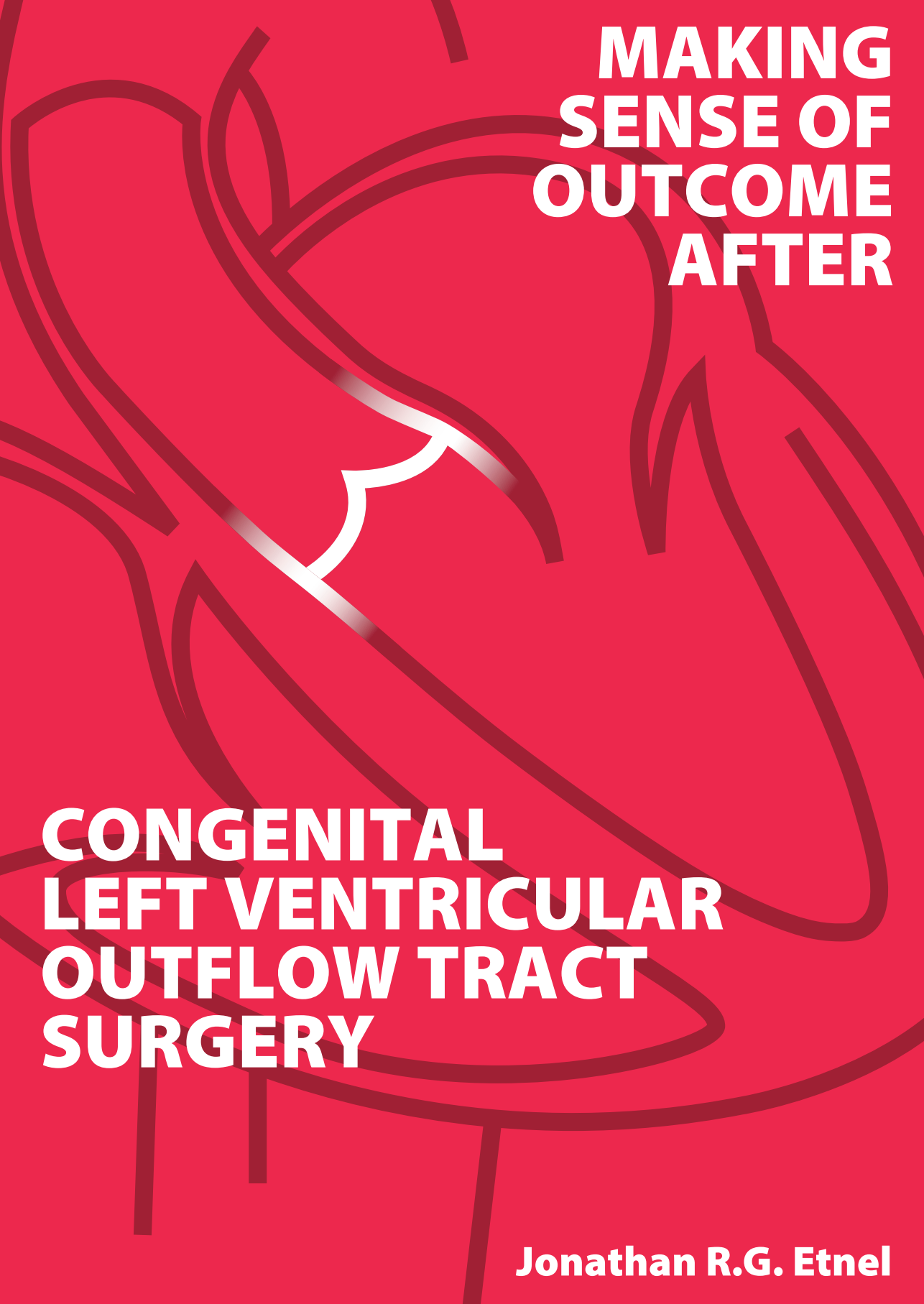
MAKING SENSE OF OUTCOME AFTER CONGENITAL LEFT VENTRICULAR OUTFLOW TRACT SURGERY



Jonathan R.G. Etnel

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COLOFON

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Making sense of outcome after congenital left ventricular outflow tract surgery

Inzichtelijk maken van uitkomsten na congenitale linkerventrikeluitstroombaan chirurgie

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
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Prof. dr. R.C.M.E. Engels

and in accordance with the decision of the Doctorate Board.
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	Prof. dr. J.W. Roos-Hesselink

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For my parents

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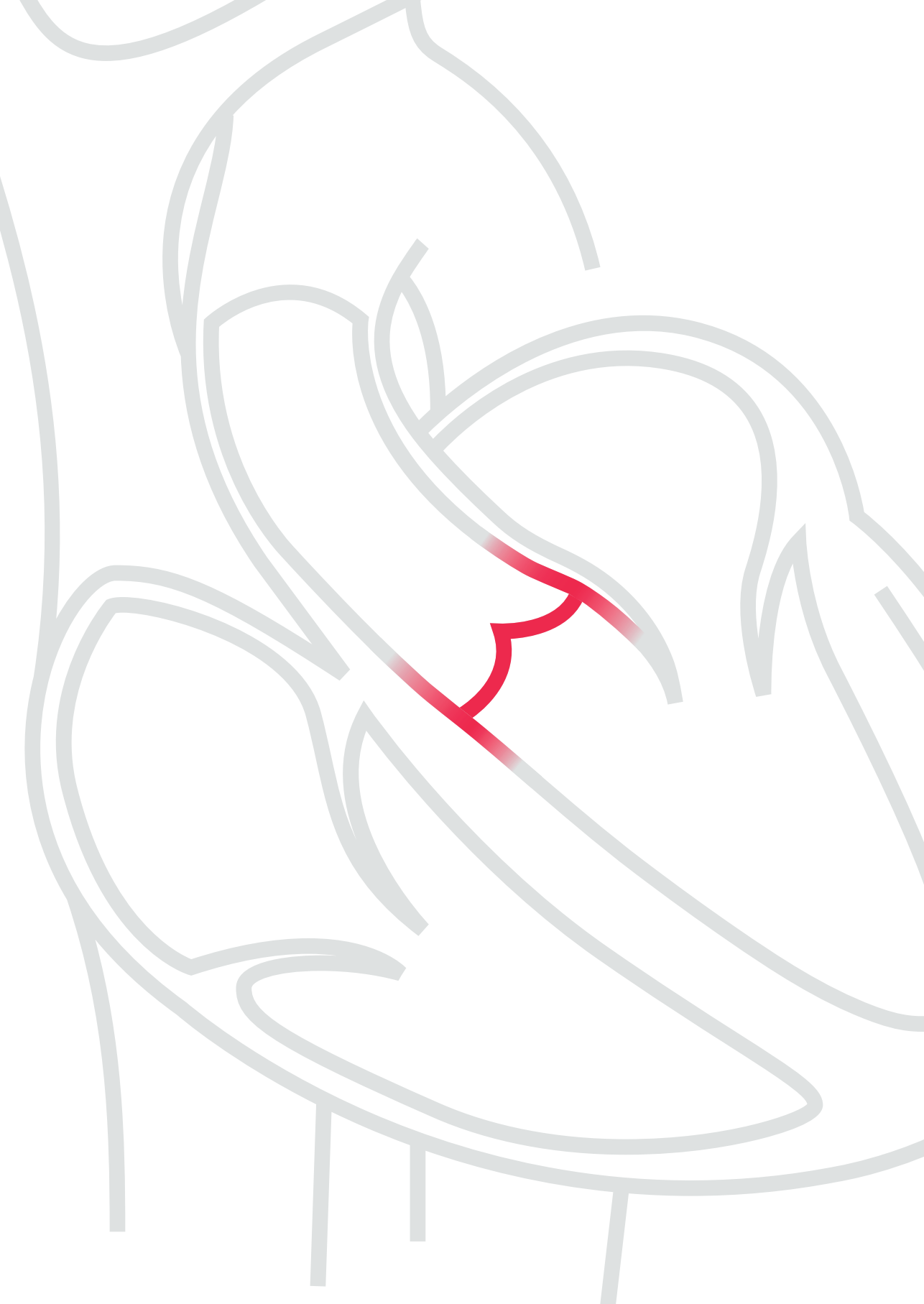

1

GENERAL INTRODUCTION

Congenital heart defects are the most common of all birth defects, occurring in approximately 1 in every 100 live births.[1-3] One of the major forms of congenital heart disease is left ventricular outflow tract disease, accounting for approximately 5-10% of cases.[1,3,4] Especially in adults, diseases of the left ventricular outflow tract and proximal aorta are becoming increasingly clinically important.

The left ventricular outflow tract connects the left ventricle to the aorta. The left ventricular outflow tract contains the aortic valve, which opens during ventricular contraction and closes during ventricular relaxation to ensure that blood only flows in the correct direction to the systemic circulation. Congenital defects of the left ventricular outflow tract usually concern obstructions (aortic stenosis), most frequently at the level of the aortic valve (aortic valve stenosis, 75% of cases) or below the level of the aortic valve (subvalvular aortic stenosis, 20%) and rarely above the level of the aortic valve (supravalvular aortic stenosis, 5%).[4,5] Defects of the left ventricular outflow tract may also concern leaking of the aortic valve (aortic regurgitation), although this is rarely the primary dysfunction of the aortic valve. Aortic regurgitation is most often secondary to other cardiac disease, concomitant to aortic stenosis or iatrogenic.[6] The functioning of a healthy aortic valve, aortic valve stenosis and aortic valve regurgitation are depicted in Figure 1.

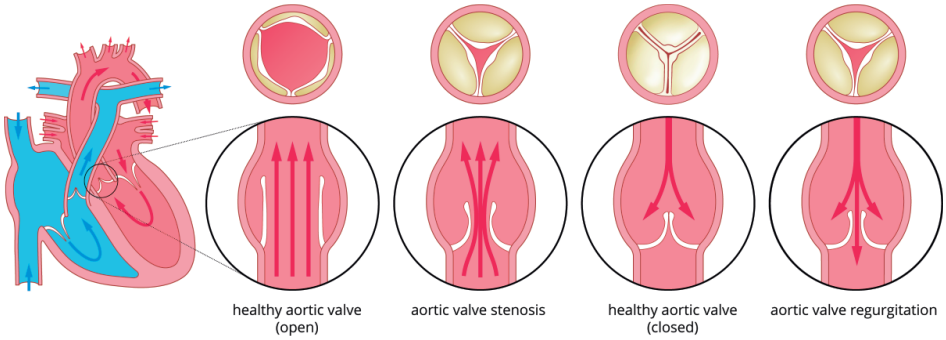

Figure 1.

The clinical presentation of aortic stenosis varies largely depending on the severity of stenosis, ranging from severe critical aortic stenosis presenting in the first year of life and requiring urgent intervention to a milder disease course only becoming apparent and/or clinically relevant in adolescence or adulthood. Aortic stenosis is usually progressive in nature and most patients diagnosed with aortic stenosis at a pediatric or young adult age will require one or multiple (surgical) interventions during the course of their lives.[7,8]

TREATMENT OPTIONS

Subvalvular aortic stenosis

Subvalvular aortic stenosis is usually treated by surgical enucleation or excision of the subvalvular obstruction, the extent of which may vary from a minor fibrous ridge (discrete subvalvular aortic stenosis) to a narrow fibromuscular tunnel. Although surgery in this regard can often be achieved with low mortality and satisfactory hemodynamic result, there is a substantial risk of recurrence and subsequent reintervention and it remains difficult to predict which patients are more prone to recurrence.[9]

Aortic valve disease

In the case of aortic valve stenosis in neonates, infants and children, the initial treatment is usually percutaneous balloon aortic valvuloplasty. However, there is a high risk of residual or recurrent valve stenosis and/or the development of valve regurgitation. Therefore, most patients will require reintervention after initial balloon valvuloplasty in the form of redo percutaneous balloon valvuloplasty, surgical valvuloplasty/aortic valve repair, or aortic valve replacement.[10-12]

In the case of substantial aortic valve regurgitation (either at initial presentation or as a result of prior percutaneous or surgical valvuloplasty) or if there is substantial residual or recurrent aortic valve stenosis after prior valvuloplasty, surgical intervention is often indicated. Surgical intervention is also usually employed as the initial intervention in adults due to poor results and limited benefit of percutaneous balloon valvuloplasty in adults.[13] If stenosis is not isolated to the valvular level, but is rather a multilevel stenosis that also includes subvalvular and/or supravalvular obstruction, surgery is also most often the treatment of choice.[9]

In aortic valve surgery, it is preferred to repair the valve whenever possible, because all currently available valve substitutes for valve replacement have drawbacks when compared to an adequately functioning native aortic valve. However, depending on the anatomy and mechanism of dysfunction, a hemodynamically satisfactory and durable result can only be achieved with valve repair in a limited proportion of cases.[14] Therefore, most patients will require replacement of the aortic valve, either if the valve is found not to be amenable to repair at initial surgery or as a reoperation after primary valve repair if there is residual or recurrent valve dysfunction.[14-16] Various valve substitutes are currently available for aortic valve replacement, each with their own benefits and drawbacks.[17-20]

Mechanical prostheses

The primary advantage of mechanical prostheses (Figure 2) is their long-term durability. They are also easily implanted and readily available. However, they require lifelong anticoagulation due to their increased thrombogenicity, which gives rise to a substantial risk of thromboembolic and bleeding complications. Furthermore, the anticoagulation required for mechanical prostheses (vitamin K antagonists) does not provide a stable level of anticoagulation with a fixed daily dose due to specific pharmacological properties. This therefore requires frequent blood testing of the anticoagulation level (international normalized ratio, INR) with subsequent changes in the daily dose of anticoagulation to be made. In addition to these requirements of INR regulation, patients are faced with the ticking sound that the valve makes with every heartbeat, restrictions on participation in certain types of athletic activity, and female patients with mechanical heart valves face a substantial risk of serious anticoagulation-related complications during future pregnancies. Consequently, mechanical valve prostheses have been found to be associated with substantial impairments in quality of life in non-elderly adult patients when compared to alternatives.[18,19] Moreover, in growing children, mechanical prostheses do not grow along with the growing child, with the consequent potential for the development of patient-prosthesis mismatch over time.[17]

Figure 2. Mechanical prosthesis (St. Jude Medical valve™, Abbott Laboratories, Chicago, Illinois, USA)

Bioprostheses

The main advantage of commercially available bioprostheses (xenografts, made from bovine or porcine tissue, see Figure 3) is that they have a lower thrombogenicity than mechanical prostheses and, therefore, do not require lifelong anticoagulation. Consequently, they are associated with lower risks of thromboembolic and bleeding complications than mechanical prostheses. They also do not carry the anticoagulation-related risks of mechanical prostheses during pregnancy and do not make any sound in normal functioning. Similar to mechanical prostheses, they are also easily implanted and readily available. However, they have a limited durability and are subject to valve deterioration

over time, particularly in younger patients. Consequently, patients with bioprostheses face a higher risk of reintervention over time than patients with mechanical prostheses. Additionally, as with mechanical prostheses, in growing children there is potential for the development of prosthesis-patient mismatch over time.[17,18]

Figure 3. Bioprosthesis (INSPIRIS RESILIA valve™, Edwards Lifesciences, Irvine, California, USA)

Pulmonary autografts

Aortic valve replacement with a pulmonary autograft, also known as the Ross procedure, involves transplantation of the patient's own pulmonary valve (pulmonary autograft) to the aortic valve position and implantation of another valve substitute, such as an allograft or bioprosthesis, in the pulmonary position. It provides an autologous, living aortic valve substitute which has been shown to provide hemodynamically superior results to mechanical prostheses and bioprostheses, diameter increase along with somatic growth in children contrary to mechanical prostheses and bioprostheses, and greater durability than bioprostheses in non-elderly patients when performed in centers of expertise. In addition, similar to a bioprosthesis, it provides low thrombogenicity, avoidance of lifelong anticoagulation, safety during pregnancy and absence of valve sound. However, the Ross procedure is far more complex and technically demanding than the implantation of a mechanical prosthesis or bioprosthesis. Moreover, the autograft is subject to structural deterioration and subsequent requirement for reintervention over time, despite numerous techniques having been developed to reinforce the autograft at implantation. Also, the valve substitute in the right ventricular outflow tract (RVOT) imparts an additional risk of reintervention.[17,18,20] Consequently, although the Ross procedure is frequently performed in growing children due to its specific benefits in this patient population, its application in adults is far more limited.[21,22]

Allografts

The aortic valve may also be replaced by an allograft (human cadaveric donor valve). However, in current practice allografts have been largely abandoned as an aortic valve substitute due to high rates of structural deterioration and (complex) reintervention along with their limited availability dependent on donor supply.[23,24] Their current role in aortic valve replacement is mostly limited to rare cases of complex endocarditis. Beyond the setting of aortic valve replacement, they are widely used for right ventricular outflow tract reconstruction in both children and adults.

Tissue engineered valves and TAVI

Tissue engineered heart valves are currently under development and aim to provide a living autologous heart valve substitute without the limitations of currently available valve substitutes. Additionally, there is growing interest in transcatheter aortic valve implantation (TAVI) as a primary intervention in increasingly younger and lower risk patients. However, tissue engineered heart valves are still experimental and have not yet reached clinical practice and transcatheter aortic valve implantation is currently limited to elderly patients. These ongoing developments are therefore beyond the scope of this thesis.

OUTCOME AFTER SURGERY AND DECISION-MAKING

Considering the above, clinicians and (parents of) patients often face many difficult decisions during the course of these patients' lives. Congenital left ventricular outflow tract disease usually allows for an active life well into adulthood, but often with important consequences for lifestyle and life planning and requiring multiple crucial treatment decisions to be made along the way.[13,19,25] These decisions often have important implications for the patient's further life with regard to longevity, pregnancy, career planning, athletic endeavors and daily life, particularly in young patients with dynamic lifestyles.[13,26] Consequently, such decisions are highly value-sensitive and often difficult. For instance, in the selection of a valve substitute for aortic valve replacement, it has been demonstrated that there is an exceedingly wide variation in preferences between individual physicians: for a given patient with a specific patient profile some physicians would *always* choose a mechanical prosthesis while other physicians would *always* choose a bioprosthesis for the very same patient.[27] This large individual variability in preferences has also been demonstrated among patients undergoing aortic valve surgery in trade-offs between quality of life and quantity of life.[28,29] Considering the complexity and value-sensitivity of such decisions and their consequences for the patients' further lives, it is of crucial importance to involve patients in decision-making. Therefore, recent

international clinical practice guidelines recommend a shared decision-making process in prosthetic heart valve selection that accounts for the informed patient's values and preferences.[30,31]

However, adequately informed physicians and (parents of) patients are an essential requirement for effective decision-making. Although there have been decades of experience worldwide with the aforementioned treatment modalities and a wealth of follow-up has been obtained, there remains substantial uncertainty about outcome after surgery. Evidence on outcome after surgery is scattered across an exceedingly large number of publications and reported outcome varies strongly among publications.[20,32] Moreover, outcomes are often reported in formats that are not meaningful for incorporation in daily practice and may not be readily interpretable by physicians and (parents of) patients alike. This makes it difficult for physicians and (parents of) patients to draw inferences on what patients can be expected to face after surgery, which complicates decision-making. As a further consequence, as demonstrated in middle-aged and elderly patients undergoing aortic valve replacement, limited disease-related knowledge among patients also makes it difficult for patients to be as involved in decision-making as patients and physicians would prefer, despite broad support for shared decision-making among physicians and patients alike.[27,33]

There is increasing international evidence that (parents of) patients may not always be sufficiently informed and involved, which has been previously shown to lead to substantial impairments in quality of life, anxiety, depression, poor treatment adherence, poor health behaviour, suboptimal treatment decisions and poorer clinical outcome, and also to poorer healthcare utilization and higher healthcare costs.[34-48]

AIM

In response to the above, this thesis aims to make sense of outcome after congenital left ventricular outflow tract surgery and improve evidence-based decision-making, patient information and patient involvement by investigating the following research questions:

What is long-term outcome after congenital left ventricular outflow tract surgery?

This research question will be investigated by:

- Obtaining robust estimates of long-term outcome after left ventricular outflow tract surgery in children and young adults (Chapters 2-7)
- Exploring possibilities for patient-tailored outcome modeling and decision-making by developing methodology for tailoring outcome models to patient- and procedure-related factors (microsimulation, Chapters 4-6) and investigating factors associated with outcome (Chapter 2)
- Investigating methodology for evaluating developments in the treatment of these patients aimed at improving outcome (Chapter 8)

How can evidence on outcome be effectively conveyed to physicians and patients for implementation of informed shared decision-making in practice?

This research question will be investigated by:

- Exploring methodology for translating evidence on outcome to a format that is meaningful to physicians and (parents of) patients alike and can be readily implemented in clinical practice (microsimulation, Chapters 4-6)
- Investigating patient/parent disease-related knowledge, the availability of patient information and patient/parent comprehension of the available information (Chapter 9)
- Developing and testing interventions for improving patient information and (shared) decision-making (Chapters 10-12)

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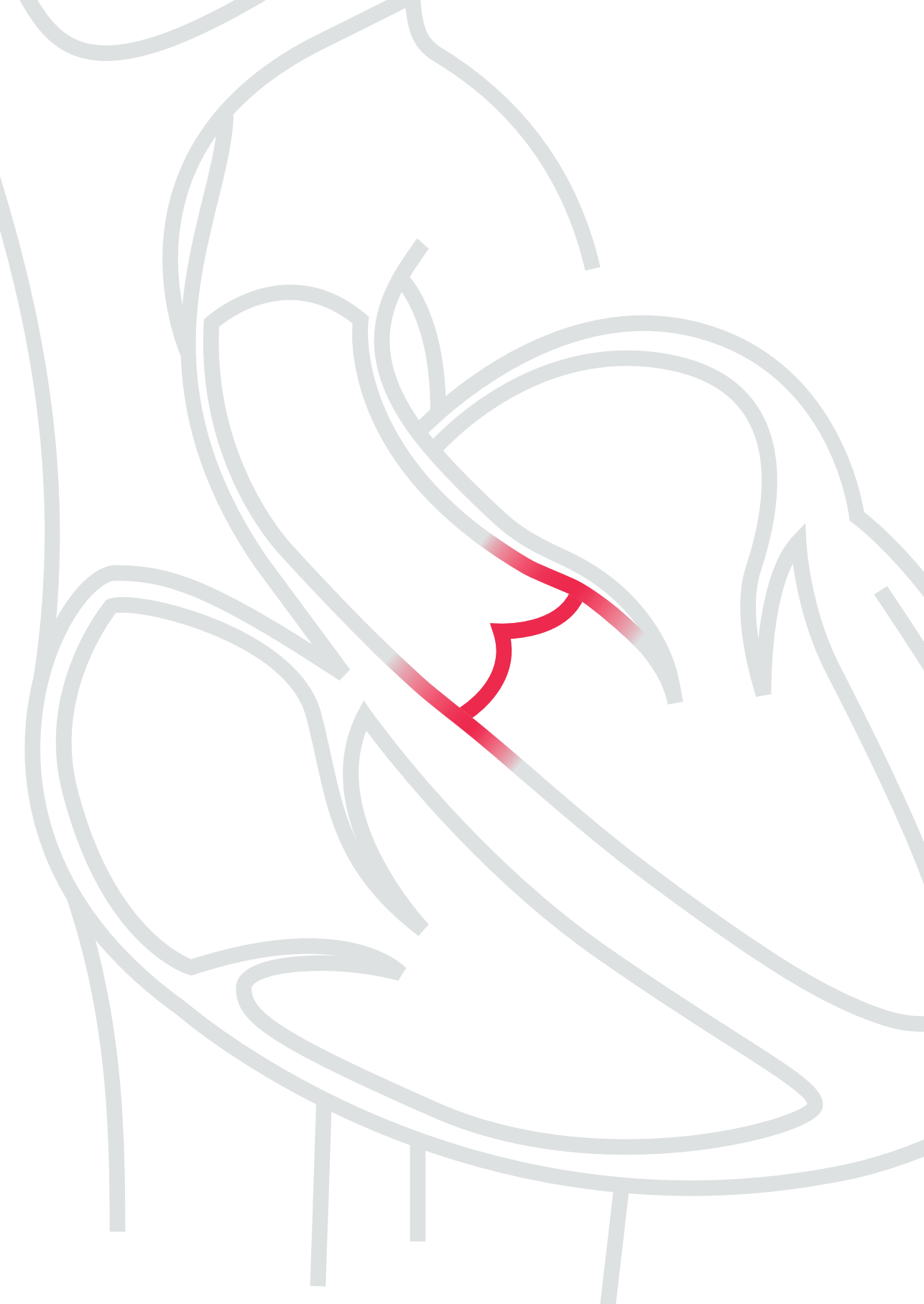

2

Paediatric subvalvular aortic stenosis: a systematic review and meta-analysis of natural history and surgical outcome

Jonathan R.G. Etnel, Johanna J.M. Takkenberg, Laura G. Spaans, Ad J.J.C. Bogers, Willem A. Helbing

Eur J Cardiothorac Surg. 2015 Aug;48(2):212-20.

