudes toward shared decision making

With increasing emphasis on patient reported outcome and experience measures and implementation of information portals and decision aids to support shared decision making, health care is transforming to optimally empower individual patients in balancing risks and benefits in their own context, both short and long term. It does require a different role pattern: for physicians to take a more guiding role, and for patients to be proactive in order to become a full member of their own heart team. In the field of prosthetic heart valve selection in the Netherlands, with physicians who vary in their attitude with regard to patient involvement [Chapter 6], and patients who experience decisional conflict and suboptimal involvement [Chapter 7], there is room for improvement with regard to shared decision making.

In current Dutch cardiovascular clinical practice involvement of patients who require aortic valve replacement is suboptimal and they often experience decisional conflict as was shown in Chapter 4 and 7. These findings do not stand alone in the literature. Suboptimal involvement is also seen in patients with severe symptomatic aortic stenosis who receive medical management [32], patients with asymptomatic abdominal aneurysm [33], patients who require an implantable cardioverter-defibrillator [34], and also in patients who need to make common medical decisions, for example initiation of medication with high blood pressure [35].

There are several factors that may influence the decision making process in prosthetic heart valve selection: physician-related factors, patient-related factors and process/ system-related factors.

Physician-related factors

Physician-related factors are discussed in Chapter 6. Possible underlying reasons for suboptimal involvement of patients in decision making are the fact that physicians are afraid that shared decision making is time consuming [33], the fact that physicians have their own established practice patterns [36], or social, economic or cultural characteristics of patients that retain physicians to start a discussion with them [35]. Physicians may think that involvement of the patient in prosthetic valve choice will require a lot of time and effort. However, applying shared decision making in daily clinical practice only seems to add a couple of minutes to the consultation [37, 38]. In this respect, a decision aid may even help physicians to save time, because patients are better informed when they enter the consulting room and they will be more able to participate in decision making.

Another reason may be that physicians are not willing to change their established practice patterns. Physicians often see a large amount of patients during the day which will easily induce routine practice. Using a decision aid is a change in their daily clinical practice. However, it is known that physicians gain interest in the use of a decision aid when they become acquainted with it within a research setting [36].

Despite the fact that there is obviously room for improvement with regard to shared decision making in prosthetic heart valve selection, the majority of Dutch cardiovascular professionals is of the opinion that patient involvement is important.

Patient-related factors

Patient-related factors are discussed in Chapter 4 and 7. The role of the patient in the patient-physician interaction is changing. Not long ago, patients had a passive role, had limited knowledge of their disease and they mostly followed the physician's advice without any discussion. Nowadays knowledge about medical care is easily available through the internet. Patients are more informed, although not always based on the right information, which results in bringing in more information and discussion in the contacts between the physician and the patient. Most patients are not willing to participate in decision making initially. However, once they receive information on their disease and treatment options they are more able and more willing to participate in decision making [39, 40]. Patients differ in their information needs. Some patients do want to know every detail of their treatment, while other patients do not want to be

involved at all. Of course, it needs to be accepted when a patient does not want to be involved. Nevertheless, each patient needs to be informed about the available options and their advantages and disadvantages and asked what they think is important for them.

A major challenge in shared decision making is the so called health illiteracy. Many patients have a limited numeracy. They have difficulties in understanding numbers and need help in understanding risks and benefits of treatment options [41]. Our decision aid, with plain language, absolute risks presented as frequencies, and pie charts to present these risks, may help patients to better understand risks and benefits in the setting of prosthetic valve selection.

Process-related factors

Implementation of shared decision making in the care path is important. This means however, that the current care path needs to be changed. Nurse practitioners or nurses can be set in to inform patients about the decision to be made, with or without the use of a decision aid, and assess patient preferences. But it can also mean that there needs to be an extra consultation in order to make a shared decision. The care path nowadays is not adjusted to shared decision making and physicians experience time pressure in their consultation with patients. It would also be helpful if shared decision making conversations in the care path will be financially compensated, in order to facilitate these conversations.

Although the internet is an important part of our lives nowadays, it is not yet an established factor in daily clinical practice. The number of decision aids is growing, but using these decision aids in the care path is one step further. Currently it is often the physician who informs the patient about the available decision aid. It would be an improvement if the decision aid becomes available as a standard part of the care path. This can be achieved when hospitals take the responsibility to incorporate available decision aids in their information system. Furthermore, hospitals can use the internet to inform patients in various ways. This can be an opportunity to change and improve daily clinical practice. Computers can replace or at least support a physician in certain tasks, which will make medicine more efficient and less expensive. An additional advantage is the opportunity to gather these data and built large datasets which can be used for quality improvement and research [42].

Decision aid for prosthetic heart valve replacement

Although prosthetic heart valve selection is highly preference sensitive, no shared decision making framework was available at the time of the development of the

decision aid. The Dutch Association for Cardiothoracic Surgery quality improvement project developed and tested a decision aid to support prosthetic heart valve selection [Chapter 8]. Despite the fact that there is obviously room for improvement with regard to shared decision making in the field of prosthetic heart valve selection [Chapter 6 and 7], the question is whether the introduction of a decision aid in the clinical setting is by itself capable of improving the quality of decision making or if more is needed to improve shared decision making in prosthetic heart valve selection.

Shared decision making is a process in which several steps can be identified. The physician informs the patient about the available treatment options, clarifies that a decision is to be made and ensures the patient that his opinion is important. After that the physicians explains the advantages and disadvantages of each available option, and checks whether the patient has understood the given information. The physician invites the patient to participate in decision making and patient preferences are clarified. At last, the physician tries to clarify whether the patient is ready to make a decision and what is needed to implement the decision [43, 44].