ABSTRACT

Background

Sub-valvular aortic stenosis (SAS) is a common form of left ventricular outflow tract (LVOT) obstruction, which can lead to aortic valve damage. Although surgery for SAS is an accepted treatment, the timing of surgical intervention of SAS remains controversial. This review aims to establish an overview of the natural history and outcome after surgery and factors associated with prognosis in paediatric SAS patients.

Methods

We searched PubMed and EMBASE for studies that reported factors that negatively affected the prognosis of patients with SAS. Studies were included if they were written in English, published between 1 January 1997 and 31 December 2012 and the mean patient age was <18 years at the time of study entry. Studies were excluded if the study size was <20 patients. A distinction was made between natural history and surgical cohorts.

Results

Twenty-four studies were included in this review, encompassing a total of 809 natural history and 1476 surgical patients. Fifty-one percent of natural history patients required surgery. After surgery, there was a substantial reoperation rate. Higher LVOT gradient and the presence of aortic regurgitation (AR) were identified as the foremost independent predictors of a worse outcome. Valve-to-membrane distance was also found to be associated with prognosis, although the results were contradictory.

Conclusions

This systematic review underlines the importance of LVOT gradient, aortic valve-to-membrane distance and AR in surgical decision-making in paediatric SAS patients. There is need for collaborative effort to further study the optimal timing of surgery based on LVOT gradient, valve-to-membrane distance and the presence of AR.

INTRODUCTION

Sub-valvular aortic stenosis (SAS) is an important type of left ventricular outflow tract (LVOT) obstruction, which is usually progressive [1] and accounts for 8-20% of all forms of LVOT obstruction.[2] The extent of the malformation varies from a minor fibrous ridge on the sub-valvular ventricular septum (discrete SAS, DSAS; 70-80% of cases) to a narrow fibromuscular tunnel.[2] SAS can exist as an isolated disease, but is in 50-60% of the cases associated with other congenital cardiac anomalies.[3, 4] The most important and well-known late complication of SAS is aortic regurgitation (AR), which occurs in >70% of discrete SAS patients [5] and is usually progressive. A certain incidence of postoperative recurrence of obstruction is also reported in patients with SAS.[6] In exceptional cases, SAS was suggested to be related to sudden death.[7]

Patients with a stable peak LVOT gradient of 30 mmHg or less are usually treated medically. Similarly to aortic stenosis, an intervention is indicated in patients with a peak LVOT gradient of >50 mmHg. In patients with a peak LVOT gradient between 30 and 50, surgery is considered based on symptoms, age and rate of disease progression.[8]

In this setting, timing of surgery remains an issue of dispute. There may be practice variation, fitting with a lack of treatment guidelines for SAS.[9] To prevent progressive valvular damage and ventricular hypertrophy, early surgery is proposed by some groups, claiming that younger patients and patients with low LVOT gradients have the best surgical outcomes.[4, 10] However, other investigators believe that prophylactic intervention has no benefits and is therefore not necessary.[11]

We carried out a systematic review to establish an overview of the natural history and outcome after surgery in paediatric SAS patients, and identify factors associated with prognosis.

METHODS

Search strategy and selection of studies

To identify prognostic markers in paediatric SAS, we conducted a systematic review according to the PRISMA guidelines.[12] We carried out a PubMed and EMBASE search with the following query: aortic stenosis[MeSH] AND (subaortic[All fields] OR subvalvular[All fields] OR subvalvar[All fields]). We limited our search to studies that were conducted in humans, published in the last 15 years (1 January 1997-31 December 2012) and written in English. We also applied a limit on the mean age of the patients at diagnosis (<18 years old). If the age at diagnosis was not reported, mean age at surgery <18 years was used.

The resulting papers were then screened manually on relevance by two independent investigators (Jonathan R.G. Etnel and Laura G. Spaans). Studies were included if they reported clinical outcome in patients with SAS. Studies were excluded if the study size was <20 patients or if the full text was not available. If there was an overlap in study populations, only the most recent or most complete study was included. In case of disagreement on including a paper, an agreement was negotiated.

The following baseline variables were recorded: mean age at diagnosis, mean age at surgery and last follow-up, gender, SAS-type (discrete or tunnel-type) and the presence of concomitant cardiac lesions such as bicuspid aortic valve (AV), ventricular septal defect (VSD), atrial septal defect and coarctation of the aorta.

Adverse outcome was defined as overall mortality for the natural history cohort studies, early (<30 days after surgery) and late mortality for the surgical cohort studies, the development and/or presence of AR, AR progression, mitral regurgitation (MR), LVOT obstruction progression, surgical intervention, postoperative residual LVOT gradient, postoperative arrhythmia, recurrence and reoperation. All reported pressure gradients were measured by echocardiography.

Upon inclusion, studies were grouped as follows: (i) studies that reported the natural history of SAS and (ii) those that reported the outcomes in surgical patients, the core distinction between the two groups being that the natural history studies included both surgical and non-surgical patients and the surgical studies included only surgical patients. If a natural history study reported the outcomes of their surgical sub-cohort separately, the respective sub-cohort was assigned to the surgical study group for data pooling.

Statistics

Inverse variance weighted pooling was performed on all patient characteristics and outcomes using Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA). Early mortality and postoperative arrhythmia risk and linearized event occurrence rates, expressed as a percentage per year, were pooled on a logarithmic scale. In case a particular event was reported not to occur in an individual study, then for the analyses it was as-

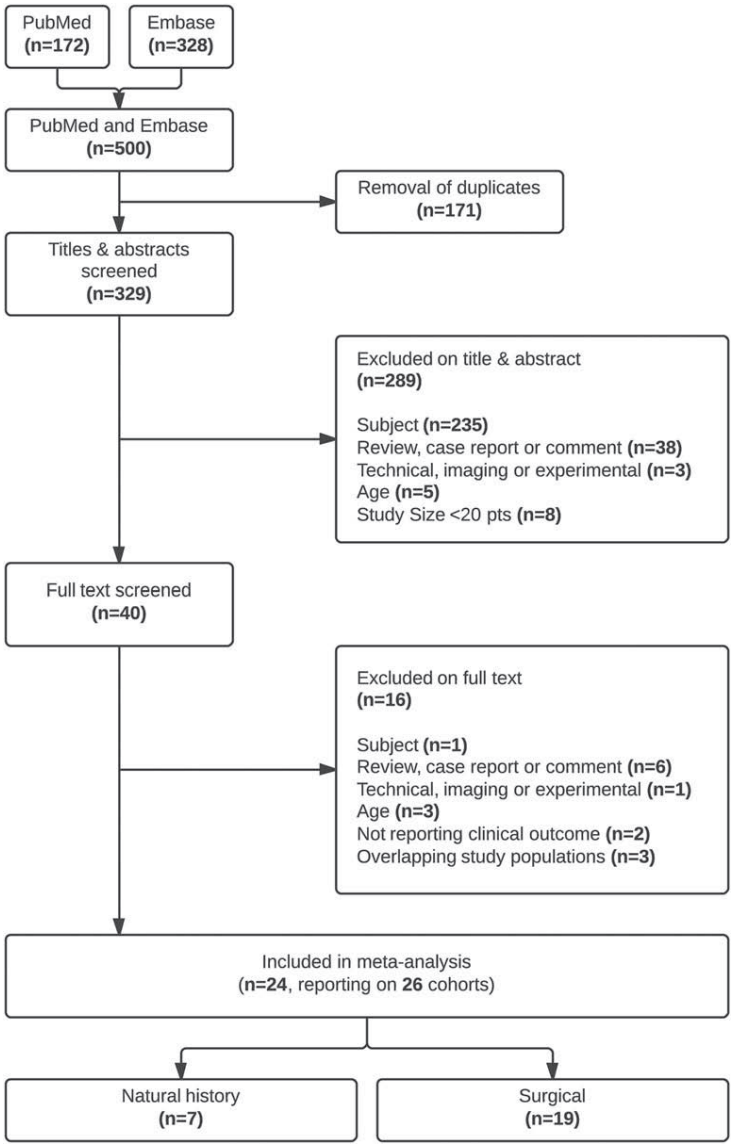

Figure 1. Flowchart of study selection.

sumed that 0.5 patient experienced the event. If means were not reported, medians were used as a substitute. When only the range or interquartile range was provided as opposed to the standard deviation (SD), the range was divided by 4 and the interquartile range was divided by 1.35 as an approximation of the SD. Funnel plots were used to investigate publication bias. Heterogeneity among the included studies was analysed with both the Cochran Q statistic and the I^2 index. Statistical significance was inferred at a $P < 0.05$.

To compare annual mortality rates of the pooled natural history studies with the general population, Dutch population death rates for gender-matched 6-year olds were obtained from the Central Bureau of Statistics.

RESULTS

Literature search

Figure 1 illustrates the literature search process. A total of 24 studies, 7 natural history and 17 surgical studies, were included in the systematic review. These were all retrospective cohort studies. Summaries of the characteristics of all included studies are illustrated in Table 1. Two of the included natural history studies [13, 14] also reported the outcomes of their surgical sub-cohort separately. These results were included in the pooling and analysis of the outcomes of the surgical studies. The funnel plots showed evidence of possible publication bias with regard to early mortality.

Natural history

A total of seven natural history studies met the inclusion criteria.[8, 13-18] Table 2 shows the pooled patient characteristics of the subjects included in the natural history studies. Table 3 shows the pooled outcome measures of the natural history studies. Figure 2 represents the cumulative incidence of mortality based on the pooled linearized mortality rate of the natural history studies compared with the general age- and gender-matched population. Table 4 shows an overview of all the reported statistically significant independent predictors of surgery, LVOT obstruction progression and AR found by multivariable analysis in the included natural history studies. Additionally, McMahon et al. [8] identified thin AV leaflets and associated VSD as independent predictors of being a low-risk patient (no DSAS surgery, no AR, peak LVOT gradient ≤30 mmHg).

Surgical outcome

A total of 17 surgical studies [1, 9, 19-33] were included in this review, and 2 of the included natural history studies [13, 14] also reported the outcomes of their surgical sub-cohort separately, for a combined total of 19 surgical cohorts. Table 2 shows the patient char-

acteristics of the subjects included in the surgical studies. Table 5 shows the pooled outcome measures of the surgical studies. Figure 2 represents the cumulative incidence of mortality and reoperation based on the pooled linearized mortality and reoperation rates of the surgical studies. Table 6 shows an overview of all the reported statistically significant independent predictors of AV dysfunction, mitral valve (MV) dysfunction,

Table 1. Characteristics of included studies

First author	Year of publication	Inclusion period	No. of patients	Age at diagnosis (years)	Mean follow-up (years)
Natural history					
Drolet	2011	1985-1998	74	5.2 ± 0.4	10.4
Lopes	2011	1982-2009	51	15.0 ± 14.0	17.7
Karamlou	2007	1975-1998	313	0.6 ± 4.25	9.1
Babaoglu	2006	1990-2004	78	4.3 ± 4.5	4.8
McMahon	2004	-	220	3.9 ± 12.6	7.2[a]
Tutar	2000	1993-1998	21	<18	2.1
Bezold	1998	1988-1993	52	-	-
Total			**809**		
Surgical					
Van der Linde	2012	1980-2011	313	17.1 ± 14.9[b]	12.9[a]
Drolet	2011	1985-1998	49	7.8 ± 0.6[b]	10.4
Lopes	2011	1982-2009	34	-	17.7
Valeske	2011	1994-2009	81	4.8 ± 4.1	7.5
Booth	2010	1995-2006	48	7.2 ± 6.0[b]	3.4
Hirata	2009	1990-2007	106	7.2 ± 4.9[b]	6.9
Dodge-Khatami	2008	1994-2006	58	4.3 ± 3.4[b]	2.7[a]
Geva	2007	1984-2001	111	5.4 ± 8.7[b]	8.2[a]
Darcin	2006	1995-2001	21	12.6 ± 16.2	3.3
Ruzmetov	2006	1960-2005	140	9.4 ± 4.7[b]	9.8
Marasini	2003	1994-2000	45	<18	2.0
Cohen	2002	1994-2000	73	9.5 ± 15.3	3.3
Paul	2002	1994-2001	21	-	-
Talwar	2001	1990-1998	45	-	5.6
Parry	1999	1992-1996	37	7.5 ± 8.6[b]	2.3
Serraf	1999	1980-1997	160	10.0 ± 7.5[b]	13.3[a]
Lampros	1998	1982-1996	36	7.1 ± 11.6	7.4
Brauner	1997	1982-1995	75	6.0 ± 11.0[b]	6.7
Rayburn	1997	1980-1994	23	13.3 ± 2.5	3.3
Total			**1476**		

'-': variable not reported. [a]Median follow-up. [b]Age at surgery.

Table 2. Patient characteristics

Study	Age at diagnosis[a]	Age at surgery[a]	Male (%)
Natural history			
Drolet (2011)	5.2 ± 0.4	7.8 ± 0.5	64.9
Lopes (2011)	15.0 ± 14.0	14.0 ± 2.9	54.9
Karamlou (2007)	0.6 ± 4.25	3.8 ± 4.7	61.0
Babaoglu (2006)	4.3 ± 4.5	-	-
McMahon (2004)	3.9 ± 12.6	-	59.1
Tutar (2000)	6.7 ± 3.3	-	66.7
Bezold (1998)	-	-	-
Pooled total	**5.03 (4.95-5.13)**	**7.72 (7.59-7.85)**	**60.59 (56.92-64.26)**
I^2	*99%*	*100%*	*0%*
χ^2 *P-value*	*<0.0001*	*<0.0001*	*0.77*
Surgical			
Van der Linde (2012)	8.0 ± 8.1	17.1 ± 14.9	52.1
Drolet (2011)	4.5 ± 0.4	7.8 ± 0.6	-
Lopes (2011)	-	-	-
Valeske (2011)	-	4.8 ± 4.1	65.4
Booth (2010)	-	7.2 ± 6.0	60.4
Hirata (2009)	-	7.2 ± 4.9	57.5
Dodge-Khatami (2008)	-	4.3 ± 3.4	-
Geva (2007)	3.7 ± 8.7	5.4 ± 8.7	61.3
Ruzmetov (2005)	-	9.4 ± 4.7	56.4
Darcin (2003)	-	12.6 ± 16.2	57.1
Marasini (2003)	-	7.3 ± 4.1	57.8
Cohen (2002)	-	9.5 ± 15.2	-
Paul (2002)	-	-	-
Talwar (2001)	8.0 ± 5.3	-	64.4
Parry (1999)	-	7.5 ± 8.6	-
Serraf (1999)	-	10 ± 7.5	66.9
Lampros (1998)	-	7.1 ± 11.6	69.4
Brauner (1997)	-	6.0 ± 11.0	58.7
Rayburn (1997)	-	13.3 ± 4.5	-
Pooled total	**4.56 (4.46-4.68)**	**7.95 (7.79-8.10)**	**59.18 (56.40-61.97)**
I^2	*96%*	*96%*	*28%*
χ^2 *P-value*	*<0.0001*	*<0.0001*	*0.23*

Expressed as: 'mean ± SD' and 'percentage (95% CI)'.
In case a characteristic was reported not to occur, for pooling purposes, it was assumed that the characteristic was present in 0.5 patient.

	Tunnel-type (%)	Bicuspid AV (%)	VSD (%)	ASD (%)	CoA (%)
	0.7	13.5	-	-	-
	9.8	2.0	9.8	5.9	5.9
	0.1	10.9	-	-	-
	-	-	-	-	-
	0.2	25.5	31.8	-	19.5
	-	-	47.6	-	-
	1.0	23.1	11.5	-	13.5
	0.23 (0.00-0.58)	**10.68 (8.49-12.88)**	**21.89 (17.69-26.08)**	**5.88 (0.00-12.34)**	**14.01 (10.29-17.74)**
	32%	*92%*	*90%*	-	*81%*
	0.32	*<0.0001*	*<0.0001*	-	*0.02*
	-	-	23.0	5.8	15.3
	1.0	-	-	-	-
	-	-	-	-	-
	-	-	-	-	34.6
	-	20.8	-	-	-
	-	-	-	-	-
	3.4	-	29.3	20.7	5.2
	0.5	32.4	23.4	-	13.5
	0.4	-	17.1	6.4	16.4
	-	-	28.6	4.8	2.4
	-	20.0	11.1	8.9	15.6
	-	-	-	-	-
	-	-	-	-	-
	-	-	-	-	-
	1.4	-	-	-	-
	21.3	-	-	-	-
	-	-	-	-	-
	9.3	22.7	-	-	-
	-	-	13.0	-	8.7
	0.90 (0.20-1.62)	**25.10 (20.05-30.15)**	**20.60 (17.65-23.55)**	**6.61 (4.60-8.62)**	**12.75 (10.48-15.02)**
	88%	*29%*	*44%*	*49%*	*81%*
	<0.0001	*0.37*	*0.15*	*0.16*	*<0.0001*

'-': variable not reported; AV: aortic valve; ASD: atrial septal defect; CoA: coarctation of the aorta; FUP: follow-up; VSD: ventricular septal defect.

[a]Age in years.

Table 3. Outcome measures of natural history studies

Study	Surgery (%)	Mortality (%/year)
Drolet (2011)	66.2 (55.4-77.0)	0.06 (0.00-0.63)
Lopes (2011)	66.7 (53.7-79.6)	-
Karamlou (2007)	50.8 (45.3-56.3)	0.14 (0.12-0.36)
Babaoglu (2006)	30.8 (20.5-41.0)	-
McMahon (2004)	49.5 (42.9-56.2)	0.06 (0.03-0.36)
Tutar (2000)	47.6 (26.3-69.0)	1.13 (0.02-11.02)
Bezold (1998)	-	-
Pooled total	**50.81 (47.31-54.31)**	**0.12 (0.02-0.78)**
I^2	*87%*	*0%*
χ^2 *P-value*	*0.0002*	*1.00*

Expressed as percentage (95% CI).
In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event.
'-': variable not reported.

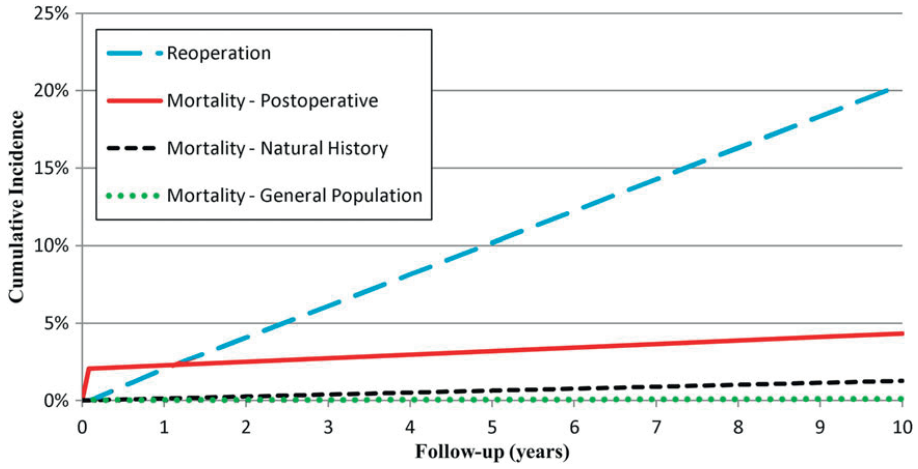

Figure 2. Cumulative incidence of death and reoperation extrapolated from meta-analysis.

recurrence and reoperation found by multivariable analysis in the included surgical studies. Additionally, Serraf et al. [9] found preoperative NYHA functional class to be an independent predictor of early mortality. When viewing overall mortality rate, hypoplastic aortic annulus and mitral stenosis were both identified as independent risk factors. Also, Parry et al. [20] identified higher preoperative peak LVOT gradient as an independent predictor of higher residual early postoperative peak LVOT gradient.

Table 4. Significant independent predictors found by multivariable analysis in the natural history studies

Author/year of publication	Predictors of surgery	Predictors of LVOTO progression	Predictors of AR	LVOT gradient cut-off values
Drolet (2011)	↑ preoperative peak LVOT gradient, presence of preoperative AR	-	-	-
Lopes (2011)	-	-	Peak LVOT gradient >50 mmHg at diagnosis, ↑ left ventricular mass	50 mmHg peak
Karamlou (2007)	↑ mean LVOT gradient at diagnosis, ↑ " mean LVOT gradient at diagnosis, "	Mean LVOT gradient >30 mmHg at diagnosis, initial aortic valve thickening, attachment of SAS to the mitral valve	↑ AR progression: Mean LVOT gradient >30 mmHg, ↑ time from diagnosis	30 mmHg mean
McMahon (2004)	-	-	≥Moderate AR: peak LVOT gradient ≥50 mmHg at diagnosis, age ≥17 years at diagnosis	50 mmHg peak
Bezold (1998)	-	↑ initial peak LVOT gradient (mmHg), anterior MV leaflet involvement, ↓ end-diastolic indexed AV-to-membrane distance	-	(non-progressive) <20 mmHg <(intermediate) <40 mmHg <(progressive) peak

AV: aortic valve; AR: aortic regurgitation; LVOT(O): left ventricle outflow tract (obstruction); MV: mitral valve.

Table 5. Outcome measures of surgical studies

Study	Early mortality (%)	Late mortality (%/year)	Reoperation (%/year)	Postoperative arrhythmia (%)
Van der Linde (2012)	0.3 (0.2-1.8)	0.2 (0.2-0.3)	1.4 (1.4-1.8)	5.4 (5.3-8.7)
Drolet (2011)	1.0 (0.0-9.9)	0.2 (0.0-1.6)	3.3 (3.1-6.1)	6.1 (5.1-18.1)
Lopes (2011)	-	-	1.3 (1.2-2.6)	23.5 (22.1-46.6)
Valeske (2011)	1.2 (0.6-7.1)	0.1 (0.0-0.8)	4.1 (4.0-6.1)	11.1 (10.5-21.2)
Booth (2010)	1.0 (0.0-10.1)	0.3 (0.0-3.0)	4.3 (4.0-8.9)	-
Hirata (2009)	0.9 (0.5-5.4)	0.1 (0.1-0.8)	1.1 (1.0-2.2)	-
Dodge-Khatami (2008)	0.9 (0.0-8.4)	0.6 (0.3-3.6)	7.0 (6.7-12.6)	1.7 (0.9-9.9)
Geva (2007)	-	-	1.8 (1.7-2.9)	-
Ruzmetov (2005)	2.9 (2.5-7.4)	0.3 (0.3-0.9)	1.1 (1.1-1.8)	-
Darcin (2003)	2.4 (0.0-23.1)	0.7 (0.0-7.0)	2.9 (2.2-10.6)	9.5 (7.2-35.0)
Marasini (2003)	1.1 (0.0-10.8)	0.6 (0.0-5.4)	1.1 (0.6-6.4)	-
Cohen (2002)	0.6 (0.0-6.7)	0.2 (0.0-2.0)	3.3 (3.1-6.6)	-
Paul (2002)	-	-	-	-
Talwar (2001)	1.1 (0.0-10.8)	0.2 (0.0-1.9)	-	-
Parry (1999)	1.4 (0.0-13.1)	0.6 (0.0-5.8)	0.6 (0.0-2.3)	-
Serraf (1999)	3.1 (2.8-7.4)	0.2 (0.2-0.5)	-	-
Lampros (1998)	1.4 (0.0-13.5)	0.2 (0.0-1.8)	3.8 (3.6-6.9)	-
Brauner (1997)	0.7 (0.0-6.5)	0.1 (0.0-1.0)	2.6 (2.5-4.4)	1.3 (0.7-7.6)
Rayburn (1997)	2.2 (0.0-21.1)	1.3 (0.7-7.5)	2.6 (2.0-9.6)	13.0 (10.9-38.6)
Pooled total	**2.05 (0.61-6.41)**	**0.22 (0.09-0.55)**	**2.04 (1.52-2.62)**	**7.66 (3.60-13.57)**
I^2	*0%*	*0%*	*61%*	*67%*
χ^2 P-value	*0.95*	*1.00*	*0.001*	*0.007*

Expressed as percentage (95% CI).
In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event.
'-': variable not reported.

Table 6. Significant independent predictors found by multivariable analysis in the surgical studies

Author/year of publication	Predictors of AV/MV dysfunction	Predictors of recurrence/ reoperation	LVOT gradient cut-off values
Van der Linde (2012)	≥Moderate postoperative AR: preoperative peak LVOT gradient ≥80 mmHg	Reoperation: Female gender, ↑ LVOTO progression, preoperative peak LVOT gradient ≥80 mmHg, ↑ difference between preoperative and postoperative gradients	80 mmHg peak
Drolet (2011)	-	-	-
Lopes (2011)		Recurrence: Peak LVOT gradient >50 mmHg at diagnosis, ↓ time from diagnosis to surgery	50 mmHg peak
Booth (2010)	-	Recurrence: ↓ Age at surgery	
Hirata (2009)	-	Recurrence: ↓ Age at surgery, ↑ preoperative peak LVOT gradient, resection without myectomy[a] Reoperation: Associated CoA, resection without myectomy[a]	
Dodge-Khatami (2006)	-	No independent predictors identified	-
Geva (2007)	-	Recurrence: Diastolic AV-to-membrane distance <5 mm and associated Shone's syndrome. Reoperation: Systolic AV-to-membrane distance <6 mm and peak LVOT gradient ≥60 mmHg	60 mmHg peak
Ruzmetov (2005)	-	No independent predictors identified	-
Paul (2002)	MR: Diastolic indexed AV-to-membrane distance ≥8 mm/m	-	-
Talwar (2001)	-	-	-
Parry (1999)	≥Mild early postoperative AR: ↑ preoperative peak LVOT gradient, mild/moderate preoperative AR ≥Mild late postoperative AR: ≥mild early postoperative AR, ↑ early postoperative peak LVOT gradient	-	-
Serraf (1999)	-	Recurrence and Reoperation: ↑ Early postoperative peak-to-peak LVOT gradient, aortic coarctation	-
Brauner (1997)	Postoperative AR progression: ↑ preoperative peak LVOT gradient	Recurrence: ↓ Age, preoperative gradient, residual end-operative peak LVOT gradient >10 mmHg, tunnel-type stenosis. • Only in DSS: ↑ preoperative peak LVOT gradient. Late reoperation: ↑ preoperative peak LVOT gradient	40 mmHg peak

[a]Only in patients who underwent previous cardiac operations.

AV: aortic valve; AR: aortic regurgitation; LVOT(O): left ventricle outflow tract (obstruction); MR: mitral regurgitation; MV: mitral valve; CoA: coarctation of the aorta.

DISCUSSION

This systematic review provides an overview of published data on the natural history of paediatric SAS and outcome after surgery, and identifies several determinants of prognosis in paediatric cases of SAS, including factors that are helpful in establishing surgical indications in these patients.

Natural history

This systematic review shows that SAS usually presents before the age of 10 years and 60% concerns males. Associated cardiac anomalies appear to be less common than previously reported.[3, 4] The progressive nature of the disease is underlined by the common need for surgery in half of the included patients. Mortality rates are slightly higher than in the age- and gender-matched general population.

Left ventricular outflow tract gradient

Five of the seven included natural history studies [8, 13-15, 17] confirm that a higher LVOT gradient at diagnosis is an independent predictor of various adverse outcomes such as AR, faster AR progression, faster progression of LVOT obstruction and surgical intervention. One of the other studies [16] found that the peak LVOT gradient was significantly higher in patients with progressive AR than in those whose AR showed no signs of progression, but did not perform multivariable analyses on their data. The observation that LVOT outflow tract obstruction severity is correlated with AR progression provides important information for prognostication and clinical decision-making.

Valve-to-membrane distance

Although the sub-valvular obstruction may be a complex 3D structure that does not necessarily encircle the LVOT, a level can often be identified to allow measurement of its distance to the AV. Interestingly, two studies [8, 15] found a longer distance of the sub-valvular obstruction from the base of the AV to be associated with less progressive LVOT obstruction and potentially predictive of being a low-risk patient (no DSAS surgery, no AR, peak LVOT gradient ≤30 mmHg). However, based on the earlier echocardiographic studies on this factor reporting contradictory findings, the prognostic role of this factor remains controversial.[34, 35]

Surgical outcome

The patient characteristics of the surgical population were similar to those of the natural history cohort with respect to age at presentation, gender distribution and the relatively low incidence of concomitant cardiac anomalies when compared with earlier reports [3, 4]. On average, the patients underwent surgery ~3 years after diagnosis with low operative

mortality and late mortality rates slightly higher than in the age- and gender-matched general population, but with a significant reoperation rate.

Left ventricular outflow tract gradient

In 7 of the 19 surgical (sub)cohorts,[9, 19, 20, 24, 26, 28] higher LVOT gradient (at diagnosis, pre- and postoperative) was identified as an independent predictor of various adverse postoperative outcomes such as postoperative AR, faster AR progression, MR, postoperative residual LVOT gradient, faster progression of LVOT obstruction, recurrence and reoperation. Two additional studies [21, 25] found a higher LVOT gradient to be associated with a worse outcome. However, in these studies, these associations did not reach statistical significance in multivariable analysis.

In short, a higher LVOT gradient has serious consequences, in both medically and surgically managed patients, which negatively affect the prognosis and are often irreversible. Our review confirms the general consensus of the LVOT gradient being an important criterion, when considering surgical treatment of SAS.

There is an ongoing discussion on which LVOT gradient can best be used as a cut-off value to discriminate between low- and high-risk patients. Among the included studies, the used cut-off value ranged from 30 to 80 mmHg. Brauner et al.,[19] for instance, used a cut-off value of 40 mmHg in their statistical analyses, but retrospectively conducted an ROC sensitivity analysis to determine LVOT gradients that best predicted outcome. They found the best preoperative peak LVOT gradient cut-off values in prediction of recurrence, reoperation and late progression of AV disease to be 45, 46 and 46 mmHg, respectively. Based on these results, further collaborative studies are needed to evaluate the optimal cut-off value in the use of LVOT gradient as an indication for surgery.

Aortic regurgitation

One study [20] showed that the presence of AR, regardless of severity, in SAS patients, either at diagnosis, preoperatively or at early or late follow-up, was a significant predictor of AR at a later point in the follow-up. One natural history study [13] found that the presence of AR preoperatively was predictive of surgical intervention. Thus, AR is a major sequela in SAS patients with significant prognostic implications and should therefore play an integral role in the surgical decision-making process.

Valve-to-membrane distance

The prognostic relevance of the valve-to-membrane distance was illustrated by the aforementioned natural history studies. However, we came upon a dilemma in the

potential use of the valve-to-membrane distance as a prognostic marker. Paul et al. [22] found a longer valve to-membrane distance to be predictive of MR.

On the contrary, Geva et al. [24] and the two natural history studies [8, 15] found a shorter valve-to-membrane distance to be prognostically unfavourable, which would suggest earlier surgical intervention be considered in patients with a shorter valve-to-membrane distance, as opposed to the results reported by Paul et al. [22] However, none of these three studies looked into MV function, as Paul et al. [22] did.

On the basis of these contradicting findings, we are unable to formulate clear surgical advice with regard to the valve-to-membrane distance, as both high and low values of this variable seem to have adverse effects on the course of the disease. Further scientific studies on the precise prognostic impact of the valve-to-membrane distance are warranted, as they may clarify the value of this potentially relevant factor.

Other than these foremost prognostic indicators, there are many other factors to consider when contemplating surgical intervention such as patient age, MV involvement, AV/MV annulus size, thickness of the AV leaflets and concomitant cardiac anomalies. As our results show, all of these factors further influence outcome in SAS patients and should, therefore, beweighed into the decision-making process.

Study limitations

This is a systematic review of retrospective observational studies. As such, the inherent limitations of combining data from retrospective observational studies should be taken into consideration.[36-38] For this reason, no sub-group analyses or meta-regression was attempted.

CONCLUSIONS

This systematic review underlines the importance of LVOT gradient in surgical decision-making in paediatric SAS patients; the majority of the included studies found a higher LVOT gradient to be associated with adverse outcome. The presence of AR and the valve-to-membrane distance should also be taken into consideration as prognostic determinants in these patients. Given the small sample size of most series, there is need for collaborative effort to further study the optimal timing of surgery based on LVOT gradient, the presence of AR and to further investigate the predictive role of the valve-to-membrane distance.

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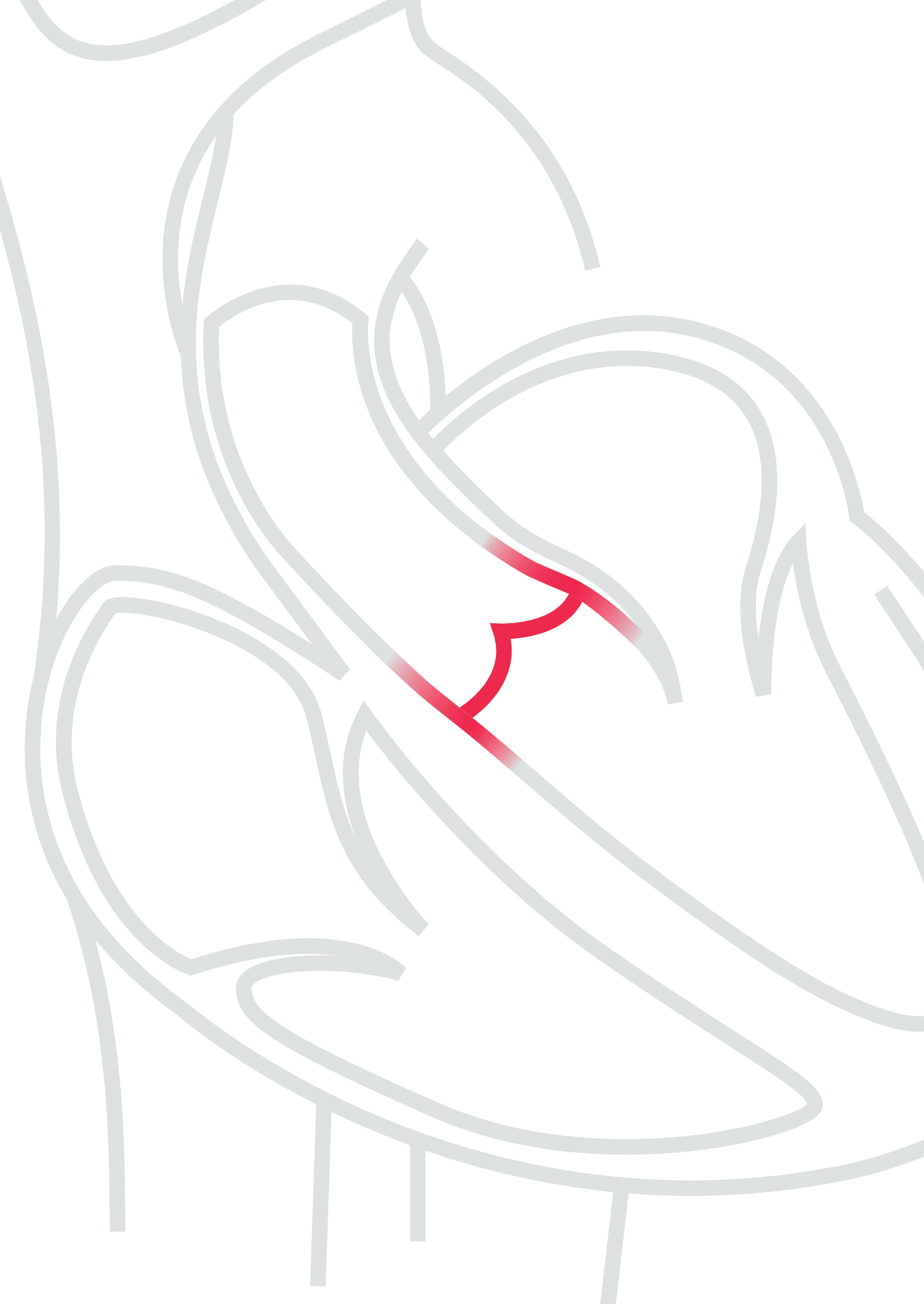

3

Outcome after aortic valve replacement in children: a systematic review and meta-analysis

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ABSTRACT

Background

Despite an increasing interest in pediatric aortic valve repair, aortic valve replacement in children may be unavoidable. The evidence on outcome after pediatric aortic valve replacement is limited and usually reported in small case series. This systematic review and meta-analysis aims to provide an overview of reported outcome of pediatric patients after aortic valve replacement.

Methods

A systematic literature search for publications reporting outcome after pediatric aortic valve replacement published between January 1990 and May 2015 was conducted. Studies written in English with a study size of more than 30 patients were included.

Results

Thirty-four publications reporting on 42 cohorts were included in this review: 26 concerning the Ross procedure (n = 2409), 13 concerning mechanical prosthesis aortic valve replacement (n = 696), and 3 concerning homograft aortic valve replacement (n = 224). There were no studies on bioprostheses that met our inclusion criteria. The pooled mean patient age was 9.4 years, 12.8 years, and 8.9 years for Ross, mechanical prosthesis, and homograft recipients, respectively. Pooled mean follow-up was 6.6 years. The Ross procedure was associated with lower early (4.20%; 95% confidence interval [CI], 3.37-5.22 vs 7.34%; 95% CI, 5.21-10.34 vs 12.82%; 95% CI, 8.91-18.46) and late mortality (0.64%/y; 95% CI, 0.49-0.84 vs 1.23%/y; 95% CI, 0.85-1.79 vs 1.59%/y; 95% CI, 1.03-2.46) compared with mechanical prosthesis aortic valve replacement and homograft aortic valve replacement, respectively. No significantly different aortic valve reoperation rates were observed between the Ross procedure and mechanical prosthesis aortic valve replacement (1.60%/y; 95% CI, 1.27-2.02 vs 1.07%/y; 95% CI, 0.68-1.68, respectively), whereas homograft aortic valve replacement was associated with significantly higher aortic valve reoperation rates (5.44%/y; 95% CI, 4.24-6.98). The Ross procedure-associated right ventricular outflow tract reoperation rate was 1.91% per year (95% CI, 1.50-2.44).

Conclusions

This systematic review illustrates that all currently available aortic valve substitutes are associated with suboptimal results in children, reflecting the urgent need for reliable and durable repair techniques and innovative replacement solutions for this challenging group of patients.

INTRODUCTION

Although pediatric aortic valve repair is rapidly developing and meets great interest, aortic valve replacement (AVR) often cannot be avoided. The outcome after AVR in pediatric patients is reported infrequently and usually in small retrospective case series. All currently available surgical options in children have certain limitations, and the choice of valve substitute is determined by several factors. In addition to the occurrence of valve-related complications,[1] the influence of patient growth has a major impact on valve performance in children. In current clinical practice, 4 types of aortic valve substitutes can be offered to children who require AVR: the Ross procedure, mechanical prostheses (MPs), homografts (HGs), and bioprostheses. The Ross procedure (a pulmonary autograft in the aortic valve position and an allograft in the pulmonary position) is considered the preferred surgical option for children who require AVR.[2,3] It is the only living valve substitute and has proven to be hemodynamically superior without the need for long-term anticoagulation, shows diameter increase along with somatic growth, and is associated with a low risk of endocarditis.[4,5] Nevertheless, the Ross procedure is a complex surgical procedure, and both the pulmonary autograft and the valve substitute in the right ventricular outflow tract (RVOT) may require reintervention.[6] The primary advantage of MPs is long-term performance. However, in addition to bleeding complications due to lifelong anticoagulation, prosthesis-patient mismatch (PPM) can cause deterioration of ventricular function in growing children.[7-11] Furthermore, female patients with mechanical heart valves face a substantial risk of serious complications during future pregnancies.[12] HGs have a low thrombogenicity and favorable tissue characteristics that allow for complex reconstruction of the aortic root, but have a limited durability because of early calcifications and may not be readily available.[8,13,14] Bioprostheses have the advantage of commercial availability and assumingly perform similar to HGs; however, high rates of early degeneration, calcification, and structural failure have been reported in young recipients.[8,9,15-18]

The balance of the risks and benefits of the various pediatric AVR alternatives remains a point of discussion, and an overview of reported outcomes is lacking. Therefore, the aim of this systematic literature review and metaanalysis is to provide an overview of the published evidence reporting outcomes after contemporary pediatric AVR with pulmonary autografts, MPs, HGs, and bioprostheses.

METHODS

Search strategy

To establish an overview of published evidence on outcome after pediatric AVR, we conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[19] On March 19, 2015, PubMed and Embase were searched (Supplement 1). The search was limited to studies that included 30 or more patients, were conducted in humans, were published after January 1, 1990, and were written in English. We also applied a limit on mean patient age (<18 years) and maximum patient age (<21 years) at the time of surgery. All results were screened for study design and outcome (early and late mortality, reoperations, and complications). Only the most recent or most complete study was included in case study populations were overlapping. A second independent reviewer (MMM) assessed whether inclusion and exclusion were performed correctly. In case of disagreement, an agreement was negotiated. References of selected articles were cross-checked for other relevant studies.

Data extraction

Microsoft Office Excel 2011 (Microsoft Corp, Redmond, Wash) was used for data extraction. Publications were categorized by prosthetic valve type: Ross procedure, MP AVR, HG AVR, and bioprosthetic AVR. Studies describing more than 1 type of AVR procedure were included as separate cohorts according to the type of AVR procedure performed. Studies that included only infants and neonates were pooled separately. Year of publication, number of patients, study design, and follow-up (patient-years and mean/median follow-up) were recorded as study characteristics. If follow-up was not reported in patient-years, mean or median follow-up was multiplied by the reported number of patients. The following baseline patient characteristics were recorded: mean age at time of AVR, gender, indication for AVR surgery, previous cardiac interventions, concomitant procedures, and annular enlargement procedures. The indication for surgery was categorized by cause of valve disease (eg, congenital, rheumatic, and endocarditis). Morbidity and mortality were documented according to the guidelines as described by Akins and colleagues.[20] The following events were documented: early mortality (%), late mortality (%/year), reoperation (%/year), and complications (%/year). Early mortality was defined as death within 30 days after AVR, and late mortality was defined as death after 30 days postoperatively. All reoperations after initial AVR, including percutaneous interventions, were registered. Reoperations were divided into aortic valve reoperations and for the Ross procedure RVOT reoperations. A distinction was made between all-cause reoperations and reoperations for structural valve deterioration (SVD)/ nonstructural valve dysfunction (NSVD). Reoperations for neoaortic root dilatation/aneurysm after the Ross procedure were recorded as reoperations for SVD/NSVD. The following complications

occurring more than 30 days after AVR were documented: thromboembolism (TE)/valve thrombosis (VT), bleeding, and endocarditis.[20] Functional health status measured by the New York Heart Association (NYHA) classification was registered when described in the study.

Statistical analyses

Weighted pooled baseline patient characteristics were calculated for each prosthetic valve type group. The Student *t* test and the chi-square test were used to test for differences in continuous and categoric baseline characteristics, respectively. Early mortality risk and linearized occurrence rates of late mortality, sudden unexpected and unexplained death, reoperations, and complications after AVR were calculated and pooled with the use of inverse variance weighting on a logarithmic scale, because the Shapiro-Wilk test revealed a significantly skewed distribution among the included studies in the majority of outcome measures. When the number of studies was sufficiently large to reliably estimate the tau-squared statistic (≥4 studies), a random effects model was used to estimate pooled effects. When estimating pooled effects from less than 4 studies, a fixed effects model was used. 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 an event. The Cochran Q statistic and the I^2 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, and case mix. Funnel plots were used to investigate publication bias. Statistical analyses were performed in Microsoft Office Excel 2011 (Microsoft Corp), IBM SPSS Statistics (version 21.0.0.1. IBM Corp, Armonk, NY), and the R statistical software (version 3.1.0. R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the metafor package. The authors had full access to and take full responsibility for the integrity of the data.

RESULTS

The search resulted in 1218 publications after removal of duplicates. After applying inclusion and exclusion criteria, a total of 34 publications were included in the systematic review, reporting on 42 cohorts: 26 concerning the Ross procedure (n = 2409),[11,13,16,21-43] 13 concerning MP-AVR (n = 696),[15,16,23,31,44-52] and 3 concerning HG-AVR (n = 224)[13,23,53] (Figure 1). There were no studies on bioprosthetic AVR that met our inclusion criteria, because all of them had a sample size of less than 20 patients. This systematic review encompasses a total of 3329 patients with 21,110 patient-years of follow-up.

Study characteristics and baseline patient characteristics

Table 1 provides an overview of the publications included in the present study. Pooled mean follow-up was 6.6 years. Indication for AVR was mainly congenital heart disease. By excluding studies that included only neonates and infants, the pooled mean age was 9.5 ± 4.9 years (range, 5.17-14.0 years) for the Ross procedure, 12.8 ± 3.6 years (range, 9.0-16.6 years) for MP-AVR, and 8.9 ± 4.1 years (range, 4.9-12.5 years) for HG-AVR.

When comparing patients undergoing the Ross procedure (excluding studies that included only neonates and infants) with patients undergoing MP-AVR, patients undergoing the Ross procedure were significantly younger (P<.001), less frequently had rheumatic valve disease (19.2% vs 36.1%, P <.001), and more frequently had undergone previous cardiac interventions (56.8%vs 47.6%, P = .001), whereas the number of concomitant procedures (27.7% vs 26.0%, P = .480) and annular enlargement procedures (19.3% vs 16.5%, P = .127) was comparable between the 2 groups. Paucity of baseline patient data in the HG-AVR group precluded pooled analysis.

Study outcomes

Pooled outcome measures (mortality, reoperations, and complications) after the Ross procedure in the general pediatric patient population are shown in Table 2, and for neonates and infants, these are shown in Table 3. Pooled outcome measures after MP-AVR and HG-AVR are shown in Tables 4 and 5, respectively. In studies reporting on postoperative NYHA functional class (n = 13),[11,21,28,31,32,34,36,37,41,42,45,47,49] 93% of the patients were in NYHA class I at last follow-up.

Heterogeneity and publication bias

Significant heterogeneity was found in the pooling of reoperation rates after the Ross procedure and MP-AVR and endocarditis rates after the Ross procedure.With regard to reoperations on the aortic valve after the Ross procedure, an outlier in mean follow-up[22] was identified as an isolated source of heterogeneity. Likewise, an outlier in inclusion period[13] caused heterogeneity in endocarditis rates after the Ross procedure. Heterogeneity in aortic valve reoperation rates after MP-AVR was also caused by a single outlier,[48] although we were unable to identify any explanatory study or patient characteristics. Exploratory exclusion of these studies eliminated significant heterogeneity but did not cause a major change in the pooled estimates.