A decision aid is merely a tool that can be used to support the process of shared decision making described above. The results of our multicenter randomized controlled trial show that a decision aid to support shared decision making in prosthetic heart valve selection does result in more knowledgeable, better informed, less anxious and depressed patients with a better mental wellbeing, but it did not lower decisional conflict [Chapter 8]. A decision aid informs patients and helps them to make a choice that reflects their own values and preferences [45, 46]. However, more knowledge may not necessarily lead to less uncertainty and improved decision making [33, 47]. Although every patient needs to be informed about their disease, in order to understand their condition and participate in decision making, people differ in their need for information. Personal factors, like education, cultural background, and personality may play a role in these differences. It would be useful to personalize the quantity and quality of information for different types of people, based on their personal factors. And informing patients and clarifying their preferences is just one important part of shared decision making. Exploring and discussing the patient's emotions should not be forgotten [48]. Although there is room for expressing emotions in our decision aid, this should also be picked up in the preoperative counselling by the treating physician.

In the process of developing this decision aid, we have identified several challenges. The Netherlands has an increasingly diverse population with many nationalities and cultural backgrounds. It would be useful to expand the language options of the decision aid in order to reach non-native speakers.

In this digital era the majority of patients are able to use a computer. However, there are still patients, mostly elderly, who are not able to work with a computer or who do not have access to a computer. The delivery modes of the decision aid should therefore be expanded and we should also provide a paper version.

In order to participate in decision making patients should be able to understand what the available prosthetic valve options and their associated risks and benefits are. Although we tried to present statistical information in an understandable way it is possible that some patients were not able to understand the given information. An improvement of the decision aid would be to present statistical information in a more interactive way, for example with an animation or movie.

Not only patients, but also physicians should be prepared to the use of a decision aid in the clinical care path. With regard to the development of future decision aids we should not only focus on the refinement of the decision aid, but also on the formal implementation of the decision aid in the care path and education of the treating physicians. Physicians need to gain knowledge with regard to shared decision making and learn how to apply it in daily medical practice [28]. An implementation trial should be the last step in the development process of the prosthetic heart valve decision aid.

Decision aids are increasingly used and developed in the field of cardiovascular diseases. Interestingly, a randomized trial of a PCI choice decision aid for stable coronary artery disease published two months prior to our prosthetic valve selection decision aid trial, reported comparable outcomes: better patient knowledge but no change in decisional quality [47]. In addition, the same group studied cardiovascular physicians' perceptions of shared decision making following use of the PCI choice decision aid and identified gaps in clinician knowledge around shared decision making, and reluctance among clinicians to modify their baseline practice, although they express their interest in using decision aids after they have been exposed to them in a research setting [36]. This suggests that the introduction of decision aids in cardiovascular clinical practice may not only be effective in empowering patients, but may also help to instruct clinicians on optimal implementation of shared decision making in their clinical practice [47]. Another interesting tool that is currently being tested in a randomized trial is the anticoagulation choice conversation tool. The aim of this trial is to assess if the tool promotes shared decision making and influences anticoagulation uptake and adherence in patients with atrial fibrillation at risk of strokes [49]. The increasing amount of available evidence on the development, testing and implementation of decision aids in cardiovascular care will help to improve the quality of future decision aids and will identify and hopefully help to solve obstacles for the use of decision aids in the clinical care path.

Conclusion and future perspectives

Clinical and quality of life outcomes after aortic valve replacement in non-elderly adults

This thesis illustrates that mechanical valves for aortic valve replacement or aortic root replacement are still associated with suboptimal survival in non-elderly adult patients. Patients have a good perceived quality of life 1-10 years after surgery, but quality of life is influenced by prosthetic valve type. Improvement in outcomes after aortic valve replacement in non-elderly adults can be achieved in two ways. Firstly, innovations with regard to aortic valve substitutes, like tissue engineered valves and transcatheter implantation of aortic valves may improve survival and minimize the disadvantages that are associated with the nowadays available aortic valve substitutes. Secondly, serial measurements of quality of life can be incorporated in the clinical care path regarding aortic valve replacement. Standardized online measurements of quality of life are valuable for monitoring and improving the quality of cardiovascular care, but also for the patient to get insight in his or her own quality of life.

Patient and physician attitudes toward shared decision making

The field of prosthetic heart valve selection in the Netherlands is characterized by suboptimal involvement of patients. There seem to be two important facilitators to incorporate shared decision making in prosthetic heart valve selection. Firstly, physicians need to be trained with regard to shared decision making and learn how to apply it in daily medical practice. Secondly, the rapidly evolving digital world can be used to facilitate patient centered care. Patients can use their smartphone for example to get insight in their own test results or to measure quality of life over time. In the upcoming years, the world of medicine is about to change dramatically with the forecast of a patient revolution in healthcare, with digitized medicine and patient centered care [50], and shared decision making will play a central role.

Decision aid for prosthetic heart valve replacement

The amount of decision aids in clinical practice is growing. Next step is to carefully implement shared decision making in the care paths and link decision aids to the patient portal of the hospital information system. The decision aid can support the patient in decision making, but can also be of use after a decision is made: monitoring how the patient is doing, by serial measurements of quality of life, will inform the treating physicians, but also be of value to the patient.

At this point in time test implementation of the prosthetic heart valve decision aid has been completed in the care path of two Dutch hospitals where cardiac surgery

is performed, and an implementation toolkit has been developed based on the test implementations. The decision aid has now been adopted by the Dutch Heart Registration as an innovation project and is expected to be implemented in the care paths of Dutch heart centers in the coming year, combining shared decision making support with Dutch outcome data from the Netherlands Heart Registration. When this has been achieved, we are one step closer to true value-based care for patients who require heart valve replacement.