We were unable to identify the cause of heterogeneity in RVOT reoperations after the Ross procedure. The funnel plots showed evidence of possible publication bias in all outcome measures (Supplement 2). Smaller studies with relatively high event rate estimates seemed less likely to be published.

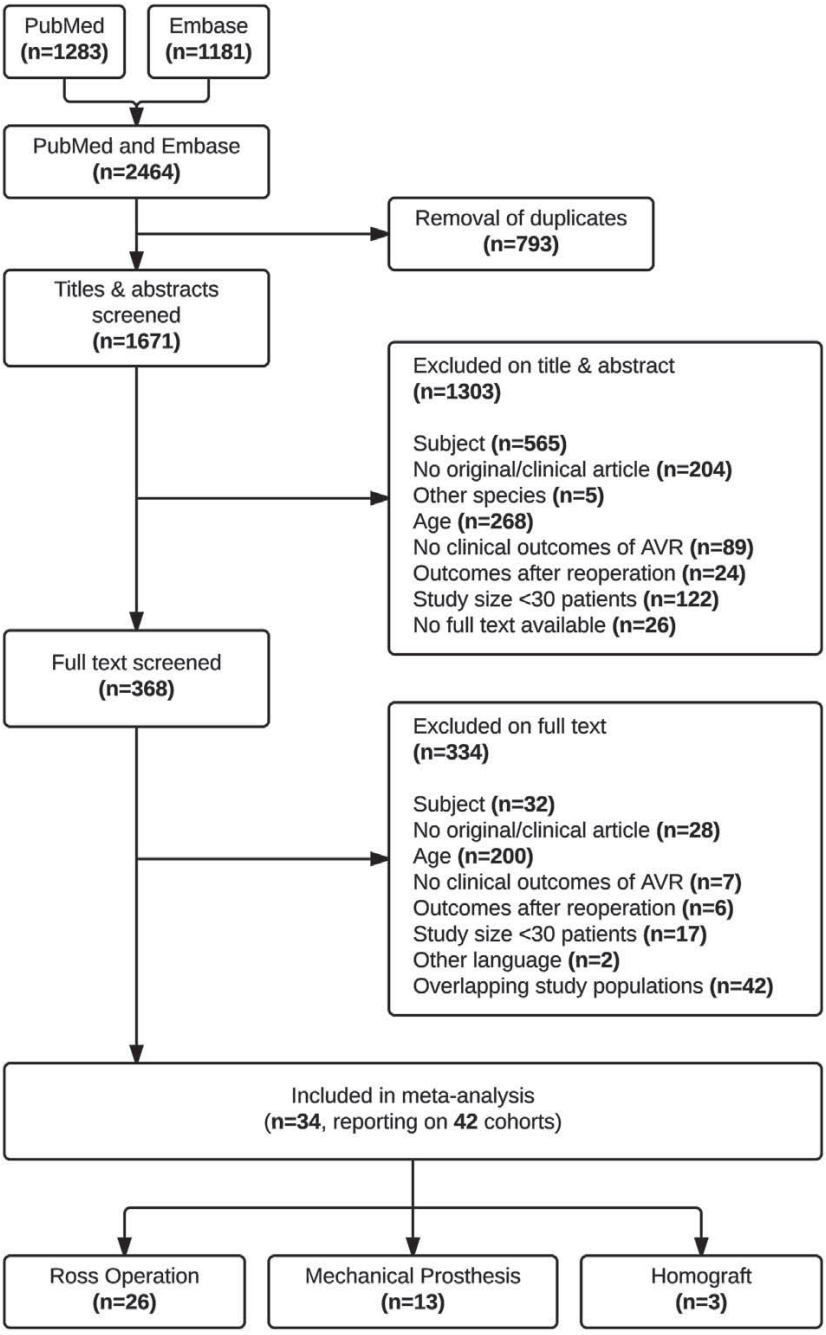

Figure 1. Flowchart of study selection.

Table 1. Overview of publications

First author	Year of publication	No. of patients	Study type	Mean follow-up (y)	Mean age (y)	Cause (most frequent)	Previous cardiac interventions (%)*	Concomitant procedures (%)‡	Annular enlargement procedures (%)*
Ross procedure									
Gerosa	1991	43	Retrospective	6.9	14	-	34.9	14.0	-
Reddy	1998	41	Retrospective	2.6	7.8#	Congenital	80.5	56.1	29.3
Elkins	2001	178	Retrospective	5.2#	9.6	-	51.1	23.0	6.2
Simon	2001	30	Retrospective	4.3	11.3	Congenital	-	-	0.0
Hazekamp	2005	53	Retrospective	5.5	9.2	Congenital	69.8	24.5	5.7
Bohm	2006	60	Retrospective	3.5	12.6	Congenital	65.0	21.7	6.7
Kalavrouziotis	2006	35	Retrospective	4.1	10.6	-	85.7	-	0.0
Ruzmetov	2006	81	Retrospective	5.3	5.3	-	-	-	-
Stewart	2007	46	Retrospective	5.4	12.9	Congenital	-	15.2	0.0
Kadner	2008	52	Retrospective	3.6#	5.2	-	65.4	21.2	30.8
Alsoufi	2009	215	Retrospective	5.7	11.4	Rheumatic	-	-	14.9
El Behery	2009	41	Retrospective	6	10.2	Congenital	-	24.4	-
Piccardo	2009	55	Retrospective	5.5	10	Congenital	-	12.7	16.4
Charitos	2012	263	Prospective	6.9	8	Congenital	53.6	-	-
Talwar	2012	36	Retrospective	7.9	11.3	-	-	27.8	-
Woods (age<1 y)	2012	145	Retrospective	-	- (<1)	-	-	-	-
Elder (age<1 y)	2013	34	Retrospective	10.6	0.5	Congenital	-	-	-
Khan	2013	68	Retrospective	6.7	5.9#	-	-	-	23.5
Ruzmetov	2013	78	Retrospective	8.8	11.1	Congenital	-	29.5	23.1
Tan Tanny	2013	100	Retrospective	7.3	8.6	Congenital	-	29.0	29.0
Luciani	2014	305	Retrospective	8.4	9.4	-	30.4	29.2	23.9
Luciani (age<1 y)	2014	37	Retrospective	8.4	0.3	-	-	54.1	70.3
Bansal	2015	210	Retrospective	5.0	8.1	-	-	37.1	-
Bansal (age<1 y)	2015	41	Retrospective	6.1	0.3	-	-	-	-
Nelson	2015	240	Retrospective	10.8	-	Congenital	73.8	-	32.5
Nelson (age<1 y)	2015	44	Retrospective	9.8	-	Congenital	75.0	-	68.2
Total		**2409**							
Mechanical prosthesis									
Abid	1992	64	Retrospective	7	12	Rheumatic	-	28.1	10.9
Cabalka	1995	36	Retrospective	3.3	- (<18)	Congenital	58.3	-	-
Yamak	1995	37	Retrospective	2.9	16.6	Rheumatic	-	24.3	10.8
Champsaur	1997	54	Retrospective	5.8	12.8	Congenital	51.9	46.3	16.7

Table 1. Overview of publications (continued)

First author	Year of publication	No. of patients	Study type	Mean follow-up (y)	Mean age (y)	Cause (most frequent)	Previous cardiac interventions (%)*	Concomitant procedures (%)ǂ	Annular enlargement procedures (%)*
Mazzitelli	1998	30	Retrospective	6.6	- (<18)	-	-	-	-
Lupinetti	1999	50	Retrospective	5.4	12.1	Congenital	62.0	10.0	12.0
Alexiou	2000	56	Retrospective	7.3	11.2	Congenital	64.3	26.8	50.0
Shanmugam	2005	55	Retrospective	13	13	Congenital	-	18.2	21.8
Ruzmetov	2006	47	Retrospective	7.7	7.7	-	-	-	-
Burczynski	2007	55	Retrospective	6.4	12.8	Congenital	-	20.0	0.0
Masuda	2008	45	Retrospective	9.2	9	-	44.4	33.3	55.6
Alsoufi	2009	131	Retrospective	8.3	14	Rheumatic	31.3	-	2.3
Khan	2013	36	Retrospective	4.6	14.0#	-	-	-	5.6
Total		**696**							
Homograft									
Gerosa	1991	103	Retrospective	8.4	12.5	-	43.7	-	-
Clarke	1993	47	Retrospective	2.3	7.1	-	89.4	-	76.6
Khan	2013	74	Retrospective	4	4.9#	-	-	-	12.2
Total		**224**							

"-" = variable not reported. *Number of patients. ǂNumber of procedures (excluding annular enlargement procedures). #Median.

Table 2. Pooled outcome estimates after the Ross procedure (excluding studies that concerned only neonates and infants)

Study	Early mortality %	Late mortality %/y	SUUD %/y	AV reoperation %/y
Gerosa (1991)	11.63 (5.10-26.51)	1.68 (0.71-4.01)	-	1.68 (0.71-4.01)
Reddy (1998)	2.44 (0.35-16.90)	0.47 (0.03-7.50)	0.47 (0.03-7.50)	1.89 (0.48-7.45)
Elkins (2001)	4.49 (2.28-8.85)	0.31 (0.10-0.95)	-	1.23 (0.70-2.16)
Simon (2001)	1.67 (0.11-26.04)	0.78 (0.11-5.46)	0.39 (0.02-6.16)	0.78 (0.11-5.46)
Hazekamp (2005)	5.66 (1.89-16.99)	1.03 (0.33-3.17)	0.17 (0.01-2.74)	1.72 (0.72-4.09)
Bohm (2006)	0.83 (0.05-13.17)	0.95 (0.24-3.78)	0.24 (0.01-3.79)	0.24 (0.01-3.79)
Kalavrouziotis (2006)	1.43 (0.09-22.39)	0.70 (0.10-4.91)	0.35 (0.02-5.54)	0.35 (0.02-5.54)
Ruzmetov (2006)	1.23 (0.18-8.66)	0.23 (0.03-1.65)	0.12 (0.01-1.86)	1.63 (0.78-3.40)
Stewart (2007)	1.09 (0.07-17.12)	0.20 (0.01-3.20)	0.20 (0.01-3.20)	2.81 (1.35-5.83)
Kadner (2008)	9.62 (4.18-22.12)	1.61 (0.52-4.95)	0.27 (0.02-4.27)	1.07 (0.27-4.26)
Alsoufi (2009)	2.33 (0.98-5.53)	0.04 (0.00-0.65)	0.04 (0.00-0.65)	2.28 (1.58-3.29)
El Behery (2009)	4.88 (1.26-18.85)	0.20 (0.01-3.24)	0.20 (0.01-3.24)	0.20 (0.01-3.24)
Piccardo (2009)	1.82 (0.26-12.68)	0.66 (0.17-2.63)	0.17 (0.01-2.64)	0.99 (0.32-3.06)
Charitos (2012)	3.42 (1.80-6.50)	0.58 (0.30-1.12)	0.13 (0.03-0.52)	0.91 (0.54-1.53)
Talwar (2012)	2.78 (0.40-19.19)	1.40 (0.53-3.71)	0.18 (0.01-2.80)	1.75 (0.74-4.18)
Khan (2013)	1.47 (0.21-10.29)	0.44 (0.11-1.75)	-	0.66 (0.21-2.03)
Ruzmetov (2013)	3.85 (1.27-11.67)	0.58 (0.22-1.55)	0.29 (0.07-1.16)	2.91 (1.89-4.49)
Tan Tanny (2013)	6.00 (2.76-13.03)	0.55 (0.21-1.46)	0.14 (0.02-0.97)	1.23 (0.64-2.36)
Luciani (2014)	3.28 (1.78-6.03)	0.47 (0.27-0.82)	0.02 (0.00-0.31)	1.44 (1.05-1.99)
Bansal (2015)	4.29 (2.26-8.12)	0.05 (0.00-0.76)	0.05 (0.00-0.76)	-
Nelson (2015)	4.17 (2.27-7.64)	0.66 (0.41-1.05)	-	2.66 (2.11-3.36)
Pooled (random effects)	**4.20 (3.37-5.22)**	**0.64 (0.49-0.84)**	**0.16 (0.09-0.29)**	**1.60 (1.27-2.02)**
Heterogeneity test	*χ^2 20.78 (P = .41)* *I^2 = 3%*	*χ^2 23.77 (P = .25)* *I^2 = 16%*	*χ^2 6.32 (P = .98)* *I^2 = 0%*	*χ^2 40.97 (P = .00)* *I^2 = 54%*

Data expressed as percentage (95% CI). "-"=variable not reported. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event. SUUD, Sudden, unexpected, unexplained death; AV, aortic valve; RVOT, right ventricular outflow tract; SVD, structural valve deterioration; NSVD, nonstructural valve dysfunction; TE, thromboembolism; VT, valve thrombosis.

RVOT reoperation %/y	Reoperation for SVD/NSVD %/y	TE/VT %/y	Bleeding %/y	Endocarditis %/y
0.34 (0.05-2.38)	0.34 (0.05-2.38)	0.17 (0.01-2.69)	-	1.68 (0.71-4.01)
0.47 (0.03-7.50)	1.89 (0.48-7.45)	-	-	-
0.92 (0.48-1.77)	1.95 (1.25-3.05)	0.05 (0.00-0.82)	-	0.21 (0.05-0.82)
0.39 (0.02-6.16)	0.78 (0.11-5.46)	0.39 (0.02-6.16)	0.39 (0.02-6.16)	0.39 (0.02-6.16)
1.03 (0.33-3.17)	2.74 (1.39-5.44)	-	-	-
4.76 (2.60-8.72)	4.76 (2.60-8.72)	0.24 (0.01-3.79)	0.24 (0.01-3.79)	0.24 (0.01-3.79)
1.39 (0.35-5.52)	1.39 (0.35-5.52)	-	-	-
1.40 (0.63-3.09)	3.03 (1.77-5.17)	0.12 (0.01-1.86)	0.12 (0.01-1.86)	0.12 (0.01-1.86)
0.40 (0.06-2.84)	3.21 (1.62-6.35)	0.20 (0.01-3.20)	0.20 (0.01-3.20)	-
3.22 (1.47-7.08)	4.29 (2.18-8.46)	0.27 (0.02-4.27)	-	0.27 (0.02-4.27)
-	-	0.04 (0.00-0.65)	0.04 (0.00-0.65)	0.16 (0.04-0.65)
1.63 (0.62-4.30)	0.81 (0.20-3.23)	-	-	0.81 (0.20-3.23)
0.99 (0.32-3.06)	0.66 (0.17-2.63)	-	-	0.33 (0.05-2.34)
2.72 (2.02-3.67)	2.98 (2.24-3.96)	0.58 (0.30-1.12)	0.03 (0.00-0.52)	0.65 (0.35-1.20)
0.70 (0.18-2.79)	-	0.18 (0.01-2.80)	0.18 (0.01-2.80)	0.70 (0.18-2.79)
3.51 (2.17-5.68)	-	-	-	-
2.33 (1.44-3.78)	5.24 (3.82-7.21)	-	-	-
2.74 (1.78-4.22)	-	-	-	-
1.44 (1.05-1.99)	2.77 (2.20-3.49)	0.08 (0.02-0.31)	0.02 (0.00-0.31)	0.08 (0.02-0.31)
-	-	-	-	-
2.20 (1.70-2.84)	-	-	-	-
1.91 (1.50-2.44)	**2.75 (2.13-3.53)**	**0.22 (0.11-0.43)**	**0.10 (0.04-0.27)**	**0.40 (0.22-0.73)**
χ^2 44.49 (P = .00) *I^2 = 59%*	*χ^2 35.59 (P = .00)* *I^2 = 60%*	*χ^2 12.09 (P = .27)* *I^2 = 17%*	*χ^2 4.08 (P = .77)* *I^2 = 0%*	*χ^2 21.60 (P = .03)* *I^2 = 49%*

Table 3. Pooled outcome estimates after the Ross procedure in neonates and infants

Study	Early mortality %	Late mortality %/y	SUUD %/y	AV reoperation %/y
Woods (2012)	15.86 (10.90-23.08)	-	-	-
Elder (2013)	11.76 (4.69-29.54)	0.14 (0.01-2.21)	0.14 (0.01-2.21)	0.28 (0.04-1.96)
Luciani (2014)	21.62 (11.71-39.93)	2.57 (1.30-5.10)	-	1.93 (0.87-4.26)
Bansal (2015)	17.07 (8.70-33.52)	0.20 (0.01-3.19)	0.20 (0.01-3.19)	-
Nelson (2015)	18.18 (9.71-34.03)	0.70 (0.23-2.15)	-	0.46 (0.12-1.85)
Pooled	**16.88 (13.12-21.73)***	**0.76 (0.21-2.78)***	**0.17 (0.02-1.18)†**	**1.14 (0.60-2.18)†**
Heterogeneity test	*χ^2 1.38 (P = .85)* *I^2 = 0%*	*χ^2 9.05 (P = .03)* *I^2 = 67%*	*χ^2 0.03 (P = .85)* *I^2 = 0%*	*χ^2 5.32 (P = .07)* *I^2 = 62%*

Data expressed as percentage (95% CI). "-" = variable not reported. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event. SUUD, Sudden, unexpected, unexplained death; AV, aortic valve; RVOT, right ventricular outflow tract; SVD, structural valve deterioration; NSVD, nonstructural valve dysfunction; TE, thromboembolism; VT, valve thrombosis. *Random effects. †Fixed effects.

Table 4. Pooled outcome estimates after aortic valve replacement with mechanical prosthesis

Study	Early mortality %	Late mortality %/y	SUUD %/y	AV reoperation %/y
Abid (1992)	12.50 (6.54-23.90)	2.60 (1.41-4.79)	0.13 (0.01-2.07)	1.30 (0.54-3.10)
Cabalka (1995)	5.56 (1.44-21.36)	0.85 (0.12-6.02)	-	0.43 (0.03-6.79)
Yamak (1995)	8.11 (2.74-23.99)	0.49 (0.03-7.83)	0.49 (0.03-7.83)	0.49 (0.03-7.83)
Champsaur (1997)	12.96 (6.49-25.87)	2.30 (1.04-5.07)	0.19 (0.01-3.05)	1.15 (0.37-3.54)
Mazzitelli (1998)	1.67 (0.11-26.04)	1.52 (0.49-4.66)	0.25 (0.02-4.02)	2.53 (1.06-6.00)
Lupinetti (1999)	10.00 (4.35-22.97)	1.48 (0.56-3.91)	0.18 (0.01-2.94)	3.69 (2.01-6.78)
Alexiou (2000)	5.36 (1.78-16.11)	0.74 (0.24-2.29)	0.12 (0.01-1.97)	0.74 (0.24-2.29)
Shanmugam (2005)	0.91 (0.06-14.35)	0.15 (0.02-1.07)	0.08 (0.00-1.20)	0.60 (0.23-1.60)
Ruzmetov (2006)	6.38 (2.14-19.08)	0.83 (0.27-2.56)	0.14 (0.01-2.20)	1.38 (0.58-3.30)
Burczynski (2007)	0.91 (0.06-14.35)	0.57 (0.14-2.26)	0.14 (0.01-2.26)	0.28 (0.04-2.01)
Masuda (2008)	2.22 (0.32-15.43)	0.48 (0.12-1.93)	0.24 (0.03-1.71)	0.48 (0.12-1.93)
Alsoufi (2009)	6.11 (3.12-11.95)	1.75 (1.12-2.73)	-	0.74 (0.37-1.47)
Khan (2013)	1.39 (0.09-21.78)	0.60 (0.09-4.26)	-	0.60 (0.09-4.26)
Pooled (random effects)	**7.34 (5.21-10.34)**	**1.23 (0.85-1.79)**	**0.18 (0.08-0.41)**	**1.07 (0.68-1.68)**
Heterogeneity test	*χ^2 14.78 (P = .32)* *I^2 = 18%*	*χ^2 18.79 (P = .13)* *I^2 = 36%*	*χ^2 1.22 (P = 1.00)* *I^2 = 0%*	*χ^2 25.57 (P = .01)* *I^2 = 53%*

Data expressed as percentage (95% CI). "-" = variable not reported. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event. SUUD, Sudden, unexpected, unexplained death; AV, aortic valve; SVD, structural valve deterioration; NSVD, nonstructural valve dysfunction; TE, thromboembolism; VT, valve thrombosis.

	RVOT reoperation %/y	Reoperation for SVD/NSVD %/y	TE/VT %/y	Bleeding %/y	Endocarditis %/y
	-	-	-	-	-
	4.16 (2.54-6.83)	-	-	-	0.28 (0.04-1.96)
	-	-	-	-	-
	-	-	-	-	-
	4.41 (2.84-6.84)	-	-	-	-
	4.30 (3.09-5.97)‡	**-**	**-**	**-**	**0.28 (0.04-1.96)**‡
	χ^2 0.03 (P = .87) *I^2 = 0%*	-	-	-	-

	Reoperation for SVD/NSVD %/y	TE/VT %/y	Bleeding %/y	Endocarditis %/y
	0.78 (0.25-2.41)	1.30 (0.54-3.10)	0.52 (0.13-2.07)	0.78 (0.25-2.41)
	0.43 (0.03-6.79)	0.85 (0.12-6.02)	1.71 (0.43-6.75)	0.43 (0.03-6.79)
	0.49 (0.03-7.83)	0.49 (0.03-7.83)	0.49 (0.03-7.83)	0.49 (0.03-7.83)
	1.15 (0.37-3.54)	0.77 (0.19-3.05)	0.38 (0.05-2.71)	-
	1.52 (0.49-4.66)	1.01 (0.25-4.01)	0.51 (0.07-3.57)	-
	2.58 (1.24-5.37)	1.11 (0.36-3.41)	0.18 (0.01-2.94)	0.74 (0.19-2.94)
	0.49 (0.12-1.97)	0.49 (0.12-1.97)	0.12 (0.01-1.97)	0.12 (0.01-1.97)
	0.45 (0.15-1.40)	0.08 (0.00-1.20)	0.15 (0.02-1.07)	0.30 (0.08-1.20)
	0.83 (0.27-2.56)	0.14 (0.01-2.20)	0.14 (0.01-2.20)	0.55 (0.14-2.20)
	0.14 (0.01-2.26)	0.57 (0.14-2.26)	0.14 (0.01-2.26)	0.57 (0.14-2.26)
	0.24 (0.03-1.71)	0.97 (0.36-2.56)	-	0.24 (0.03-1.71)
	-	0.37 (0.14-0.98)	0.28 (0.09-0.85)	0.09 (0.01-0.65)
	-	1.21 (0.30-4.79)	-	-
	0.86 (0.53-1.42)	**0.76 (0.53-1.09)**	**0.39 (0.22-0.68)**	**0.45 (0.27-0.75)**
	χ^2 14.81 (P = .19) *I^2 = 32%*	*χ^2 9.62 (P = .72)* *I^2 = 0%*	*χ^2 7.97 (P = .72)* *I^2 = 0%*	*χ^2 5.67 (P = .84)* *I^2 = 0%*

Table 5. Pooled outcome estimates after aortic valve replacement with homograft

Study	Early mortality %	Late mortality %/y	SUUD %/y	AV reoperation %/y
Gerosa (1991)	15.53 (9.90-24.37)	1.62 (0.96-2.72)	-	2.77 (1.87-4.12)
Clarke (1993)	12.77 (6.05-26.95)	0.93 (0.13-6.51)	0.46 (0.03-7.35)	6.48 (3.16-13.26)
Khan (2013)	4.05 (1.34-12.28)	1.69 (0.71-4.03)	-	9.12 (6.37-13.07)
Pooled (fixed effects)	**12.82 (8.91-18.46)**	**1.59 (1.03-2.46)**	**0.46 (0.03-7.35)**	**5.44 (4.24-6.98)**
Heterogeneity test	*χ^2 8.37 (P = .04)* *I^2 = 76%*	*χ^2 0.51 (P = .91)* *I^2 = 0%*	-	*χ^2 13.89 (P = .00)* *I^2 = 86%*

Data expressed as percentage (95% CI). "-" = variable not reported. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event. SUUD, Sudden, unexpected, unexplained death; AV, aortic valve; SVD, structural valve deterioration; NSVD, nonstructural valve dysfunction; TE, thromboembolism; VT, valve thrombosis.

DISCUSSION

This is the first study that systematically compiles the available evidence on reported outcome after contemporary AVR in the pediatric population into a comprehensive overview. It highlights the imperfections of currently available aortic valve substitutes in children. It seems that the Ross procedure in children aged more than 1 year is associated with low early and late mortality rates, lower compared with MP-AVR and HG-AVR. However, this study also shows that RVOT reoperations after the Ross procedure are required in approximately 20%of the general pediatric patient population and in more than 40% of neonates and infants in the first postoperative decade. In addition, the results of our study indicate that HG-AVR is associated with a significantly higher rate of aortic valve reoperations compared with both the MP-AVR and the Ross procedure. The initial search resulted in only 6 studies on bioprostheses, all of which had a sample size of less than 20 patients, reflecting the abandonment of their use in pediatric AVR in contemporary practice as a result of their high rates of early degeneration, calcification, and structural failure in young recipients.[8,9,15-17,23,45]

Early mortality

The observed differences in early mortality risk between the different heart valve substitutes are probably mainly driven by patient-related factors, such as patient age, urgency of the procedure, preoperative hemodynamic status, and disease cause.

Differences in patient characteristics, surgical technique, and additional procedures performed at the time of MP-AVR may explain the higher early mortality rate in this patient group. However, our pooled analysis of patient characteristics and surgical details revealed differences that were not consistently in favor of the Ross procedure.

	Reoperation for SVD/NSVD %/y	TE/VT %/y	Bleeding %/y	Endocarditis %/y
	2.43 (1.59-3.70)	0.06 (0.00-0.92)	0.06 (0.00-0.92)	0.23 (0.06-0.92)
	5.55 (2.55-12.08)	0.93 (0.13-6.51)	2.78 (0.91-8.47)	1.85 (0.47-7.30)
	-	-	-	-
	2.93 (2.02-4.25)	**0.37 (0.07-1.82)**	**1.62 (0.57-4.55)**	**0.66 (0.25-1.75)**
	χ^2 0.88 (P = .64) *I^2 = 0%*	*χ^2 2.95 (P = .23)* *I^2 = 66%*	*χ^2 3.14 (P = .21)* *I^2 = 68%*	*χ^2 1.54 (P = .46)* *I^2 = 35%*

Whereas rheumatic valve disease was more frequent in patients undergoing MP-AVR, patients undergoing the Ross procedure more frequently had undergone previous cardiac interventions. The number of concomitant procedures and annular enlargement procedures was comparable between the 2 groups. The 2 included studies that compared the characteristics of patients undergoing the Ross procedure with those of mechanical valve recipients further support the differences we found in pooled baseline patient characteristics.[23,31] Although we did not find conclusive evidence of selection bias, residual hidden selection bias may explain the higher mortality rate associated with MP-AVR. With regard to the Ross procedure, younger age at the time of operation seems to be associated with a less favorable outcome and is most likely representative of very complex (critical) aortic stenosis. This is confirmed by our observations in the studies concerning the Ross procedure in neonates and infants that showed a substantially higher early mortality risk than the older pediatric patients undergoing the Ross. Next to patient-related factors, the era of operation may have influenced early mortality risk, analogous to findings in young adults who undergo valve replacement.[54] The early mortality risks were higher in studies conducted in the early 1990s when compared with more recent studies.[13,49,50,53] Improved early patient outcome in more recent years is most likely the result of improvements in diagnostic workup, surgical timing, intensive care, and anesthesia.

Late mortality

Similar to observations in young adult patient populations,[55] the Ross procedure in children is associated with significantly lower late mortality rates compared with MP-AVR and HG-AVR (0.64%/y vs 1.23%/y vs 1.59%/y, respectively). PPM and suboptimal hemodynamic performance of MPs and HGs may have contributed to the observed excess mortality, particularly in growing children.

In addition, as with early mortality, the higher late mortality rate in MP-AVR may be explained by the fact that children who undergo MP-AVR more often have rheumatic

valve disease and connective tissue disease, which may have given rise to substantial selection bias, although we did not find conclusive evidence thereof.[31]

In contrast to the high early mortality risk of the Ross procedure in neonates and infants, late mortality rates in these patients are low and comparable to late mortality in the older pediatric patients undergoing the Ross procedure.

As observed with early mortality, late mortality rates after MP-AVR seem to be dependent on the era of operation, with improved survival in patients undergoing operation more recently. The only exception to this time-dependent improved survival was the study published by Alsoufi and colleagues.[31] This study describes a population of children with predominantly rheumatic valves in a developing country with suboptimal anticoagulation compliance, which might explain this observation. Late survival after the Ross procedure seems to leave little room for improvement in more recent years.

Reoperations

The rate of reoperations on the aortic valve was comparable for the Ross procedure and MP-AVR, although the indication for aortic valve reoperation differs. Although patients with an MP tend to outgrow the prosthetic valve, patients undergoing the Ross procedure often experience valve insufficiency caused by dilatation of the neoaortic root. Compared with both the Ross procedure and MP-AVR, HG-AVR was associated with a significantly higher aortic valve reoperation rate, due to both PPM in growing children and early degeneration.[56,57]

One of the major disadvantages of the Ross procedure is that single valve disease is treated with double valve replacement, placing both valves at risk of degeneration and reoperation. Failure of the pulmonary valve substitute, although usually less life threatening, does pose an additional risk of reoperation or percutaneous reintervention. When the additional risk of reoperations on the RVOT associated with the Ross procedure is taken into account, the Ross procedure is associated with a higher total reoperation rate compared with MP-AVR in the first postoperative decade, with a further increase in reoperation rates to be expected in the second postoperative decade.[6] This aspect of the Ross procedure needs to be addressed clearly to (parents of) children who are facing AVR. Of note, for neonates and infants undergoing the Ross procedure, aortic valve reoperation rates seem to be lower, whereas RVOT reoperation rates are 2 times higher compared with older children after the Ross procedure. The latter can be explained by the rapid child growth at a younger age. Studies on outcome after reoperative AVR in children and young adults report early and late mortality rates comparable to those we

observed after primary AVR, which suggests that reoperations, although challenging, are safe.[27,58-61]

Valve-related complications

When evaluating valve-related event occurrence after adult AVR with mechanical versus biological valve substitutes, basically the burden of anticoagulation therapy is compared with the burden of reoperation. In children, the growth-dependent increase in PPM needs to be considered. The present study confirms that the Ross procedure is associated with significantly lower TE/VT rates compared with MP-AVR (0.22%/y; 95% confidence interval [CI], 0.11-0.43/y vs 0.76%/y; 95% CI, 0.53-1.09/y, respectively), and there was a trend toward lower bleeding rates (0.10%/y; 95% CI, 0.04-0.27/y vs 0.39%/y; 95% CI, 0.22-0.68/y, respectively). Pooled SVD and NSVD rates after the Ross procedure are substantially higher compared with MP-AVR.

Of note, the only prospective study in this systematic review reported a very high TE/VT event rate of 0.58%/y for patients undergoing the Ross[27] compared with the other retrospective Ross studies. The prospective design of this study is the most likely explanation for this observation because there will have been less recall bias compared with retrospective studies.

As expected, pediatric HG-AVR is associated with higher valve deterioration rates than both the Ross procedure and MP-AVR. This is in line with earlier reports that show accelerated calcification and degeneration of the HG in the aortic position in children.[57]

With regard to pooled endocarditis rates, the Ross procedure and MP-AVR were comparable, whereas HG-AVR was associated with a higher rate of endocarditis. This may be explained by the fact that this finding is based on a single study in which a relatively large proportion of patients (89%) had undergone at least 1 previous cardiac intervention, which is known to be associated with prosthetic valve endocarditis.[62]

Functional health status

The majority of studies that reported NYHA functional class reported a large proportion of patients being in NYHA class I at last follow-up. However, the NYHA classification has not been designed for children, which most likely explains why preoperative NYHA classification was not assessed in most studies. Therefore, it is not possible to determine improvement in functional performance after AVR. To determine the effect of AVR on functional performance, both preoperative and postoperative functional classification should be registered for every patient. Also, questionnaires are needed to provide more insight in quality of life in relation to heart valve prostheses. There is some evidence for

better quality of life after the Ross procedure than after MP-AVR in young adult patients, but more studies are needed.[63]

Source of heterogeneity

Although heterogeneity was considerable in our meta-analysis and may have led to inaccurate results, we pursued a thorough examination of possible sources of heterogeneity. The year of operation, ranging from 1964 to 2013 among the included studies, may have affected the results because evolution of operative techniques seems to have led to lower operative risk. Furthermore, the heterogeneity in RVOT reoperation rates after the Ross procedure may be explained by possible interinstitutional variation in indications for RVOT reoperation. The cause of the higher aortic valve reoperation rate reported by Lupinetti and colleagues[48] in comparison with the other included studies remains to be elucidated.

Our findings of largely unchanged pooled estimates after exploratory exclusion of the identified sources of heterogeneity suggest that the heterogeneity caused by aforementioned studies did not have a substantial impact on the pooled estimates of the outcomes discussed and, thus, did not compromise the validity of these estimates.

Future perspectives

Recent clinical practice guidelines for adult valvular heart disease recommend the Ross procedure to be reserved for patients in whom anticoagulation is contraindicated.[64] Our results show that in particular in younger growing children the Ross procedure may be beneficial in a larger group of patients when performed in centers of expertise. Although the included studies provide limited insight into the impact of patient characteristics on outcome with the different valve options, the Ross procedure seems to be associated with more favorable early and late survival in the first postoperative decade. However, the Ross procedure is also associated with a substantial reoperation rate in the first postoperative decade, and a further increase in reoperation rates is to be expected in the second postoperative decade.[6] Unfortunately, no firm conclusions can be drawn for individual patients because most of the included publications have a mixed study population with regard to patient characteristics and cause of valve disease.

When repair of the aortic valve is not possible or has failed, replacement may be unavoidable. In search of the best AVR procedure in children, heart valve tissue engineering is a promising development.[65-67] Tissue-engineered valve technology is still in its infancy but may be a solution in the future with the prospect of a durable living heart valve that adapts to the growing child. This innovative technology aims at avoiding reoperations

and improving long-term outcome after AVR and hopefully will provide a more durable solution for children requiring AVR.

Study limitations

The present study is a systematic review and meta-analysis of observational studies, all but 1 retrospective in design. As such, the inherent limitations of meta-analyses and combining data from retrospective observational studies should be taken into consideration.[68] Selection bias may have affected the observed outcomes because unpublished data, abstracts, and presentations were not included. Finally, the mean follow-up of the included studies does not allow extensions of the observed outcomes beyond the first postoperative decade.

CONCLUSIONS

Despite improvements in diagnostic workup, surgical timing, and expertise in pediatric aortic valve repair techniques, AVR may be unavoidable. Results of AVR in children remain suboptimal with the currently available valve substitutes. The present study illustrates that both the Ross procedure and MP-AVR, although the most commonly used procedures for AVR in children, are associated with suboptimal outcome, reflecting the urgent need for reliable and durable repair techniques and innovative replacement solutions for this challenging group of patients.

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SUPPLEMENTARY MATERIAL

Supplement 1. Literature search query

PubMed (1161 results)

(((((aortic valve replacement OR ross OR (heart valve prosthesis implantation [MeSH] AND (aorta OR aortic)))) AND (allograft OR autograft OR mechanical OR prosthetic OR homograft OR bioprosthe* OR xenograft OR xenoprosthe* OR porcine OR bovine) AND (("1990/01/01"[PDat] : "3000/12/31"[PDat]) AND Humans[Mesh] AND English [lang] AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH])))))

Embase (1181 results)

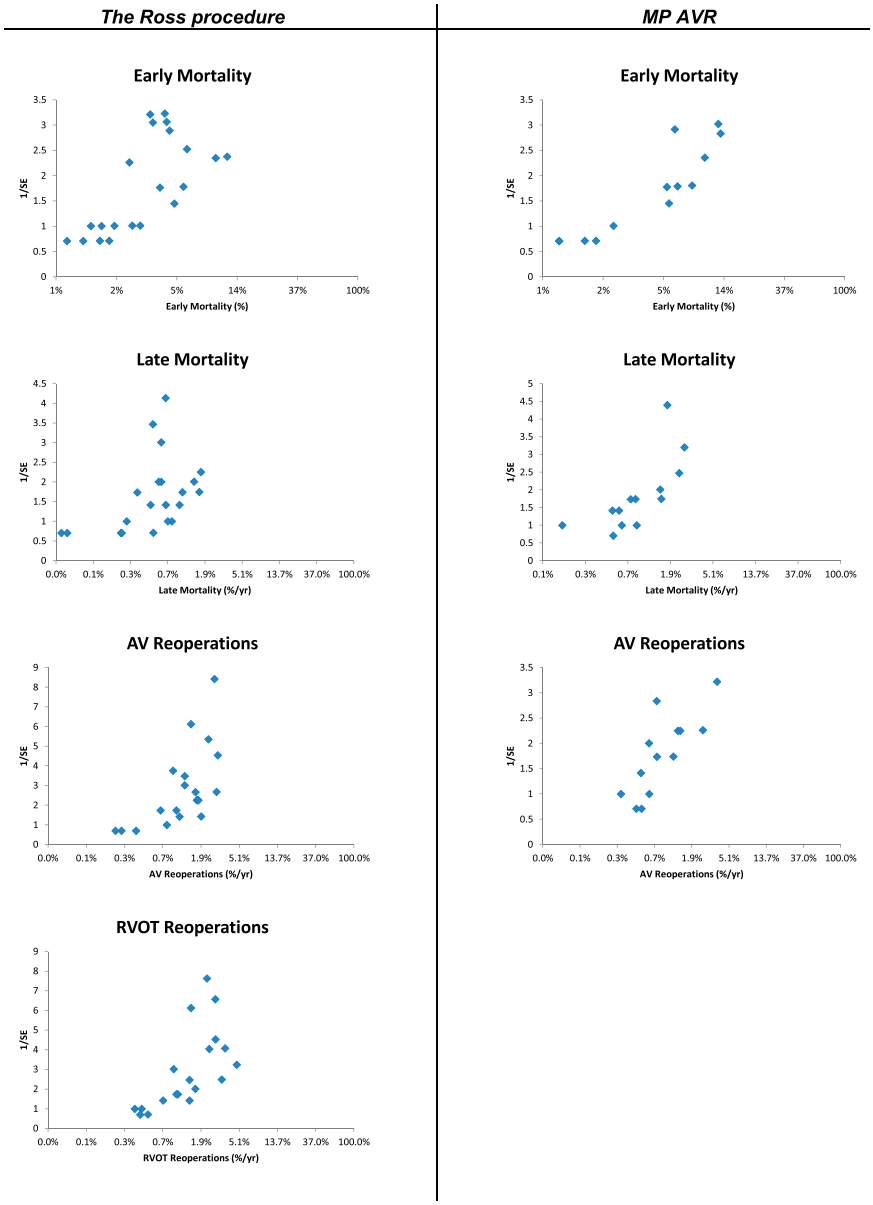
(aortic AND ('valve'/exp OR valve) AND replacement OR ross) AND ('allograft'/exp OR allograft OR 'autograft'/exp OR autograft OR mechanical OR prosthetic OR 'homograft'/exp OR homograft OR bioprosthe* OR xenograft OR xenoprosthe* OR porcine OR bovine) AND [humans]/lim AND [english]/lim AND [1990-2015]/py AND ([newborn]/ lim OR [infant]/lim OR [child]/lim OR [adolescent]/lim)

PubMed as supplied by publisher (122 results)

(((((aortic valve replacement OR ross OR (heart valve prosthesis implantation [MeSH] AND (aorta OR aortic)))) AND (allograft OR autograft OR mechanical OR prosthetic OR homograft OR bioprosthe* OR xenograft OR xenoprosthe* OR porcine OR bovine) AND (("1990/01/ 01"[PDat] : "3000/12/31"[PDat]) AND English[lang])))) AND publisher[sb]

Supplement 2. Funnel plots on a natural log x-axis.

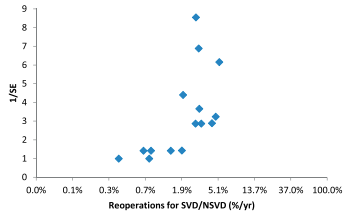
Studies that concerned only neonates and infants were excluded from these funnel plots. Studies on homograft AVR were too few to yield conclusive funnel plots. SE, Standard error; MP, mechanical prosthesis; AV (R), aortic valve (replacement); RVOT, right ventricular outflow tract; SVD, structural valve deterioration; NSVD, nonstructural valve dysfunction; TE, thromboembolism; VT, valve thrombosis.

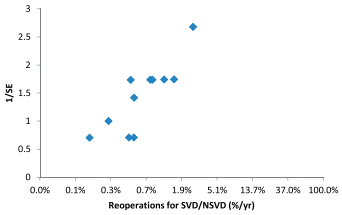


Supplement 2. (continued)

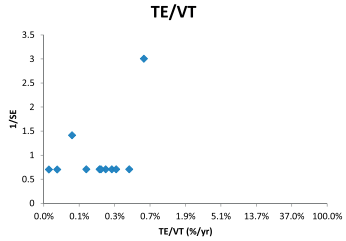
The Ross procedure	*MP AVR*

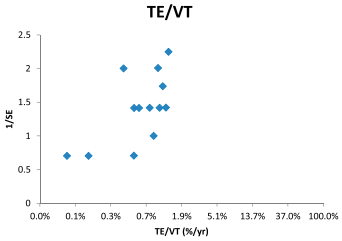
Reoperations for SVD/NSVD





TE/VT





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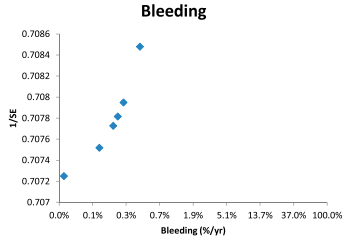
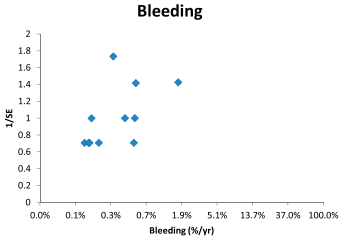
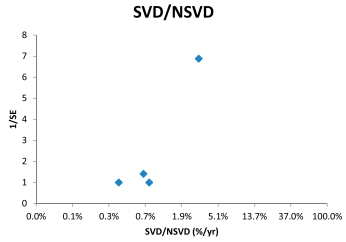
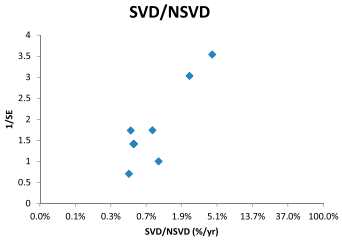


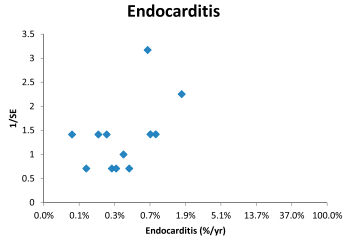


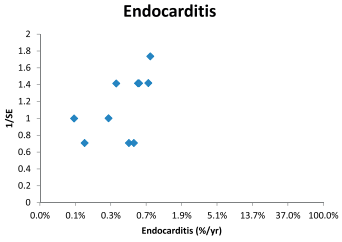
SVD/NSVD

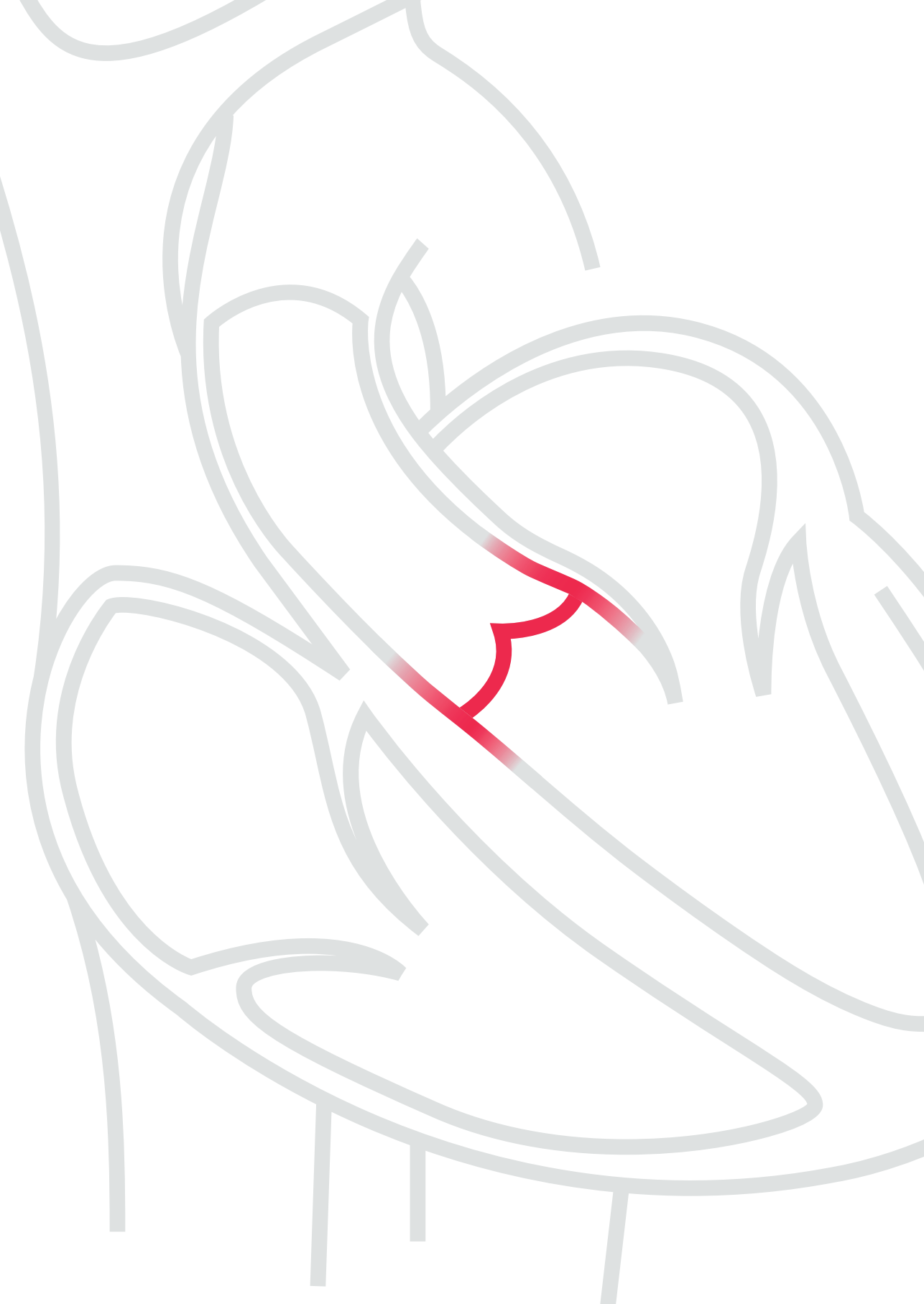




Endocarditis







4

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

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**Shared first authorship*

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ABSTRACT

Background

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

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 January 1995 and 31 December 2015. Through meta-analysis outcomes were pooled and entered into a microsimulation model to calculate (event-free) life expectancy and lifetime event risk.