REFERENCES

1. Harken DE, Taylor WJ, Lefemine AA, Lunzer S, Low HB, Cohen ML and Jacobey JA. Aortic valve replacement with a caged ball valve. Am J Cardiol. 1962;9:292-9.
2. Pibarot P and Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. J Am Coll Cardiol. 2000;36:1131-41.
3. Head SJ, Mokhles MM, Osnabrugge RL, Pibarot P, Mack MJ, Takkenberg JJ, Bogers AJ and Kappetein AP. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. Eur Heart J. 2012;33:1518-29.
4. Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ, Steyerberg EW, van Herwerden LA, Grunkemeier GL, Habbema JD and Bogers AJ. Prognosis after aortic valve replacement with the Carpentier-Edwards pericardial valve: use of microsimulation. Ann Thorac Surg. 2005;80:825-31.
5. Chan V, Malas T, Lapierre H, Boodhwani M, Lam BK, Rubens FD, Hendry PJ, Masters RG, Goldstein W, Mesana TG and Ruel M. Reoperation of left heart valve bioprostheses according to age at implantation. Circulation. 2011;124:S75-80.
6. Bourguignon T, Lhommet P, El Khoury R, Candolfi P, Loardi C, Mirza A, Boulanger-Lothion J, Bouquiaux-Stablo-Duncan AL, Marchand M and Aupart M. Very long-term outcomes of the Carpentier-Edwards Perimount aortic valve in patients aged 50-65 years. Eur J Cardiothorac Surg. 2016;49:1462-8.
7. Johnston DR, Soltesz EG, Vakil N, Rajeswaran J, Roselli EE, Sabik JF, 3rd, Smedira NG, Svensson LG, Lytle BW and Blackstone EH. Long-term durability of bioprosthetic aortic valves: implications from 12,569 implants. Ann Thorac Surg. 2015;99:1239-47.
8. van Geldorp MW, Eric Jamieson WR, Kappetein AP, Ye J, Fradet GJ, Eijkemans MJ, Grunkemeier GL, Bogers AJ and Takkenberg JJ. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. J Thorac Cardiovasc Surg. 2009;137:881-6, 886e1-5.
9. Weber A, Noureddine H, Englberger L, Dick F, Gahl B, Aymard T, Czerny M, Tevaearai H, Stalder M and Carrel TP. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. J Thorac Cardiovasc Surg. 2012;144:1075-83.
10. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C and Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol. 2000;36:1152-8.
11. Chan V, Jamieson WR, Germann E, Chan F, Miyagishima RT, Burr LH, Janusz MT, Ling H and Fradet GJ. Performance of bioprostheses and mechanical prostheses assessed by composites of valve-related complications to 15 years after aortic valve replacement. J Thorac Cardiovasc Surg. 2006;131:1267-73.
12. Aboud A, Breuer M, Bossert T and Gummert JF. Quality of life after mechanical vs. biological aortic valve replacement. Asian Cardiovasc Thorac Ann. 2009;17:35-8.

13. Sedrakyan A, Hebert P, Vaccarino V, Paltiel AD, Elefteriades JA, Mattera J, Lin Z, Roumanis SA and Krumholz HM. Quality of life after aortic valve replacement with tissue and mechanical implants. J Thorac Cardiovasc Surg. 2004;128:266-72.
14. Maliwa MA, van der Heijden GJ, Bots ML, van Hout BA, Casselman FP, van Swieten H and Vermeulen FE. Quality of life and NYHA class 30 years after mechanical aortic valve replacement. Cardiovasc Surg. 2003;11:381-7.
15. Notzold A, Huppe M, Schmidtke C, Blomer P, Uhlig T and Sievers HH. Quality of life in aortic valve replacement: pulmonary autografts versus mechanical prostheses. J Am Coll Cardiol. 2001;37:1963-6.
16. Zacek P, Holubec T, Vobornik M, Dominik J, Takkenberg J, Harrer J and Vojacek J. Quality of life after aortic valve repair is similar to Ross patients and superior to mechanical valve replacement: a cross-sectional study. BMC Cardiovasc Disord. 2016;16:63.
17. Ruel M, Kulik A, Lam BK, Rubens FD, Hendry PJ, Masters RG, Bedard P and Mesana TG. Long-term outcomes of valve replacement with modern prostheses in young adults. Eur J Cardiothorac Surg. 2005;27:425-33; discussion 433.
18. Aicher D, Holz A, Feldner S, Kollner V and Schafers HJ. Quality of life after aortic valve surgery: replacement versus reconstruction. J Thorac Cardiovasc Surg. 2011;142:e19-24.
19. Franke UF, Isecke A, Nagib R, Breuer M, Wippermann J, Tigges-Limmer K and Wahlers T. Quality of life after aortic root surgery: reimplantation technique versus composite replacement. Ann Thorac Surg. 2010;90:1869-75.
20. Jarral OA, Kidher E, Patel VM, Nguyen B, Pepper J and Athanasiou T. Quality of life after intervention on the thoracic aorta. Eur J Cardiothorac Surg. 2016;49:369-89.
21. Akhyari P, Bara C, Kofidis T, Khaladj N, Haverich A and Klima U. Aortic root and ascending aortic replacement. Int Heart J. 2009;50:47-57.
22. Lehr EJ, Wang PZ, Oreopoulos A, Kanji H, Norris C and Macarthur R. Midterm outcomes and quality of life of aortic root replacement: mechanical vs biological conduits. Can J Cardiol. 2011;27:262 e15-20.
23. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL and Group ESCSD. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739-2791.
24. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM, 3rd and Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e1159-e1195.
25. Mokhles MM, Huygens SA, Takkenberg JJM. The Risk in Avoiding Risk: Optimizing Decision Making in Structural Heart Disease Interventions. Structural Heart. 2017; 2:1, 30-36.
26. Ware JE, Jr. and Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.