Results

Twenty-nine publications, encompassing a total of 5728 patients with 32 515 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% confidence interval (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 7 December 2015, a systematic literature search was conducted in Embase, MEDLINE, The Cochrane Collaboration andWeb 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 January 1995 were considered for inclusion. Studies were included if >90% of the cohort received bileaflet prostheses. Studies limited to patients with pre-existing 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 patientyears 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 I^2 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 formales 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 USA 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 US 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 ourmeta-analysis.

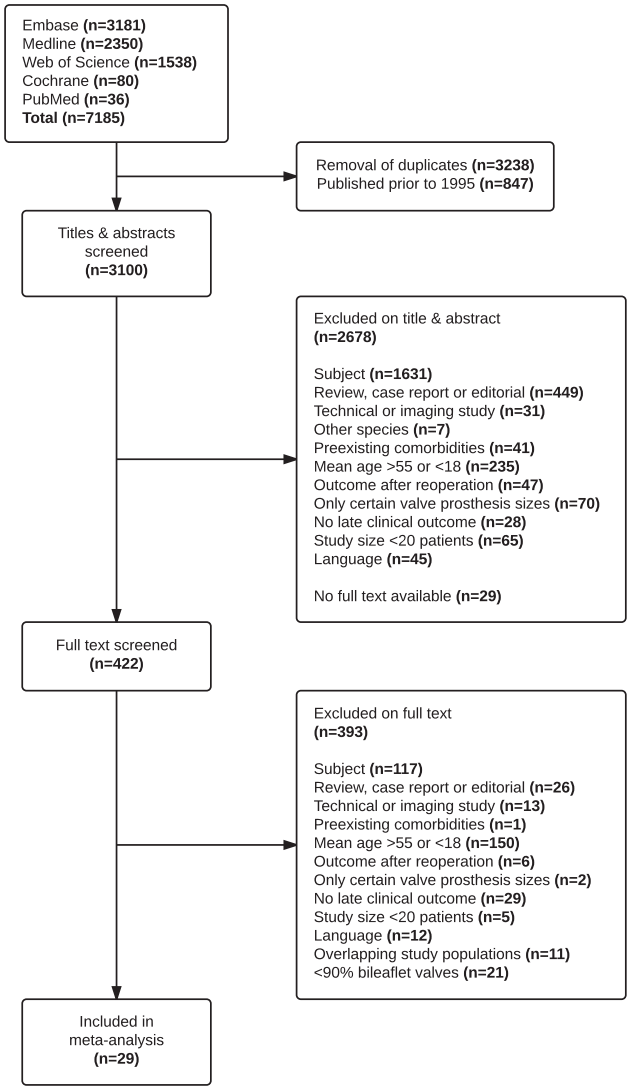

Figure 1. Flowchart of systematic literature search.

RESULTS

The systematic literature search identified 3100 publications, of which 29 were included in the meta-analysis, encompassing a total of 5728 patients with 32 515 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.

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 haemodynamics	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.

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

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[a]	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)[c]	$I^2 = 83\%$ ($P < 0.001$)	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)[d]	$I^2 = 79\%$ ($P < 0.001$)	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)[d]	$I^2 = 67\%$ ($P < 0.001$)	26
SVD (%/year)	0.00[b]	-	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

Pooled estimates presented as 'percentage (95% confidence interval)'.
SUD, sudden unexplained death; SVD, structural valve deterioration; NSVD, nonstructural valve dysfunction.
[a]The reported *P*-values are the *P*-values of Cochran's Q test for heterogeneity.
[b]There were zero events of SVD in the 15 studies that reported this outcome.
[c]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.
[d]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[8]).

calibrated well with the pooled mortality observed in our meta-analysis over the first postoperative decade (see 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 thromboembolism, bleeding and reintervention were 18%, 15%, and 10%, respectively.

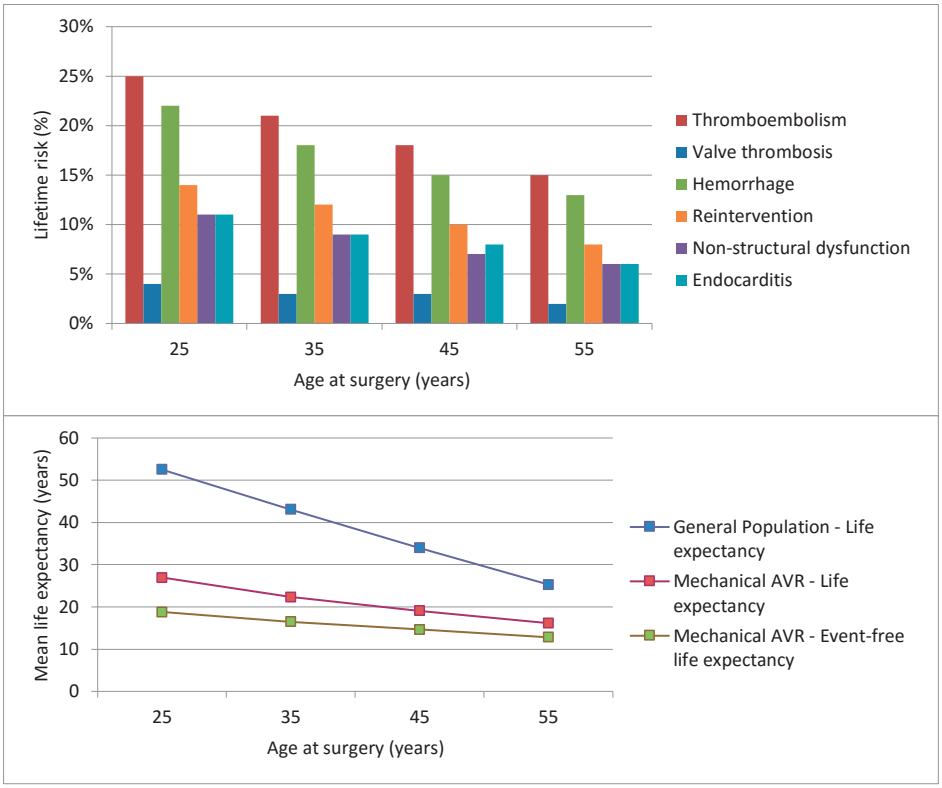

Figure 2. Microsimulation-based age-specific life expectancy and lifetime risk of valve-related morbidity. AVR, aortic valve replacement.

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]).

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-effectsmeta-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 pre-operative 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.[9] 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%).[10] Prosthetic valve-associated hemodynamic factors, such as prosthesis-patient mismatch, may play a role in this observed excess mortality.[11,12] 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 comparable to patients undergoing the Ross procedure.[13]

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.[14-16] 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.[16] 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.[14]

Reintervention, nonstructural valve dysfunction, 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.[17-22] 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 centres 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 decisionmaking process is of great importance.[2,23] Innovative solutions such as patient information portals and decision aids may prove useful in this setting.[24]

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.[25,26] Furthermore, we found aortic regurgitation vs. stenosis to be associated with more favourable reported outcome with regard to bleeding and NSVD rates, while regurgitation has been previously described to be associated with less favourable outcome.[25] This discrepancy may be explained by the strong correlation we found in our meta-regression between aortic valve haemodynamics 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.[27] 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.[28] 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 populationmortality 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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SUPPLEMENTARY MATERIAL

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)
Nistal	1996	209	1989-1992	Retrospective	2.5
Gaudino	1997	20	1988-1996	Retrospective	2.5
Katircioglu	1997	865	1986-1996	Retrospective	3.3
Renzulli	1997	305	1982-1994	Retrospective	3.1
Natsuaki	1998	37	1985-1997	Retrospective	5.3
Jamieson	1999	384	1989-1994	Retrospective	2.5
Chang	2001	256	1988-1997	Retrospective	5.3
Imanaka	2001	126	1990-1996	Retrospective	6.3
Ozeren	2001	70	1998-2000	Retrospective	1.3
Kuwaki	2002	69	1990-2000	Retrospective	6.5
Aagaard	2003	55	1987-2000	Retrospective	7.6[a]
Emery	2003	271	1977-1997	Retrospective	7.2
Chang	2005	179	1988-1999	Retrospective	7.9
Concha	2005	62	1997-2003	Prospective	2.5
Sakamoto	2005	46	1995-2002	Retrospective	6.2
Kandemir	2006	174	1992-2004	Retrospective	6.2
Klieverik	2006	204	1991-2001	Retrospective	6.2
Kilian	2007	147	1990-1998	Retrospective	8.1
Rodrigues	2009	117	1995-2003	Retrospective	4.0
Torella	2010	396	2001-2005	RCT	5.6[a]
Doss	2011	20	-	RCT	1.0
Weber	2012	103	2000-2009	Prospective	2.8
Cohoon	2013	60	1994-2000	Retrospective	6.6
Andreas	2014	173	1991-2008	Retrospective	7.9
McClure	2014	361	1992-2011	Retrospective	6.0[a]
Nazarov	2014	211	2003-2004	Prospective	5.1
Nishida	2014	220	1990-2012	Retrospective	12.0
Bouhout	2015	450	1997-2006	Prospective	9.1
Nishida	2015	157	1981-2014	Retrospective	11.8

[a]Median. -, variable not reported; RCT, randomized controlled trial; NR, not reported.

Mean age (y)	Gender (% male)	Prosthesis model
54.1	74.2	Carbomedics
46.5	85.0	Sorin Bicarbon (n=10)/Carbomedics (n=5)/St. Jude (n=3)
42.9	-	St. Jude
50.4	-	Carbomedics (n=200)/St. Jude (n=82)/Sorin Bicarbon (n=23)
52.0	78.4	St. Jude
52.3	74.2	St. Jude/Carbomedics (n=NR)
43.9	-	St. Jude (n=142)/Carbomedics (n=114)
51.2	59.5	Carbomedics
33.8	-	ATS
48.9	68.1	Carbomedics
33.0[a]	76.4	Carbomedics
40.0	74.2	St. Jude
44.4	-	Carbomedics
37.7	75.8	Carbomedics (n=38)/St. Jude (n=24)
54.0	91.3	St. Jude
47.7	77.6	Carbomedics (n=94)/St. Jude (n=80)
45.0	73.0	St. Jude (n=199)/ATS (n=4)/Björk-Shiley (n=1)
54.8	85.0	Sorin Bicarbon
45.0	69.2	St. Jude
49.7	69.2	Sorin Bicarbon (n=292)/St. Jude (n=92)/Edwards MIRA(n=7)/ Carbomedics (n=5)
48.0	55.0	Edwards MIRA
50.0	84.5	St. Jude/ATS (n=NR)
46.0	83.3	St. Jude
41.0	75.1	Carbomedics/Medtronic Hall/On-X/Edwards/St. Jude (n=NR)
53.2	70.4	St. Jude (n=318)/On-X (n=23)/Carbomedics (n=19)/Unknown (n=1)
52.2	-	Cardiamed
54.9	72.7	Carbomedics
53.0	67.6	Carbomedics (n=402)/St. Jude (n=35)/Medtronic Advantage (n=13)
50.6	49.7	St. Jude

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.

[a]There were zero events of SVD in the 15 studies that reported this outcome.

[b]The reported p-values are the p-values of Cochran's Q test for heterogeneity.

	Thromboembolism (%/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
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

Supplement 4. (continued)

Covariate	β	95%CI-	95%CI+	SE	p-value
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
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)

- Reintervention
- Thromboembolism
- Valve thrombosis
- Bleeding
- Endocarditis
- Structural valve deterioration (SVD)
- 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]

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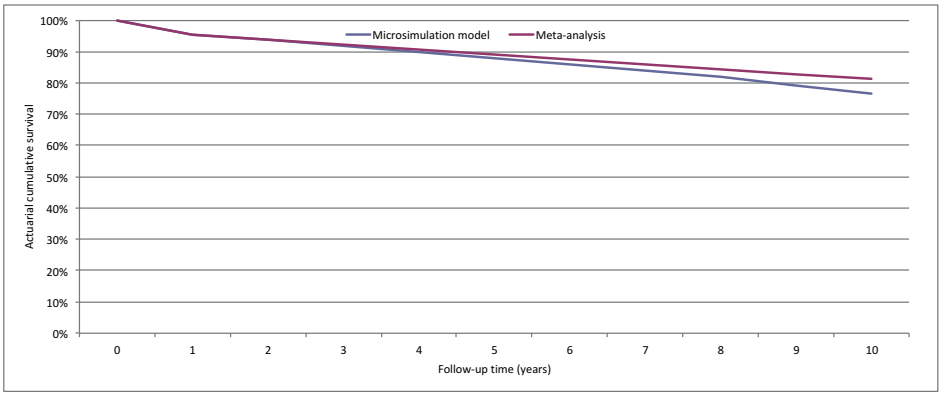
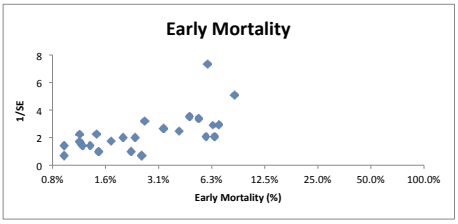
Supplement 7. Microsimulation model calibration plot.

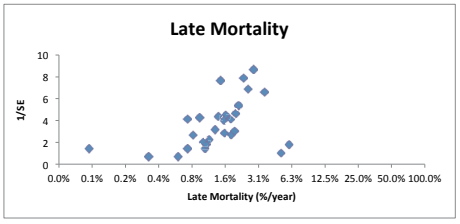
The actuarial survival curve obtained from the microsimulation model run for 10,000 iterations at the pooled mean age (48 years) and male/female ratio (72.0% male) of the included studies compared to the pooled overall mortality observed in our meta-analysis.

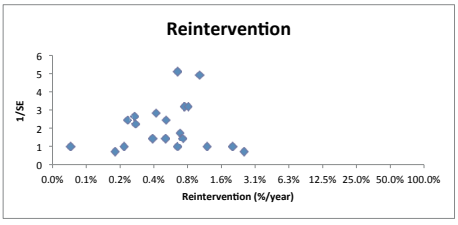


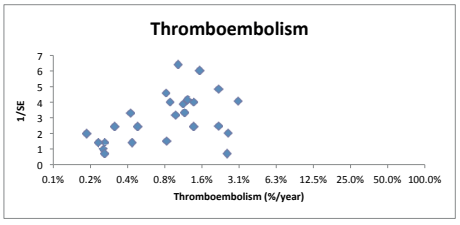
Supplement 8. Funnel plots.

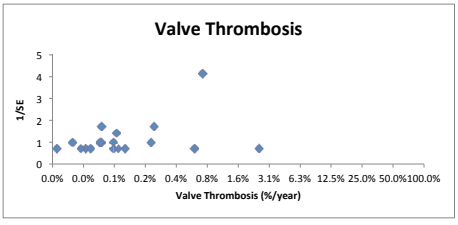
Funnel plots on a natural log x-axis. SE, standard error; SVD, structural valve deterioration; NSVD, nonstructural valve dysfunction.

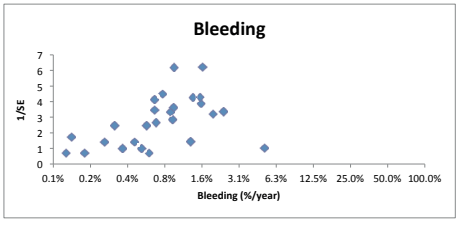


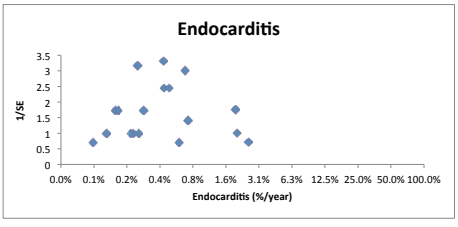


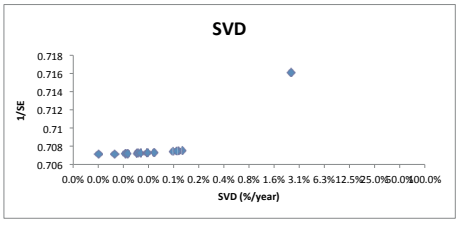


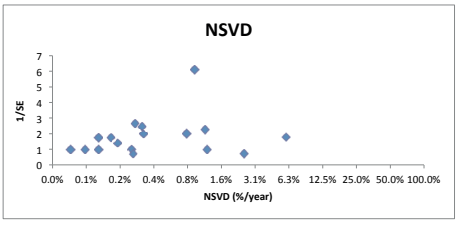


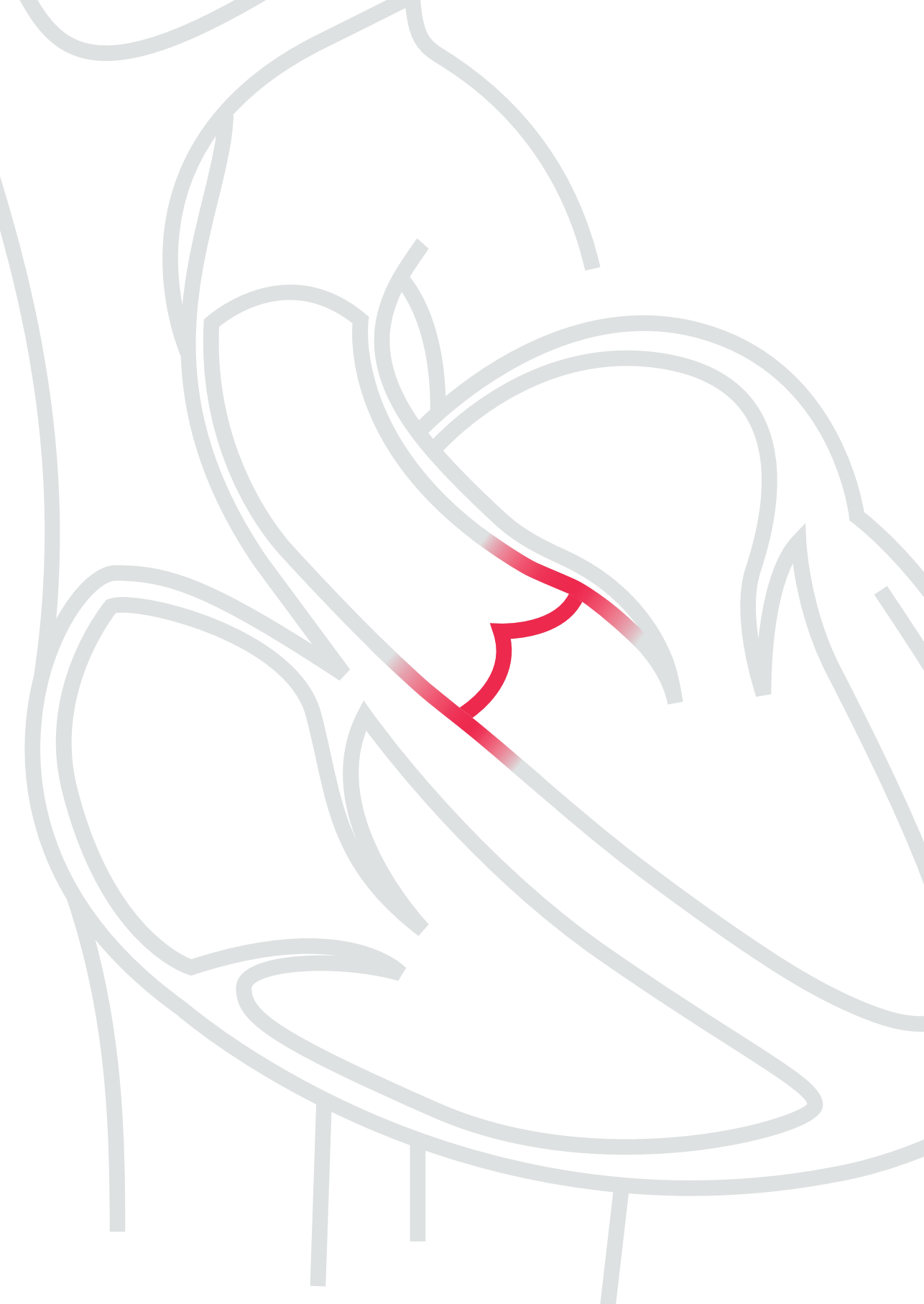












5

The Ross procedure: a systematic review, meta-analysis, and microsimulation

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ABSTRACT

Background

To support decision-making in aortic valve replacement in children and adults, we provide a comprehensive overview of outcomeafter the Ross procedure.

Methods

A systematic search was conducted for publications reporting clinical outcome after the Ross procedure, published between January 1, 2000, and November 22, 2017. Reported event rates and time-to-event data were pooled and entered into a microsimulation model to calculate life expectancy and lifetime event risk.

Results

Ninety-nine publications were included (13 129 patients; total follow-up: 93 408 patient-years, pooled mean follow-up: 7.9±5.3 years). Pooled mean age at surgery was 9.4±5.5 years for children and 41.9±11.4 for adults. For children and adults, respectively, pooled early mortality risk was 4.19% (95% CI, 3.21-5.46) and 2.01% (95% CI, 1.44-2.82), late mortality rate was 0.54%/y (95% CI, 0.42-0.70) and 0.59%/y (95% CI, 0.46-0.76), autograft reintervention 1.28%/y (95% CI, 0.99-1.66) and 0.83%/y (95% CI, 0.68-1.01), and right ventricular outflow tract reintervention 1.97%/y (95% CI, 1.64-2.36) and 0.47%/y (95% CI, 0.37-0.59). Pooled thromboembolism and bleeding rates were low and comparable to the general population. Lifetime risks of autograft and right ventricular outflow tract reintervention were, respectively, 94% and 100% for children and 49% and 19% for a 45-year-old. Estimated life expectancy after surgery was 59 years for children (general population: 64 years) and 30 years for a 45 years old (general population: 31 years).

Conclusions

Through excellent survival and avoidance of the burden of anticoagulation, the Ross procedure provides a unique opportunity for patients whose preferences do not align with the outcome provided by mechanical valve replacement and for growing children who also benefit from autograft diameter increase along with somatic growth. On the downside, almost all pediatric and many adult Ross patients will require a reintervention in their lifetime.

INTRODUCTION

Replacement of the aortic valve with a pulmonary autograft (the Ross procedure) was introduced in the late 1960s by Donald Ross.[1] It provides many benefits over other options for aortic valve replacement (AVR) in children and young adults because of the favorable hemodynamic characteristics, low risk of endocarditis, low thrombogenicity, avoidance of anticoagulation therapy, and the diameter increase it shows along with somatic growth.[2] However, the Ross procedure is a technically demanding operation, and both the autograft in aortic position and the valve substitute in the right ventricular outflow tract (RVOT) are susceptible to valve deterioration and subsequent reintervention over time.

Reports on outcome after the Ross procedure are scattered, and although survival after this procedure is reported almost uniformly as excellent, rates of valve-related morbidity, especially autograft and allograft deterioration and reintervention, vary strongly among reports. This makes it difficult to draw inferences on what patients can be expected to face after the Ross procedure, information essential in guiding decision-making in children and young adults requiring AVR.

Since the publication of a prior systematic review on reported outcome after the Ross procedure by our group in 2009,[2] a wealth of additional patient series has been published, substantially longer follow-up has been accrued of the included patients, and our group has implemented advanced methods of meta-analysis of time-to-event data and microsimulation that allow for a much better insight into long-term outcome in these patients. We therefore provide an update of the systematic literature search, applying the latest methods of meta-analysis and calculating microsimulationbased estimates of age-specific life expectancy and lifetime risk of valve-related events.

METHODS

Search strategy and selection of studies

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[3] and registered in the PROSPERO registry (CRD42016039676). The data, analytic methods, and study materials will be made available on request to the corresponding author.

On November 22, 2017, Embase, MEDLINE, Web of Science, The Cochrane Library, and Google Scholar were searched by a biomedical information specialist using keywords related to the Ross procedure/pulmonary autograft (Supplement 1).

All studies were screened by 2 independent reviewers (J.R.G. Etnel, S.A. Huygens). Observational studies and randomized controlled trials reporting clinical outcome after the Ross procedure published in English after January 1, 2000, were considered for inclusion. Studies limited to patients with preexisting comorbidities or a history of previous AVR were excluded. Studies with a study size <20 patients or focusing only on certain aortic/pulmonary valve/annulus/root sizes were also excluded. In case of multiple publications on overlapping study populations, the publication with the greatest total follow-up in patient-years or overall completeness of data was included for each outcome of interest separately. In case of disagreement between the reviewers, a consensus was negotiated.

Data extraction

Microsoft Office Excel 2010 (Microsoft Corp, Redmond, WA) was used for data extraction. Data were extracted independently by 2 reviewers (J.R.G. Etnel, P. Grashuis). After data extraction, each reviewer verified the other reviewer's data entries. Recorded study characteristics, baseline patient characteristics, operative characteristics and outcome events are listed in Supplement 1. Functional class was defined according to the New York Heart Association for adults and Ross[4] for children.

Morbidity and mortality were documented according to the 2008 guidelines by Akins et al.[5] 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 total follow-up duration in patient-years was not reported, it was calculated by multiplying the number of patients with the mean follow-up duration of that study.

Statistical analyses

Statistical software used is listed in Supplement 1.

Continuous variables are presented as mean±SD. Categorical variables are presented as counts and percentages. Linearized event occurrence rates (constant hazard rates over time) are presented as percentages per year.

For all analyses, studies were grouped by age: pediatric (reported as concerning only children and mean age <18 years), adult (reported as concerning only adults and mean age ≥18 years), and all ages (combined pediatric and adult series). Pooled baseline pa-

tient characteristics were calculated with the use of sample size weighting. Early risks of mortality and linearized occurrence rates of late morbidity and mortality were calculated for each individual study and pooled with the use of inverse variance weighting in a random-effects model according to the DerSimonian and Laird method. Outcomes were pooled 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, it was assumed that 0.5 patient experienced that event for the purpose of inverse variance weighting (continuity correction). Cochran's Q statistic and the I2 statistic were used to assess heterogeneity between studies. Potential causes of heterogeneity were explored by investigating the effect of all baseline patient characteristics and operative details listed in Table 1 as well as study design (retrospective versus prospective/ randomized controlled trial) and median year of surgery by means of univariable random-effects meta-regression. The influence of potential publication bias on pooled outcome was investigated by conducting sensitivity analyses by temporarily excluding the smallest quartile (by sample size) of included studies in the all ages group.

Kaplan-Meier meta-analysis

Pooled Kaplan-Meier time-to-event meta-analysis was conducted by extrapolating and pooling estimates of individual patient time-to-event data from published Kaplan-Meier curves for survival and reintervention. Published Kaplan-Meier curves were digitized, and an estimate of the individual patient time-to-event data was then extrapolated from the digitized curve coordinates, assuming a constant rate of censorship between each time point at which the number of patients at risk was specified.[6] If there were no Kaplan-Meier curves available, but time points of each event were reported or there were no events, the individual patient time-to-event data were manually reconstructed up to a maximum follow-up of the mean follow-up +2 SDs, under the same assumption of a constant rate of censorship. Reconstructed individual patient time-to-event data of each study were then combined.

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.[7,8] A description of the concept of the microsimulation model and a schematic overview of the hypothetical scenario that each simulated patient is run through are provided in Supplement 1.

Table 1. Pooled baseline patient characteristics and operative details

	All Ages		Pediatric	
	Pooled Estimate	**No. of Studies**	**Pooled Estimate**	**No. of Studies**
Total number of patients	13 129	91*	2743	36
Follow-up		85		34
Mean, y	7.9±5.3		7.4±4.5	
Total, patient-years	93 408		18 557	
Mean age, y	30.9±11.5	81	9.4±5.5	30
Male	72.6% (51.0-87.1)	71	70.6% (60.8-91.7)	25
Urgent	4.6% (0.0-50.0)	11	2.3% (0.0-2.6)	2
Preoperative NYHA/Ross class		25		3
I/II	62.9% (25.5-100.0)		91.2% (85.7-100.0)	
III/IV	37.1% (0.0-74.5)		8.8% (0.0-14.3)	
Hemodynamics		72		25
Aortic stenosis	36.5% (11.1-78.3)		29.5% (12.1-76.0)	
Aortic regurgitation	32.7% (9.0-61.5)		25.9% (7.9-48.0)	
Combined	30.8% (0.0-75.8)		44.6% (14.3-75.8)	
Bicuspid AV	63.6% (17.5-94.4)	50	61.7% (40.0-80.0)	15
Cause		45		14
Congenital	57.3% (0.7-100.0)		80.5% (49.8-100.0)	
Degenerative/calcification	7.4% (0.0-44.4)		1.6% (0.0-7.1)	
Rheumatic	14.2% (0.0-52.9)		12.3% (1.0-45.8)	
Endocarditis	13.3% (0.0-100.0)		3.9% (0.0-10.0)	
Other/unknown	7.8% (0.0-51.2)		1.8% (0.0-6.7)	
Previous cardiac intervention	35.5% (7.8-100.0)	41	67.4% (38.0-100.0)	18
AV intervention	31.4% (0.0-100.0)		60.6% (41.8-80.0)	
Percutaneous	15.5% (0.0-72.0)		33.1% (9.1-72.0)	
AV surgery	19.0% (0.0-66.7)		32.3% (0.0-60.0)	
AVR	3.9% (0.0-13.3)		2.3% (0.0-12.2)	
Technique		67		26
Total root replacement	93.9% (46.3-100.0)		97.4% (65.9-100.0)	
Subcoronary	2.1% (0.0-21.6)		1.6% (0.0-12.3)	
Inclusion cylinder	3.9% (0.0-42.8)		1.0% (0.0-6.0)	
RVOT conduit		57		20
Allograft	89.1% (0.0-100.0)		86.1% (0.0-100.0)	
Bioprosthesis	10.9% (0.0-78.9)		13.9% (0.0-100.0)	
Concomitant procedures		40		20
CABG	4.7% (0.0-44.1)		6.5% (0.0-44.1)	
Ascending aortic surgery	10.7% (0.0-60.0)		5.1% (0.0-24.3)	
Annular enlargement procedure	9.6% (0.0-52.9)		18.3% (0.0-42.0)	
Other valve repair or replacement	5.4% (0.0-40.0)		8.4% (1.7-40.0)	
Other	8.2% (0.0-38.1)		12.0% (2.6-25.2)	

	Adult	
	Pooled Estimate	No. of Studies
	6892	35
		31
	8.4±4.7	
	49 435	
	41.9±11.4	30
	73.0% (51.0-87.1)	26
	4.0% (1.1-50.0)	7
		17
	61.8% (30.0-100.0)	
	38.2% (0.0-70.0)	
		28
	40.9% (11.1-72.6)	
	33.1% (9.0-61.5)	
	26.0% (0.0-55.1)	
	62.9% (34.1-93.5)	21
		18
	52.2% (37.9-84.1)	
	8.4% (1.4-44.4)	
	14.4% (1.9-29.7)	
	19.4% (3.9-100.0)	
	5.5% (4.6-18.1)	
	12.8% (7.8-72.2)	11
	11.2% (3.1-100.0)	
	3.3% (0.3-38.9)	
	8.8% (0.0-66.7)	
	4.3% (0.0-12.8)	
		27
	95.3% (50.0-100.0)	
	0.8% (0.0-19.0)	
	3.8% (0.0-42.8)	
		21
	86.0% (0.0-100.0)	
	14.0% (0.0-75.7)	
		18
	5.1% (0.0-25.9)	
	15.8% (0.0-60.0)	
	1.5% (0.0-7.4)	
	4.8% (0.0-23.3)	
	7.3% (0.0-38.1)	

Data presented as mean±SD or percentage (range). AV indicates aortic valve; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; Preop., preoperative; and RVOT, right ventricular outflow tract.

*Twenty-seven pediatric+31 adult+33 unique studies.

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. Separate estimates were obtained for children and adults from the respective subgroup analyses of our meta-analysis. The hazard of structural valve deterioration of the autograft and RVOT conduit were assumed to be time-varying and were modeled by fitting a Gompertz distribution to our pooled time-to-event data. The hazards of all other events were assumed to be constant over time. Additional excess mortality not directly resulting from valve-related events was estimated for the all ages, pediatric and adult subgroups separately using the least squares method (details in Supplement 1). The background mortality of the general population was obtained for the pooled median year of surgery among included studies (2001, assuming a constant incidence rate over time in each study) and for the regions that the majority of the included study population originated from (Europe, 52% of patients; North America, 34% of patients) from the World Health Organization Global Health Observatory Data Repository for Europe and from the US Life Tables for North America.[9,10]

To obtain estimates of life expectancy and lifetime risk of valve-related morbidity, taking into account both first-order uncertainty (random variability in outcomes between identical patients) and second-order uncertainty (uncertainty in the input parameter estimates), probabilistic sensitivity analysis was conducted. The microsimulation model was run iteratively for 500 simulations with a sample size of 1000 patients per simulation (these amounts were based on the methods described by O'Hagan et al[11]). In each of the 500 simulations, the values of the input parameters were randomly drawn from distributions corresponding with each parameter's point estimate and variance, obtained from the meta-analysis as described above. This yielded a complete set of outcome estimates for each of the 500 simulated patient populations. For each outcome measure, the mean of outcome estimates across all 500 simulated populations was considered the point estimate of outcome, and the 2.5th and 97.5th percentile were considered the lower and upper limits of the 95% credible interval, respectively.

To obtain age-specific estimates, this process was repeated separately for the pediatric group at the pooled mean age and SD of that subgroup (9.4±5.5 years) and also for the adults for the specific ages 25, 35, 45, and 55 years and at the male/female ratio obtained from our meta-analysis (pediatric 70.6% male, adult 73.0% male).

For the purposes of internal validation, the model was additionally run for 10 000 iterations at the pooled mean age (30.9±11.5 years) and pooled male/female ratio (72.6% male) of the all ages group, excluding early mortality. The actuarial survival curve

obtained from this model was then plotted against the pooled overall survival curve observed in our Kaplan-Meier meta-analysis, excluding early mortality.

RESULTS

The systematic literature search identified 4252 publications, of which 99 were included in the meta-analysis, encompassing a total of 13 129 patients with 93 408 patient-years of follow-up (pooled mean follow-up: 7.9±5.3 years) (Figure 1). Supplement 2 represents the characteristics of the included studies (references listed in Supplement 7).

Pooled baseline patient characteristics are shown in Table 1.

Pooled risks of early mortality 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). Early morbidity was reported too inconsistently to be included in the analyses. Pooled Kaplan-Meier curves of freedom from all-cause mortality, autograft reintervention, and RVOT reintervention are shown in Figures 2 through 4, respectively.

Microsimulation-based age-specific estimates of lifetime risk of valve-related morbidity and life expectancy are shown in Figures 5 and 6, respectively. The microsimulation model calibrated well with the pooled mortality observed in our meta-analysis (Supplement 4). Least squares regression of survival estimates from the microsimulation model (excluding early mortality) versus those obtained from the meta-analysis of time-to-event data (excluding early mortality) revealed that excess mortality, not directly related to valve-related events, was zero in the pediatric, adult, and all ages groups alike (Supplement 5). For children, life expectancy after surgery (58.9 years; 95% credible interval [CI], 56.9-60.9) was 92.1% of that in the age- and sex-matched general population (64.0 years), for a 25-year-old 94.1% (46.3 years [95% CI, 44.6-48.0] versus 49.1 years), 35-yearold 94.8% (37.8 years [95% CI, 36.4-39.4] versus 39.9 years), 45-year-old 95.4% (29.7 years [95% CI, 28.4- 31.1] versus 31.1 years), and 55-year-old 96.1% (22.1 years [95% CI, 21.0-23.3] versus 23.0 years)

Sensitivity analyses showed that any eventual publication bias did not substantially influence our pooled outcomes, as pooled outcomes remained largely unchanged after temporary exclusion of the smallest quartile of studies by sample size (all ages group, before versus after exclusion: late mortality [0.50%/y versus 0.48%/y], autograft reintervention [1.10%/y versus 1.09%/y], RVOT reintervention [0.91%/y versus 0.89%/y], thromboembolism [0.16%/y versus 0.15%/y], and bleeding [0.09%/y versus 0.07%/y]).

Heterogeneity

There was substantial heterogeneity in early mortality, late mortality, reintervention, endocarditis, and bleeding.

Univariable random-effects meta-regression (Supplement 6) in the all ages group showed that studies with higher early mortality reported shorter mean follow-up (P<0.001), lower mean age at surgery (P=0.003), higher preoperative NYHA/ Ross class (P=0.031), more preoperative endocarditis (P=0.003), less frequent use of allografts for

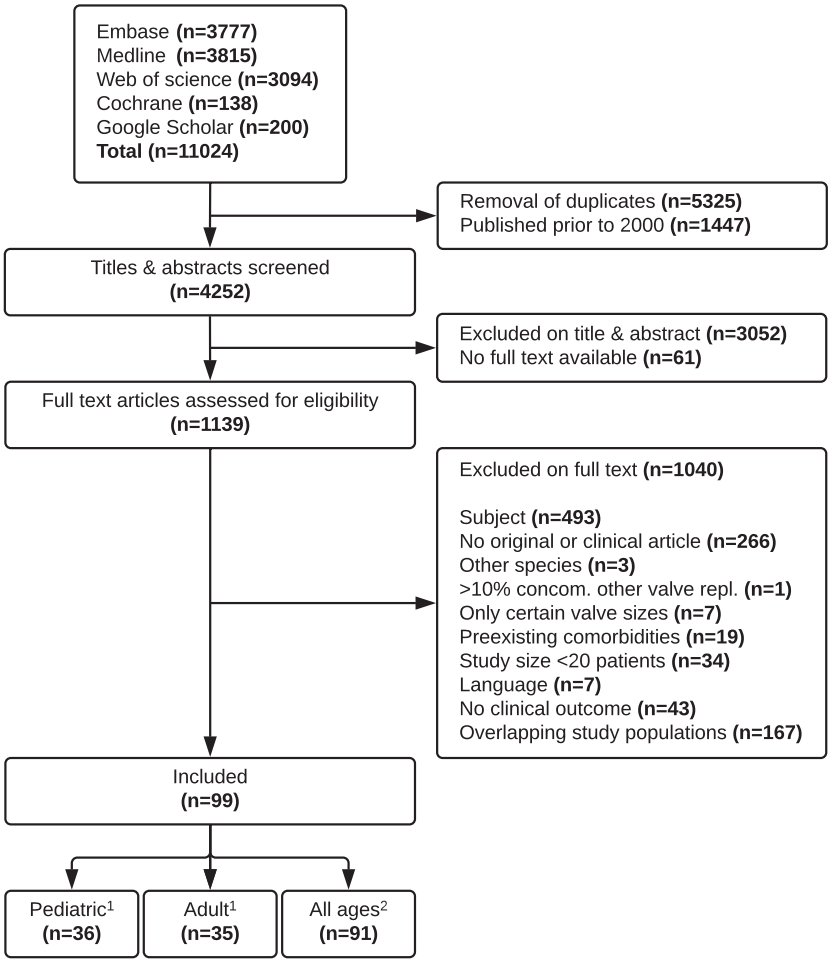

Figure 1. Flowchart of study selection.
The sum of the number of studies in the subgroups of included studies is greater than the total of 99 included studies, because of inclusion in multiple subgroups when possible. [1]Including 3 studies with both pediatric and adult subgroups. [2]26 pediatric + 31 adult + 3 both pediatric and adult subgroups + 31 no distinction.

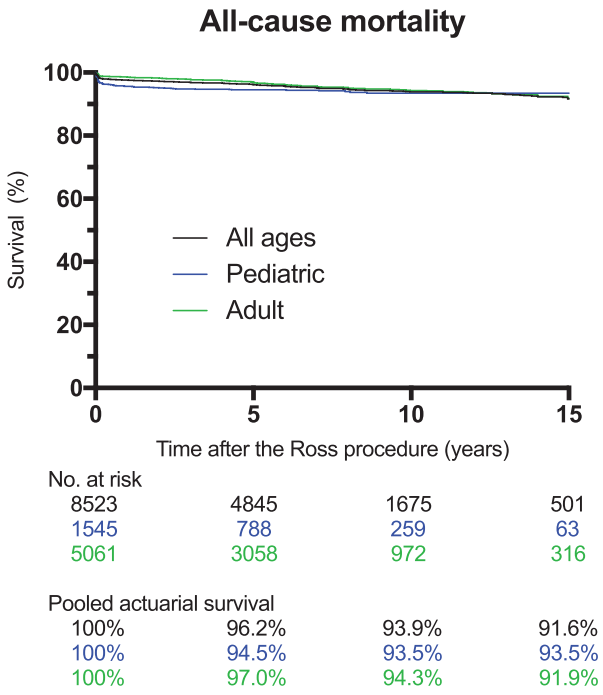

Figure 2. Pooled Kaplan-Meier freedom from all-cause mortality.

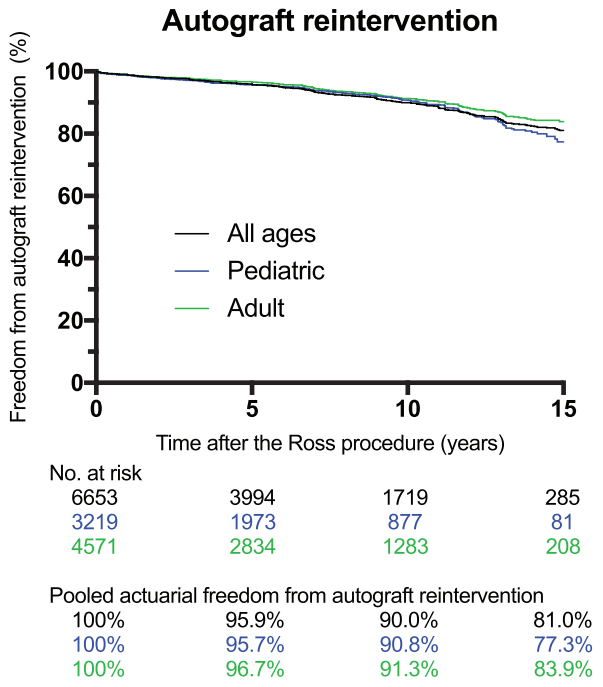

Figure 3. Pooled Kaplan-Meier freedom from autograft reintervention.

RVOT reconstruction (*P*=0.005), more concomitant valve procedures, (*P*=0.031), and less concomitant ascending aortic surgery (*P*<0.001).

Higher late mortality was associated with shorter mean follow-up (*P*=0.012), higher mean age at surgery (*P*=0.039), more urgent operations (*P*<0.001), and more preoperative endocarditis (*P*<0.001).

Higher reintervention rates were associated with lower mean age at surgery (*P*<0.001), more preoperative combined aortic stenosis and regurgitation (*P*=0.011), more previous cardiac interventions (*P*=0.014), in particular previous aortic valve interventions (*P*<0.001), and more frequent concomitant annular enlargement procedures (*P*<0.001).

Higher postoperative endocarditis rates were associated with shorter mean follow-up (*P*<0.001), less bicuspid aortic valve (*P*=0.004), and more frequent use of total root replacement (*P*=0.007) and more frequent use of bioprostheses for RVOT reconstruction (*P*=002).

Higher postoperative bleeding rates were associated with shorter mean follow-up (*P*=0.001), higher proportions of preoperative endocarditis (*P*<0.001), and more concomitant valve procedures (*P*<0.001).

Table 2. Pooled outcome estimates

	Pooled Estimate (95% CI)		
	All Ages	**Pediatric**	**Adult**
Early mortality (%)	2.87 (2.39-3.45)	4.19 (3.21-5.46)	2.01 (1.44-2.82)
Late mortality (%/y)	0.50 (0.44-0.58)	0.54 (0.42-0.70)	0.59 (0.46-0.76)
Cardiac (%/y)	0.29 (0.24-0.35)	0.41 (0.27-0.63)	0.24 (0.17-0.33)
Valve-related (%/y)	0.23 (0.19-0.28)	0.36 (0.22-0.57)	0.21 (0.14-0.32)
SUD (%/y)	0.17 (0.13-0.21)	0.20 (0.11-0.39)	0.16 (0.10-0.25)
Reintervention (%/y)	1.84 (1.49-2.27)	3.04 (2.39-3.87)	1.20 (1.01-1.42)
Autograft (%/y)	1.10 (0.94-1.29)	1.28 (0.99-1.66)	0.83 (0.68-1.01)
RVOT (%/y)	0.91 (0.74-1.12)	1.97 (1.64-2.36)	0.47 (0.37-0.59)
Endocarditis (%/y)	0.29 (0.21-0.41)	0.27 (0.15-0.48)	0.27 (0.16-0.45)
Autograft (%/y)	0.21 (0.13-0.35)	0.15 (0.04-0.61)	0.18 (0.09-0.39)
RVOT (%/y)	0.17 (0.13-0.22)	0.21 (0.06-0.71)	0.14 (0.09-0.21)
Thromboembolism (%/y)	0.16 (0.12-0.22)	0.11 (0.04-0.30)	0.17 (0.11-0.27)
Valve thrombosis (%/y)	0.06 (0.03-0.12)	0.14 (0.03-0.71)	0.03 (0.01-0.09)
Bleeding (%/y)	0.09 (0.02-0.36)	0.10 (0.03-0.41)	0.10 (0.01-0.67)
Pacemaker implantation (%/y)	0.30 (0.20-0.44)	0.33 (0.21-0.51)	0.25 (0.05-1.17)

Data presented as percentage (95% confidence interval) or linearized occurrence rate (95% confidence interval).
RVOT indicates right ventricular outflow tract; and SUD, sudden unexplained death.

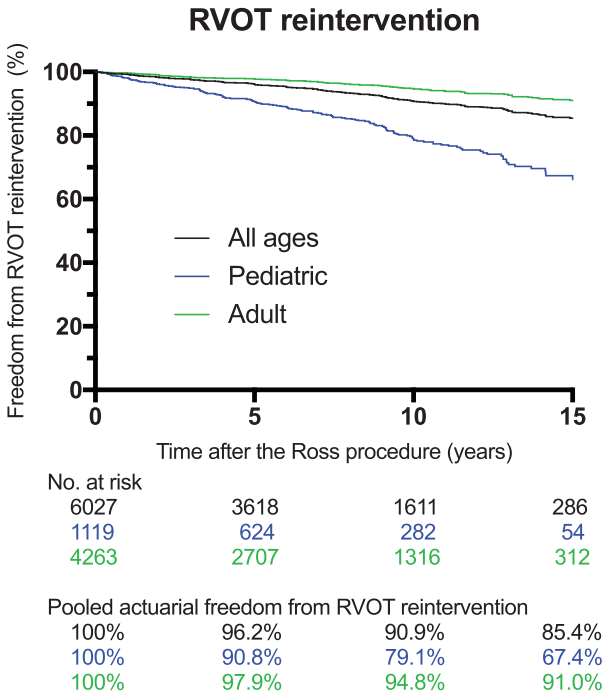

Figure 4. Pooled Kaplan-Meier freedom from right ventricular outflow tract (RVOT) reintervention.