27. de Heer F, Gokalp AL, Kluin J and Takkenberg JJM. Measuring what matters to the patient: health related quality of life after aortic valve and thoracic aortic surgery. Gen Thorac Cardiovasc Surg. 2017.
28. Kluin J, Talacua H, Smits AI, Emmert MY, Brugmans MC, Fioretta ES, Dijkman PE, Sontjens SH, Duijvelshoff R, Dekker S, Janssen-van den Broek MW, Lintas V, Vink A, Hoerstrup SP, Janssen HM, Dankers PY, Baaijens FP and Bouten CV. In situ heart valve tissue engineering using a bioresorbable elastomeric implant - From material design to 12 months follow-up in sheep. Biomaterials. 2017;125:101-117.
29. Emmert MY and Hoerstrup SP. Challenges in translating tissue engineered heart valves into clinical practice. Eur Heart J. 2017;38:619-621.
30. Motta SE, Lintas V, Fioretta ES, Hoerstrup SP and Emmert MY. Off-the-shelf tissue engineered heart valves for in situ regeneration: current state, challenges and future directions. Expert Rev Med Devices. 2018;15:35-45.
31. Stassen O, Muylaert DEP, Bouten CVC and Hjortnaes J. Current Challenges in Translating Tissue-Engineered Heart Valves. Curr Treat Options Cardiovasc Med. 2017;19:71.
32. Dharmarajan K, Foster J, Coylewright M, Green P, Vavalle JP, Faheem O, Huang PH, Krishnaswamy A, Thourani VH, McCoy LA and Wang TY. The medically managed patient with severe symptomatic aortic stenosis in the TAVR era: Patient characteristics, reasons for medical management, and quality of shared decision making at heart valve treatment centers. PLoS One. 2017;12:e0175926.
33. Stiggelbout AM, Molewijk AC, Otten W, Van Bockel JH, Bruijninckx CM, Van der Salm I and Kievit J. The impact of individualized evidence-based decision support on aneurysm patients' decision making, ideals of autonomy, and quality of life. Med Decis Making. 2008;28:751-62.
34. Hauptman PJ, Chibnall JT, Guild C and Armbrecht ES. Patient perceptions, physician communication, and the implantable cardioverter-defibrillator. JAMA Intern Med. 2013;173:571-7.
35. Zikmund-Fisher BJ, Couper MP, Singer E, Ubel PA, Ziniel S, Fowler FJ, Jr., Levin CA and Fagerlin A. Deficits and variations in patients' experience with making 9 common medical decisions: the DECISIONS survey. Med Decis Making. 2010;30:85S-95S.
36. Coylewright M, O'Neill ES, Dick S and Grande SW. PCI Choice: Cardiovascular clinicians' perceptions of shared decision making in stable coronary artery disease. Patient Educ Couns. 2017;100:1136-1143.
37. Hess EP, Knoedler MA, Shah ND, Kline JA, Breslin M, Branda ME, Pencille LJ, Asplin BR, Nestler DM, Sadosty AT, Stiell IG, Ting HH and Montori VM. The chest pain choice decision aid: a randomized trial. Circ Cardiovasc Qual Outcomes. 2012;5:251-9.
38. Montori VM, Shah ND, Pencille LJ, Branda ME, Van Houten HK, Swiglo BA, Kesman RL, Tulledge-Scheitel SM, Jaeger TM, Johnson RE, Bartel GA, Melton LJ, 3rd and Wermers RA. Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. Am J Med. 2011;124:549-56.

39. Janz NK, Wren PA, Copeland LA, Lowery JC, Goldfarb SL and Wilkins EG. Patient-physician concordance: preferences, perceptions, and factors influencing the breast cancer surgical decision. J Clin Oncol. 2004;22:3091-8.
40. van Til JA, Stiggelbout AM and Ijzerman MJ. The effect of information on preferences stated in a choice-based conjoint analysis. Patient Educ Couns. 2009;74:264-71.
41. Gigerenzer G, Gaissmaier W, Kurz-Milcke E, Schwartz LM and Woloshin S. Helping Doctors and Patients Make Sense of Health Statistics. Psychol Sci Public Interest. 2007;8:53-96.
42. Topol, E. (2015). The patient will see you now. INGRAM PUBLISHER SERVICES US
43. Stiggelbout AM, Pieterse AH and De Haes JC. Shared decision making: Concepts, evidence, and practice. Patient Educ Couns. 2015;98:1172-9.
44. https://decisionaid.ohri.ca/docs/develop/IP-SDM-Model.pdf
45. Drug and Therapeutics B. An introduction to patient decision aids. BMJ. 2013;347:f4147.
46. Knops AM, Legemate DA, Goossens A, Bossuyt PM and Ubbink DT. Decision aids for patients facing a surgical treatment decision: a systematic review and meta-analysis. Ann Surg. 2013;257:860-6.
47. Coylewright M, Dick S, Zmolek B, Askelin J, Hawkins E, Branda M, Inselman JW, Zeballos-Palacios C, Shah ND, Hess EP, LeBlanc A, Montori VM and Ting HH. PCI Choice Decision Aid for Stable Coronary Artery Disease: A Randomized Trial. Circ Cardiovasc Qual Outcomes. 2016;9:767-776.
48. Gulbrandsen P, Clayman ML, Beach MC, Han PK, Boss EF, Ofstad EH and Elwyn G. Shared decision making as an existential journey: Aiming for restored autonomous capacity. Patient Educ Couns. 2016;99:1505-10.
49. Kunneman M, Branda ME, Noseworthy PA, Linzer M, Burnett B, Dick S, Spencer-Bonilla G, Fernandez CA, Gorr H, Wambua M, Keune S, Zeballos-Palacios C, Hargraves I, Shah ND and Montori VM. Shared decision making for stroke prevention in atrial fibrillation: study protocol for a randomized controlled trial. Trials. 2017;18:443.
50. Montori, V.M. (2017). Why we revolt: A patient revolution for careful and kind care. The Patient Revolution.

“The art of decision making includes the art of questioning”

Pearl Zhu

10.

Summary

Nederlandse Samenvatting

Dankwoord/Acknowledgements

PhD Portfolio

List of Publications

About the author

SUMMARY

Chapter 1 consists of the general introduction and outline of this thesis. The aim of this thesis is to provide insight in current prosthetic heart valve selection and outcomes in non-elderly adults and to introduce a tool to support shared decision making in this setting.

Chapter 2 provides a systematic review, meta-analysis and microsimulation of outcome after contemporary mechanical aortic valve replacement in non-elderly adult patients. This study shows that outcome is characterized by suboptimal survival and considerable lifetime risk of anticoagulation-related complications and reoperation. Therefore, non-elderly adult patients who are facing prosthetic valve replacement need to be informed about the risks and benefits of both mechanical and biological valves in a shared decision making process.

Chapter 3 is a systematic review and meta-analysis of characteristics of and long-term outcome after the Bentall procedure with a mechanical valve prosthesis. The rates of aortic root reoperation after the Bentall procedure have decreased over the years. However, high late mortality rates, major bleeding and thromboembolic complications remain a concern. This systematic review may be used to benchmark the potential therapeutic benefit of novel surgical approaches, such as valve-sparing aortic root replacement.

Chapter 4 concerns the study of patient quality of life after aortic valve replacement in relation to prosthetic aortic valve selection and preferences for shared decision making. The study was conducted among 497 non-elderly adult patients 1-10 years after aortic valve replacement. Suboptimal patient involvement, broad patient support for shared decision making, and a positive association between patient involvement in prosthetic valve selection and mental health were observed. Therefore, tools to support shared decision making would be useful in the setting of heart valve replacement.

Chapter 5 is a case report of a 50-year-old patient with proven Marfan syndrome who has undergone a Bentall procedure with a mechanical valve prosthesis. He was subsequently diagnosed with bilateral subdural hematoma. The patient requested and received aortic valve replacement with a biological valve to prevent further need for anticoagulation therapy. This case illustrates that it is possible to apply shared decision making in very complex clinical decisions in which each choice has important consequences.

Chapter 6 reports a survey among 117 cardiothoracic surgeons and cardiologists that assesses opinion on: (1) patient involvement, (2) risk conveyance in prosthetic aortic valve selection, and (3) prosthetic aortic valve preferences. Patient involvement and risk conveyance in aortic valve selection was considered important by both cardiologists and cardiothoracic surgeons. Medical profession influences attitude with regard to prosthetic aortic valve selection and patient involvement, and preference for a valve substitute: cardiologists were more likely to take the lead in decision making and were leaning more toward mechanical valve implantation. The variation in valve preference among cardiothoracic surgeons and cardiologists suggests that in most patients both valve types are suitable.

In **Chapter 7** a prospective multicenter cohort study among 132 patients who underwent aortic valve replacement is reported. Patients were surveyed preoperatively and 3 months postoperatively. The study assessed: (1) experience with current clinical decision making regarding prosthetic valve selection, (2) preferences for SDM and risk presentation, and (3) prosthetic valve knowledge and numeracy. Patients experienced decisional conflict, suboptimal involvement in prosthetic valve selection, and exhibited impaired knowledge concerning prosthetic valves and limited numeracy. Finally there was broad support for shared decision making among patients.

Chapter 8 concerns a multicenter randomized controlled trial which assesses whether the use of a patient decision aid results in improved decision making in prosthetic heart valve selection. One hundred fifty-five patients were randomized 1:1 to receive either standard preoperative care (control group) or additional access to the patient decision aid (intervention group). Primary outcome was preoperative decisional conflict; secondary outcomes included patient knowledge, involvement in valve selection, anxiety and depression, (valve-specific) quality of life, and regret. The patient decision aid did not lower decisional conflict but did result in more knowledgeable, better informed and less anxious and depressed patients, with better mental well-being.

Chapter 9 is the general discussion of this thesis. The results are presented in a broader perspective.

Improvement in outcomes after aortic valve replacement in non-elderly adults can be achieved with innovations with regard to aortic valve substitutes, like tissue engineered valves and transcatheter aortic valve implantation. Furthermore, improved clinical decision making will help the patients to receive the type of prosthetic valve that fits them best, which will result in an improved quality of life following aortic valve replacement.

To facilitate incorporation of shared decision making in prosthetic heart valve selection physicians need to be trained in how to apply it in daily medical practice. Also, the rapidly evolving digital platforms can be used to facilitate patient centered care. For instance, patients can use their smartphone to measure quality of life over time.

Currently, the decision aid has been adopted by the Dutch Heart Registration as an innovation project and is expected to be implemented in the care paths of Dutch heart centers in the coming years, ideally combining shared decision making support with Dutch outcome data from the Netherlands Heart Registration.

SAMENVATTING

Hoofdstuk 1 omvat de introductie en hoofdlijnen van dit proefschrift. Het doel van dit proefschrift is inzicht te krijgen in de huidige besluitvorming rondom hartklepkeuze en uitkomsten in (jong-) volwassen patiënten, en een keuzehulp te introduceren welke gezamenlijke besluitvorming in deze setting ondersteunt.

Hoofdstuk 2 is een systematische review van de literatuur, meta-analyse en microsimulatie van de uitkomsten na hedendaagse mechanische aortaklepvervanging in (jong-)volwassen patiënten. Deze studie laat zien dat de uitkomsten gekenmerkt worden door een suboptimale overleving en een aanzienlijk levenslang risico op anticoagulantia-gerelateerde complicaties en reoperaties. Daarom is het voor jonge patiënten die een hartklepprothese krijgen belangrijk om goed geïnformeerd te worden over de risico's en voordelen van mechanische en biologische hartklepprotheses in een gezamenlijk besluitvormingsproces.

Hoofdstuk 3 is een systematische review van de literatuur en meta-analyse die de karakteristieken en lange termijn uitkomsten na de Bentall procedure met een mechanische klepprothese beschrijft. Het aantal reoperaties aan de aortawortel na de Bentall procedure is afgenomen over de jaren. Echter, een hoge late mortaliteit en een verhoogd risico op bloedingen en trombo-embolische complicaties vanwege anticoagulantiagebruik blijven een punt van zorg. Deze systematische review kan gebruikt worden als uitgangspunt voor het potentiële therapeutische voordeel van nieuwe chirurgische benaderingen, zoals klepsparende aortawortel vervangingen.

Hoofdstuk 4 betreft een studie naar de kwaliteit van leven van patiënten na een aortaklepvervanging in relatie tot de keuze voor een aortaklepprothese en voorkeuren voor gezamenlijke besluitvorming. De studie is uitgevoerd in 497 jonge patiënten 1-10 jaar na een aortaklepvervanging. Het suboptimaal betrekken van patiënten, een grote support vanuit de patiënten voor gezamenlijke besluitvorming, en een positieve associatie tussen betrokkenheid van de patiënt bij de klepkeuze en mentale gezondheid werden geobserveerd. Deze observaties benadrukken de toegevoegde waarde van hulpmiddelen die gezamenlijke besluitvorming ondersteunen in de setting van hartklepvervanging.

Hoofdstuk 5 beschrijft de casus van een 50-jarige patiënt met bewezen Marfan syndroom die na een Bentall procedure met een mechanische klepprothese werd gediagnosticeerd met bilaterale subdurale hematomen. De patiënt onderging daarom op zijn eigen verzoek een aortaklepvervanging met een biologische klep om verdere

anticoagulantia therapie te voorkomen. Deze casus illustreert dat het mogelijk is om gezamenlijke besluitvorming toe te passen in een zeer complexe klinische beslissing waarin iedere therapeutische optie belangrijke consequenties heeft.

Hoofdstuk 6 beschrijft een enquête onder 117 cardio-thoracaal chirurgen en cardiologen betreffende hun mening over (1) het betrekken van de patiënt bij hartklepkeuze, (2) het bespreken van de risico's van aortaklepprotheses en (3) en voorkeur voor aortaklepprotheses.

Het betrekken van de patiënt bij de hartklepkeuze en het bespreken van de risico's van de verschillende typen aortaklepprotheses wordt belangrijk gevonden door zowel cardiologen als cardio-thoracaal chirurgen. Het medisch specialisme beïnvloedt de attitude met betrekking tot de selectie van een aortaklepprothese, het betrekken van de patiënt en de voorkeur voor een klepprothese: zo zijn cardiologen meer geneigd de leiding te nemen in de besluitvorming en neigen ze meer naar mechanische klepimplantatie dan cardio-thoracaal chirurgen. De grote variatie in voorkeur voor een biologische klep versus mechanische klep onder cardio-thoracaal chirurgen en cardiologen suggereert dat voor de meeste patiënten beide kleptypen geschikt zijn.

Hoofdstuk 7 is een prospectieve multicenter cohort studie onder 132 (jong-) volwassen patiënten die een aortaklepvervanging ondergingen. Patiënten werden preoperatief en 3 maanden postoperatief bevraagd over hun (1) ervaring met de klinische besluitvorming omtrent hartklepkeuze, (2) voorkeuren voor gezamenlijke besluitvorming en risico presentatie en (3) kennis over hartklepprotheses en begrip van getallen over gezondheid en ziekte. Patiënten in deze studie ervoeren 'decisional conflict' en suboptimale betrokkenheid bij de selectie van een hartklepprothese, hadden beperkte kennis van klepprotheses en een beperkt vermogen om getallen over ziekte en gezondheid te begrijpen. Tot slot was er een breed draagvlak voor gezamenlijke besluitvorming onder de patiënten in deze studie.

Hoofdstuk 8 is een multicenter gerandomiseerde studie met de onderzoeksvraag of het gebruik van een keuzehulp resulteert in verbetering van besluitvorming bij hartklepkeuze. Honderdvijfenvijftig patiënten werden 1:1 gerandomiseerd naar standaard preoperatieve zorg (controle groep) of bijkomende toegang tot de patiënten keuzehulp (interventie groep). De primaire uitkomst was preoperatieve 'decisional conflict'; secundaire uitkomsten waren patiëntenkennis, betrokkenheid bij hartklepkeuze, angst en depressie, (klep-specifieke) kwaliteit van leven en spijt. Deze

studie toonde aan dat de keuzehulp 'decisional conflict' niet vermindert, maar wel resulteert in betere patiëntenkennis, patiënten die zich beter geïnformeerd voelen en minder angstig en depressief zijn met een beter mentale kwaliteit van leven.

Hoofdstuk 9 vormt de algemene discussie. De resultaten worden gepresenteerd in een breder perspectief. Verbetering in de uitkomsten na aortaklepvervanging in jonge patiënten kan bereikt worden met innovaties met betrekking tot aortaklepvervangingen, zoals lichaamseigen kleppen en implantatie van de aortaklep via de lies. Verder zal een betere besluitvorming ervoor zorgen dat patiënten de hartklepprothese krijgen die het best bij ze past, waardoor ze een betere kwaliteit van leven hebben na de aortaklepvervanging. Om de opname van gezamenlijke besluitvorming in de selectie van hartklepprotheses te faciliteren zullen artsen getraind moeten worden hoe ze dit kunnen toepassen in hun dagelijkse medische praktijk. Tevens kunnen de zich snel ontwikkelende digitale platforms gebruikt worden om patiëntgerichte zorg te faciliteren. Patiënten kunnen bijvoorbeeld hun mobiele telefoon gebruiken om kwaliteit van leven over tijd te meten.

De keuzehulp is aangenomen door de Nederlandse Hart Registratie als innovatie project en wordt de komende jaren geïmplementeerd in het zorgpad van de Nederlandse hartcentra, waarbij idealiter ondersteuning van gezamenlijke besluitvorming gecombineerd gaat worden met uitkomstgegevens van de Nederlandse Hart Registratie.

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PHD PORTFOLIO

Name PhD student:	N.M. Korteland
Erasmus MC department:	Cardiothoracic Surgery
Research school:	Cardiovascular Research School (COEUR)
PhD period:	March 2013 – January 2016
Title thesis:	Optimizing Clinical Decision Making in Prosthetic Aortic Valve Selection
Promotors:	Prof.dr. J.J.M. Takkenberg Prof.dr. A.J.J.C. Bogers
Date defense thesis:	December 18, 2018

Academic Education

Master of Science (MSc) in Clinical Research, NIHES, Rotterdam, The Netherlands
Master of Science (MSc) in Medicine, Erasmus MC, Rotterdam, The Netherlands

PhD Training	Year	Workload (ECTS)
In-depth courses		
Good Clinical Practice	2012	0.8
Atherosclerotic and Aneurysmal Disease	2012	1.5
CPO Course 'Patient Oriented Research: design, conduct and analysis'	2013	0.3
Cardiac Function and Adaptation	2013	2
Cardiovascular Imaging and Diagnostics	2013	1.5
Congenital Heart Disease	2012	1.5
Research Integrity	2014	0.3
Introduction to Medical Decision Analysis (Decision Analytic Modeling)	2014	0.3
Revise and improve your presentation for the meeting	2014	0.3
Presentations		
Decision making in prosthetic aortic valve selection (Utrecht)	2012	0.5
Cardiac surgeon view on decision making in prosthetic aortic valve selection (Utrecht)	2012	0.5
Patient's experience with decision making in prosthetic aortic valve selection (Leiden, Utrecht)	2012	1

PhD Training	Year	Workload (ECTS)
Cardiologist and cardiac surgeon view on decision making in prosthetic aortic valve selection: does specialty matter? (Rotterdam)	2013	0.5
Decision making in prosthetic aortic valve selection (Rotterdam)	2013	0.5
Cardiologist and cardiac surgeon view on decision making in prosthetic aortic valve selection (Utrecht)	2013	0.5
Keuzehulp 'Welke hartklep moet ik kiezen als mijn eigen hartklep vervangen moet worden: een mechanische klep of een biologische klep?' (Utrecht)	2013	0.5
Cardiologist and cardiac surgeon view on decision making in prosthetic aortic valve selection (Venice, Italy)	2013	0.5
De 'Hartklepkeuzehulp' (Utrecht)	2013	0.5
Cardiologist and cardiac surgeon view on decision making in prosthetic aortic valve selection (Amsterdam)	2014	0.3
Patient view on decision making in prosthetic aortic valve selection (New York, USA)	2014	0.5
De Hartklepkeuzehulp (Rotterdam)	2014	0.5
Does a decision aid improve decision making in prosthetic heart valve selection? (Utrecht, Rotterdam, Leiden, Amsterdam)	2014	2
Optimizing Prosthetic Heart Valve Selection (Antwerp, Belgium)	2014	0.5
Does the Use of a Decision Aid Improve Decision Making in Prosthetic Heart Valve Selection? A Multicenter RCT (Rotterdam)	2015	0.5
De Hartklepkeuzehulp (Amsterdam)	2015	0.5
Optimizing Prosthetic Heart Valve Selection: a Dutch Quality Improvement Project (Amsterdam)	2015	0.3
Outcome after mechanical aortic valve replacement in adult patients under 55 years: a systematic review, meta-analysis and microsimulation (New York, USA)	2016	0.5
Does the Use of a Decision Aid Improve Decision Making in Prosthetic Heart Valve Selection? A Multicenter RCT (New York, USA)	2016	0.5
Conferences and symposia		
Meeting of the Netherlands Society of Cardiology	2012	0.3
Meeting of the Dutch Association for Thoracic Surgery	2012, 2013	0.6
Meeting Platform Shared Decision Making (Utrecht)	2012-2014	0.9
Scientific Meetings Department of Cardiothoracic Surgery LUMC (Leiden)	2012, 2014	0.1

PhD Training	Year	Workload (ECTS)
Scientific Meetings Department of Cardiothoracic Surgery UMCU (Utrecht)	2012, 2014	0.1
Scientific Meetings Department of Cardiothoracic Surgery AMC (Amsterdam)	2012, 2014	0.1
Scientific Meetings Department of Cardiothoracic Surgery Erasmus MC (Rotterdam)	2012-2015	2
SKMS Meetings	2012-2015	1
SHVD and HVSA 7th Biennial Congress (Venice, Italy)	2013	1.2
Valves in the Heart of the Big Apple VIII (New York, USA)	2014	1.2
15th Biennial European Meeting of the Society for Medical Decision Making (Antwerp, Belgium)	2014	0.9
Innovation for Health Congress (Amsterdam)	2014, 2015	0.6
National Heart Valve Meeting	2015, 2016	0.6
HVS Scientific Meeting (New York, USA)	2016	1.2
Awards and grants		
KNAW Academy assistantship	2012	
KNAW Travel Grant	2013	
Finalist Lee B. Lusted Award	2015	
Jose L. Pomar Heart Valves Outcomes II Abstract Award	2016	
Teaching		
Supervising 2nd year medical students during research project, Erasmus MC, The Netherlands	2013-2014	1
Supervising 6th year pre-university secondary education students during their final assignment, Gymnasium Erasmianum, The Netherlands	2014	0.6
Supervising 2nd year medical students in writing a systematic review, Erasmus MC, The Netherlands	2014	0.6

LIST OF PUBLICATIONS

1. **Korteland NM**, Etnel JR, Arabkhani B, Mokhles MM, Mohamad A, Roos-Hesselink JW, Bogers AJ, Takkenberg JJ. Mechanical aortic valve replacement in non-elderly adults: meta-analysis and microsimulation. Eur Heart J. 2017 Dec 1;38(45):3370-3377.

2. Mookhoek A, **Korteland NM**, Arabkhani B, Di Centa I, Lansac E, Bekkers JA, Bogers AJ, Takkenberg JJ. Bentall Procedure: A Systematic Review and Meta-Analysis. Ann Thorac Surg. 2016 May;101(5):1684-9.

3. **Korteland NM**, Top D, Borsboom GJ, Roos-Hesselink JW, Bogers AJ, Takkenberg JJ. Quality of life and prosthetic aortic valve selection in non-elderly adult patients. Interact Cardiovasc Thorac Surg. 2016 Jun;22(6):723-8.

4. **Korteland NM**, Takkenberg JJ, Bogers AJ, Roos-Hesselink JW. A devilish dilemma. Interact Cardiovasc Thorac Surg. 2017 Apr 1;24(4):641-642.

5. **Korteland NM**, Kluin J, Klautz RJ, Roos-Hesselink JW, Versteegh MI, Bogers AJ, Takkenberg JJ. Cardiologist and cardiac surgeon view on decision making in prosthetic aortic valve selection: does profession matter? Neth Heart J 2014;22:336-343.

6. **Korteland NM**, Bras FJ, van Hout FM, Kluin J, Klautz RJ, Bogers AJ, Takkenberg JJ. Prosthetic aortic valve selection: current patient experience, preferences and knowledge. Open Heart, 2015. 2(1): p. e000237.

7. **Korteland NM**, Ahmed Y, Koolbergen DR, Brouwer M, de Heer F, Kluin J, Bruggemans EF, Klautz RJ, Stiggelbout AM, Bucx JJ, Roos-Hesselink JW, Polak P, Markou T, van den Broek I, Ligthart R, Bogers AJ, Takkenberg JJ. Does the Use of a Decision Aid Improve Decision Making in Prosthetic Heart Valve Selection? A Multicenter Randomized Trial. Circ Cardiovasc Qual Outcomes. 2017 Feb;10(2).

ABOUT THE AUTHOR

Nelleke M. Korteland was born in Dordrecht, The Netherlands. She began her medical career in 2003 at the Hogeschool Rotterdam in physical therapy education. After graduating cum laude in 2007, she worked as a physical therapist.

In 2008, she started medical school at the Erasmus University Rotterdam. In 2010, Nelleke was among the top 10% of medical students and was therefore selected to participate in a special program for medical students offered by the Netherlands' Institute of Health Sciences (NIHES). This program enabled her to combine her Medical Degree with a Master of Science in Clinical Research. Part of this program was spent at the Johns Hopkins University in Baltimore, USA.

In 2011, she initiated her MSc research project at the Department of Cardio-Thoracic surgery of the Erasmus University Medical Center (supervisors: prof. dr. J.J.M. Takkenberg and prof. dr. A.J.J.C. Bogers). She won a Royal Netherlands Academy of Arts and Sciences (KNAW) fellowship and travel grant for this research project concerning shared decision-making in prosthetic heart valve selection. This MSc research project culminated in a PhD project, titled "Optimizing Clinical Decision Making in Prosthetic Aortic Valve Selection", which she started in 2013 at the Department of Cardio-Thoracic Surgery of the Erasmus University Medical Center, under supervision of prof. dr. J.J.M. Takkenberg and prof. dr. A.J.J.C. Bogers.

In 2016, Nelleke was awarded the Jose L. Pomar Heart Valves Outcomes II Abstract Award for best abstract at the The Heart Valve Society Scientific Meeting in New York, USA.

Nelleke continued her medical training in 2016. She obtained her medical degree in 2018 and is currently working as a youth health care physician.

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