No. of Studies			Heterogeneity		
All Ages	Pediatric	Adult	All Ages	Pediatric	Adult
78	24	31	I^2=50.9% (*P*<0.001)	I^2=27.9% (*P*=0.102)	I^2=53.6% (*P*<0.001)
72	22	26	I^2=30.5% (*P*=0.009)	I^2=7.3% (*P*=0.363)	I^2=57.3% (*P*<0.001)
57	15	22	I^2=6.6% (*P*=0.335)	I^2=14.0% (*P*=0.296)	I^2=17.5% (*P*=0.227)
56	14	23	I^2=0.0% (*P*=0.821)	I^2=0.0% (*P*=0.736)	I^2=26.8% (*P*=0.117)
56	14	23	I^2=0.0% (*P*=0.926)	I^2=0.0% (*P*=0.951)	I^2=20.7% (*P*=0.185)
60	23	24	I^2=92.7% (*P*<0.001)	I^2=85.5% (*P*<0.001)	I^2=57.0% (*P*<0.001)
68	26	24	I^2=76.3% (*P*<0.001)	I^2=66.1% (*P*<0.001)	I^2=52.2% (*P*=0.002)
67	26	24	I^2=84.3% (*P*<0.001)	I^2=52.1% (*P*=0.001)	I^2=45.5% (*P*=0.009)
31	6	15	I^2=61.2% (*P*<0.001)	I^2=0.0% (*P*=0.770)	I^2=71.8% (*P*<0.001)
25	3	12	I^2=64.3% (*P*<0.001)	I^2=0.0% (*P*=0.877)	I^2=74.0% (*P*<0.001)
24	3	11	I^2=0.0% (*P*=0.977)	I^2=0.0% (*P*=0.727)	I^2=0.0% (*P*=0.867)
21	5	7	I^2=0.0% (*P*=0.793)	I^2=0.0% (*P*=0.935)	I^2=0.0% (*P*=0.565)
12	3	7	I^2=0.0% (*P*=0.840)	I^2=0.0% (*P*=0.957)	I^2=0.0% (*P*=0.958)
15	4	9	I^2=87.4% (*P*<0.001)	I^2=0.0% (*P*=0.609)	I^2=91.6% (*P*<0.001)
12	9	4	I^2=0.0% (*P*=0.712)	I^2=0.0% (*P*=0.607)	I^2=44.5% (*P*=0.144)

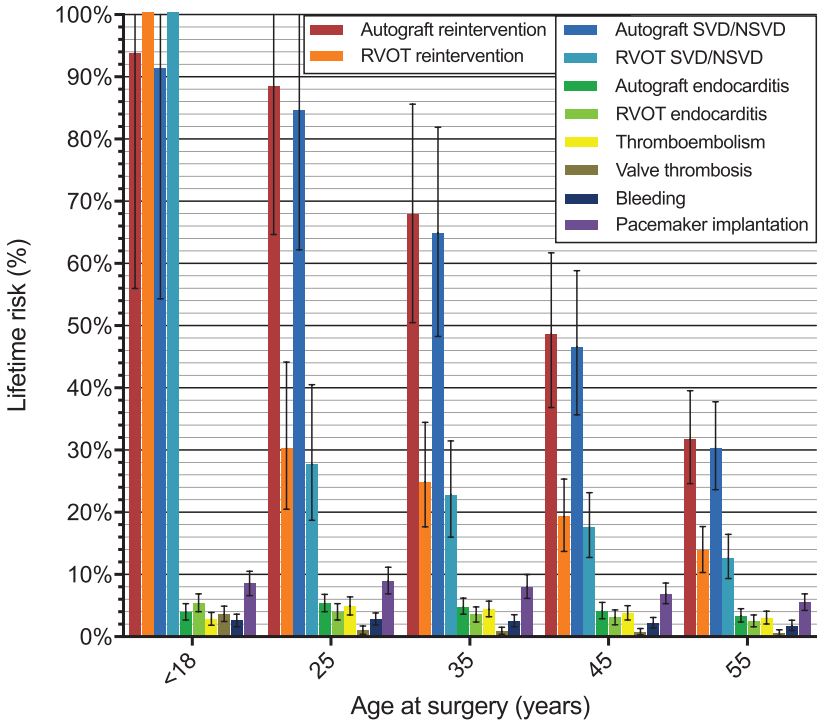

Figure 5. Microsimulation-based age-specific lifetime risks of valve-related morbidity after the Ross procedure.

Error bars represent 95% credible intervals. If no error bars are displayed, the entire credible interval lies above 100%, because of a high probability of that particular event occurring multiple times sequentially in the same patient. The hazard of structural valve deterioration of the autograft and right ventricular outflow tract (RVOT) conduit were assumed to be time-varying and were modeled by fitting a Gompertz distribution to our pooled time-to-event data. The hazards of all other events were assumed to be constant over time. NSVD indicates nonstructural valve dysfunction; and SVD, structural valve deterioration.

DISCUSSION

This study shows that the Ross procedure, when applied in a broad population of children and young adults, is associated with low early and late mortality, with a life expectancy after surgery of ≈90% to 95% of the life expectancy in the age- and sex-matched general population, depending on patient age at surgery. Thromboembolism, bleeding, and endocarditis rates are low. However, it also underlines the most important drawback of the Ross procedure: substantial late structural valve deterioration of both the autograft and the RVOT conduit, and subsequently high age-dependent reintervention rates, with lifetime risk of autograft reintervention ranging from 94% for children to 32% for 55-year-olds and for the RVOT conduit ranging from 100% for children to 14% for 55-year-olds. RVOT conduit deterioration and subsequent reintervention rates

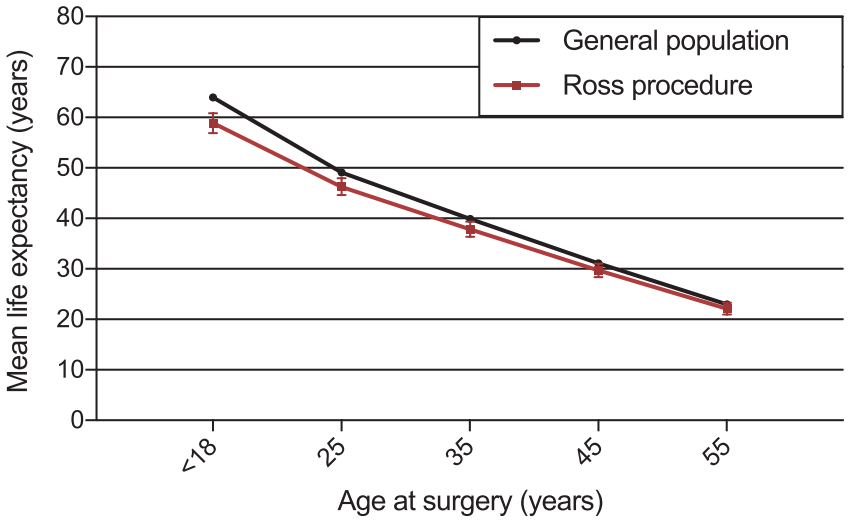

Figure 6. Microsimulation-based age-specific mean life expectancy after the Ross procedure compared with the age- and sex-matched general population.
Error bars represent 95% credible intervals. The hazard of structural valve de-terioration of the autograft and right ventricular outflow tract (RVOT) conduit were assumed to be time-varying and were modeled by fitting a Gompertz distribution to our pooled time-to-event data. The hazards of all other events were assumed to be constant over time.

are significantly higher among children undergoing the Ross procedure compared with adults and represent the predominant indication for reintervention in these children.

Mortality

Our results show that the Ross procedure is associated with low early mortality and excellent late survival with 15-year actuarial survival of 93.5% for children and 91.9% for adults and life expectancy 90% to 95% of the age- and sex-matched general population. Excess mortality not directly related to valve-related events is very low if not zero in these patients.

This mortality is substantially lower than the mortality reported after mechanical AVR, in children and adults alike, despite the considerably higher reintervention rates after the Ross procedure.[12,13] The favorable hemodynamics of the autograft in comparison with mechanical prostheses may play a role in this observed difference in mortality.[14] Furthermore, the higher mortality after mechanical AVR may be attributable in part to the thrombogenicity of mechanical valve prostheses and the subsequent requirement for anticoagulation treatment and the associated bleeding risks.[15] The often unstable International Normalized Ratio (INR) management may play a major role in this anticoagulation-related excess mortality risk after mechanical AVR, as a propensity-matched study

by Mokhles et al[16] has previously demonstrated that, with optimal self-management anticoagulation, mechanical AVR offers excellent late survival comparable to the Ross procedure. However, this study by Mokhles et al[16] also illustrates the challenges that possible differences in patient selection pose in comparisons between the Ross procedure and mechanical AVR.

Thus, when comparing survival differences between the Ross procedure and other valve substitutes, possible differences in patient characteristics and concomitant procedures performed at the time of surgery should be taken into account. Compared with published data on children and adults undergoing mechanical AVR, patients undergoing the Ross procedure are on average slightly younger, less frequently have rheumatic or degenerative disease and more frequently have congenital disease, but also have more frequently undergone prior cardiac interventions and undergo concomitant procedures slightly more often.[12,13]

Furthermore, the difference in life expectancy between patients after the Ross procedure and the general population appears to be slightly greater in children than in adults, although it should be taken into consideration that a large proportion of the mortality in the pediatric population may be attributable to neonates and infants rather than older children, as has been previously demonstrated.[12]

Autograft deterioration

Both the autograft and RVOT conduit are subject to structural valve deterioration over time.

Subsequently, almost all patients that undergo the Ross procedure at age 25 or younger are projected to undergo autograft reintervention at some point during their lifetime, predominantly because of structural valve deterioration. For older adults, this lifetime risk lies between 32% and 68%, decreasing with increasing age at surgery.

After autograft root replacement, the main mechanism of autograft deterioration is progressive autograft regurgitation because of dilatation of the neoaortic root and may be explained by factors such as age, preoperative aortic regurgitation, preoperative aortic annulus dilatation, and underlying cause of disease.[17-20]

Considering the strong influence of these patient-related factors on outcome, careful patient selection and patient-tailored decision-making are essential in achieving optimal outcome after the Ross procedure.

Given the technical complexity of the procedure, variation in surgical technique and surgeon and center volume may also affect long-term autograft function. For instance, subcoronary implantation, the inclusion technique, external prosthetic or pericardial support, and annuloplasty have all been proposed to provide a mechanically more durable result than full unsupported root replacement, with less neoaortic dilatation and subsequent regurgitation.[21-23] However, these techniques are only applied in a few centers. The technically demanding nature of these techniques and subsequent risk of distortion of the neoaortic valve apparatus remains a concern, particularly among surgeons less familiar with these techniques.[24]

Furthermore, the acute increase in mechanical stress on the autograft associated with transplanting the pulmonary valve apparatus from the pulmonary to the systemic circulation is also thought to play a role in autograft dilatation and deterioration.[25] In this light, strict postoperative systemic blood pressure control, especially in the first few months postoperative before any remodeling has occurred, has been proposed as a means to further reduce allograft dilation. The effectiveness thereof remains to be elucidated.

Although reintervention remains a concern, continued improvements in surgical techniques and perioperative management have led to vast improvements in the safety of reoperative aortic valve surgery over the years. Subsequently, reoperations can currently be successfully performed with low mortality.[23] Unfortunately, when patients undergo autograft reintervention, the advantages of the Ross procedure are often lost because the autograft is often replaced with a mechanical valve.[23] However, in cases of autograft dysfunction because of root dilatation with intact autograft valve leaflets or in cases in which the valve leaflets can be successfully repaired, the increasing experience with valve-sparing autograft reinterventions provides increasing opportunities for long-term preservation of the benefits of the Ross procedure.[26]

RVOT conduit deterioration

Although usually less life-threatening, deterioration of the RVOT conduit does pose a substantial additional reintervention hazard, especially in children.

Structural RVOT conduit deterioration is a complex multifactorial process that is not yet well defined. Contrary to the predominant regurgitation seen in autografts, deterioration of the RVOT conduit, most commonly an allograft, is characterized mostly by progressive stenosis.[27]

In allografts, immunologic factors are thought to play a role in RVOT conduit degeneration, as host immune response and AB0 blood group and human leukocyte antigen patient-donor mismatch have been demonstrated to be associated with increased structural RVOT allograft failure.[28,29] In response, decellularization techniques have been developed that aim to reduce immune response and promote autologous cell repopulation by removing donor cells from the allograft while maintaining an intact extracellular matrix. There is some early clinical experience with the application of such allografts in the Ross procedure that demonstrates satisfactory hemodynamic function.[40-44] However, longer follow-up and accumulation of larger patient series is required to produce more definitive evidence on the hypothesized effect of decellularization.

Age is another important factor related to RVOT conduit degeneration, with younger age being associated with higher rates of valve degeneration. This is also clearly reflected by our results, with significantly higher RVOT reintervention rates in the pediatric subgroup compared with the adult subgroup. Even higher rates of RVOT reintervention have been previously reported in neonates and infants (4.30%/y) compared with our pediatric subgroup which also includes older children.[12] Although the exact mechanism that underlies the effect of age on RVOT conduit degeneration is not entirely understood, age-related differences in calcium metabolism, immune activity, somatic growth, and hemodynamics are hypothesized to play a role.[45-48]

Although the additional reintervention risk imposed by substituting single valve for double valve disease in the Ross procedure is substantial, the advancement of percutaneous reinterventions on the RVOT presents a promising solution for delaying surgical reinterventions in selected patients.

Thromboembolism, bleeding, and endocarditis

One of the most important advantages of the Ross procedure is its low thrombogenicity and avoidance of anticoagulation therapy. This is reflected by our results of exceedingly low rates of thromboembolism and bleeding, comparable to the age- and sex-matched general population.[30] Endocarditis rates are also low, approximately half the endocarditis rates previously reported for mechanical AVR in patient populations with comparable proportions of preoperative endocarditis.[12,13]

Valve selection and implications for practice

In prosthetic valve selection, the risk of valve deterioration and subsequent reintervention associated with biological valve substitutes, such as the Ross procedure, is generally weighed against mechanical valve-associated thromboembolism and bleeding risk. In growing children, the Ross procedure is often considered the preferred surgical option

as it is the only living valve substitute and shows diameter increase along with somatic growth.[31] However, in older adolescents and nonelderly adults, a mechanical valve is often recommended because of its superior durability, despite the relatively high risk of thromboembolic and bleeding events, inferior hemodynamics, substantial excess mortality, and subsequent implications for pregnancy and lifestyle.[13] The 2017 US guidelines for the management of adult valvular heart disease propose the Ross procedure to be reserved for patients in whom anticoagulation is contraindicated, and the 2017 European guidelines do not even mention the Ross procedure at all.[32,33] However, our results suggest that the Ross procedure may be beneficial to a larger group of selected patients when performed in centers of expertise. Owing to its excellent hemodynamics and long-term survival, low risks of thromboembolism, bleeding and endocarditis, absence of valve sounds, avoidance of the inconvenience and risks of anticoagulation therapy, and continuous improvements in the safety and outcome of reinterventions, the Ross procedure provides an outcome profile in stark contrast to that of mechanical AVR. This provides a unique opportunity for patients whose preferences, lifestyles, and life planning do not align with the outcome profile of mechanical AVR. In this light, conveyance of patient-tailored evidence-based risks and benefits of all treatment options in a shared decision- making process is of great importance.[32,33] Innovative solutions such as patient information portals and decision aids may prove useful in this setting.[34,35]

Also, 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.

Continuous advances in the design of bioprostheses are hypothesized to improve the durability of modern bioprostheses. This has led to an increase in their use in younger patients. Further development and studies on their long-term performance in young adult patients are required to shed light on their potential as a valve substitute in young adults.

Lastly, continuous improvements in aortic valve repair techniques may increasingly provide options for native valve preservation in young adult patients, avoiding or postponing the need for valve replacement.[36]

Our outcomes provide a unique insight into what patients can be expected to face during the course of their lives after undergoing the Ross procedure, which represents valuable information to patients and clinicians in a meaningful format. This provides the opportunity to provide patients the essential information they need to support decision-making

and improve treatment adherence, follow-up compliance, health behaviors, and quality of life.[34] Our methodology also provides the basis for patient-tailored decision-making by allowing for the possibility to generate patient-tailored outcome estimates. Although we were currently only able to tailor our outcome estimates to age, further studies on the relationship between other patient-related factors and outcomes will make it possible to further tailor outcome estimates, taking other factors into account such as underlying cause of disease, hemodynamics, symptoms, medical history, and concomitant diseases. This may aid clinicians and patients in more accurately selecting the optimal treatment for each individual patient. This methodology may also provide similar opportunities in other areas of cardiovascular medicine in which long-term outcome modeling and subsequent evidence-based decision-making remain a challenge.

Furthermore, because of continuous improvements in long-term survival, quality of life (as opposed to length of life) is increasingly coming into focus. Our outcomes show that, while life expectancy after the Ross procedure approaches the life expectancy of the general population, patients may face numerous valve-related events during their lives. How these valve-related events impact quality of life in these patients remains to be elucidated, although the Ross procedure has been previously shown to be associated with superior quality of life compared with mechanical AVR and comparable to aortic valve repair.[37] The lifetime event occurrence estimates provided by our methodology may provide the basis for estimating long-term quality of life in these patients and may inform efforts aimed at improving this.

Strengths and limitations

To our knowledge, this is the first and only systematic review on this subject to use our advanced methods of meta-analysis of time-to-event data and microsimulation. These methods in conjunction with the large sample size allow us to provide robust long-term outcome estimates and age-specific estimates of life expectancy and lifetime event risk, allowing for a much better insight into long-term outcome in these patients and providing information that is crucial in decision-making and patient information.

This study has several limitations. It is a systematic review and meta-analysis of observational studies, many of which are retrospective in design. As such, the inherent limitations of meta-analyses and pooling data from retrospective observational studies should be taken into consideration.[38] Selection bias may have affected the observed outcomes, as unpublished data, abstracts, and presentations were not included. Funnel plots could not be used to investigate publication bias, as funnel plots do not allow for meaningful interpretation in case of absolute risk outcomes (as are all of our outcomes) because of substantial methodological limitations which may in itself give rise

to funnel plot asymmetry.[39] Direct comparisons with alternative valve prostheses are hampered by the lack of published comparative data. Finally, there are limitations to the microsimulation model that should be taken into account. The relationship between the occurrence rates of valve-related events after the Ross procedure and age and history of previous valve-related events remains poorly defined and could, thus, not be incorporated into 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, although this uncertainty is incorporated in the 95% credible intervals of our outcome estimates.

CONCLUSIONS

Outcome after the Ross procedure is characterized by excellent survival and low postoperative rates of thromboembolism, bleeding, and endocarditis. Lifetime risk of reintervention is high, mainly because of age-dependent structural valve deterioration of both the autograft and allograft. The Ross procedure provides a unique opportunity for patients whose preferences, lifestyles, and life planning do not align with the outcome provided by mechanical valve replacement and for growing children who also benefit from autograft diameter increase along with somatic growth. Thus, patients who are facing AVR are entitled to conveyance of evidence-based estimates of the risks and benefits of all treatment options in a shared decision-making process. Our results warrant reintroduction of the Ross procedure as a valuable option on the surgical menu for selected patients.

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SUPPLEMENTARY MATERIAL

Supplement 1. Supplementary methods

1. Search query

Embase: 3777 results

('pulmonary valve replacement'/de OR 'pulmonary valve prosthesis'/de OR 'Ross procedure'/de OR (('heart valve prosthesis'/de OR 'heart valve bioprosthesis'/exp OR 'heart valve replacement'/exp OR bioprosthesis/de OR xenograft/de OR allograft/de OR allotransplantation/de OR 'cardiovascular surgery'/de) AND ('pulmonary valve'/de OR 'pulmonary valve disease'/exp)) OR (((pulmon* OR lung) NEAR/6 (valv*) NEAR/6 (replace* OR transplant* OR allotransplant* OR allograft* OR homotransplant* OR homograft* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent* OR implant* OR substitut* OR conduit* OR melod* OR mechanical* OR insert*)) OR ((conduit OR reconstruct*) NEAR/15 (right OR pulm*) NEAR/6 ventric*) OR (reconstruct* NEAR/3 pulmon* NEAR/3 tract*) OR (rvot NEAR/3 reconstruct*) OR (Ross NEAR/3 (procedure* OR operation*)) OR (pulmonar* NEAR/3 autograft*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) NOT ('case report'/de OR ((case NEXT/1 report*)):ab,ti)

Medline: 3815 results

(((Heart Valve Prosthesis/ OR Heart Valve Prosthesis Implantation/ OR bioprosthesis/ OR heterograft/ OR allografts/ OR "Transplantation, Homologous"/ OR Cardiovascular Surgical Procedures/) AND (pulmonary valve/ OR Pulmonary Valve Insufficiency/ OR Pulmonary Valve Stenosis/ OR pulmonary artery/)) OR (((pulmon* OR lung) ADJ6 (valv*) ADJ6 (replace* OR transplant* OR allotransplant* OR allograft* OR homotransplant* OR homograft* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent* OR implant* OR substitut* OR conduit* OR melod* OR mechanical* OR insert*)) OR ((conduit OR reconstruct*) ADJ15 (right OR pulm*) ADJ6 ventric*) OR (reconstruct* ADJ3 pulmon* ADJ3 tract*) OR (rvot ADJ3 reconstruct*) OR (Ross ADJ3 (procedure* OR operation*)) OR (pulmonar* ADJ3 autograft*)).ab,ti.) NOT (exp animals/ NOT humans/) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. NOT ("case reports"/ OR ((case ADJ report*)).ab,ti.)

Web of science: 3094 results
TS=(((((pulmon* OR lung) NEAR/5 (valv*) NEAR/5 (replace* OR transplant* OR allotransplant* OR allograft* OR homotransplant* OR homograft* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent* OR implant* OR substitut* OR conduit* OR melod* OR mechanical* OR insert*)) OR ((conduit OR reconstruct*) NEAR/15 (right OR pulm*) NEAR/5 ventric*) OR (reconstruct* NEAR/2 pulmon* NEAR/2 tract*) OR (rvot NEAR/2 reconstruct*) OR (Ross NEAR/2 (procedure* OR operation*)) OR (pulmonar* NEAR/2 autograft*))) NOT (((case NEAR/1 report*)))) AND LA=(english) AND DT=(article)

Cochrane: 138 results
((((pulmon* OR lung) NEAR/6 (valv*) NEAR/6 (replace* OR transplant* OR allotransplant* OR allograft* OR homotransplant* OR homograft* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent* OR implant* OR substitut* OR conduit* OR melod* OR mechanical* OR insert*)) OR ((conduit OR reconstruct*) NEAR/15 (right OR pulm*) NEAR/6 ventric*) OR (reconstruct* NEAR/3 pulmon* NEAR/3 tract*) OR (rvot NEAR/3 reconstruct*) OR (Ross NEAR/3 (procedure* OR operation*)) OR (pulmonar* NEAR/3 autograft*)):ab,ti) NOT (((case NEXT/1 report*)):ab,ti)

Google scholar: 200 results
"pulmonary valve replacement|transplantation|allotransplantation|allograft|homotransplantation|homograft|xenotransplantation|xenograft|heterotransplantation|heterograft|prosthesis|bioprosthesis|implant|conduit"|"Ross procedure|operation"

2. List of recorded variables

Study characteristics:

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

Baseline patient and operative characteristics:

- Mean age
- Sex
- 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)
- New York Heart Association/Ross functional class

- Urgency of the operation
- Technique (total root replacement, subcoronary implantation or inclusion cylinder)
- Type of right ventricular outflow tract prosthesis (allograft, bioprosthesis or other)
- Concomitant procedures

Outcome events:

- Early outcome events (<30 days after surgery)
  - Early mortality (all-cause mortality within the first 30 postoperative days)
  - Re-exploration for bleeding
  - Pacemaker implantation
  - Deep sternal infection/mediastinitis
  - Endocarditis
  - Stroke
  - Transient ischemic attack
  - Myocardial infarction
  - Valve thrombosis
  - Peripheral bleeding
- Late outcome events (>30 days after surgery)
  - Late mortality
    - Cardiac death
    - Valve related death
    - Sudden, unexplained death (SUD)
  - Reintervention
    - Autograft
    - Right ventricular outflow tract (RVOT)
  - Thromboembolism
  - Valve thrombosis
  - Bleeding
  - Endocarditis
    - Autograft
    - Right ventricular outflow tract (RVOT)
  - Structural valve deterioration (SVD)
    - Autograft
    - Right ventricular outflow tract (RVOT)
  - Nonstructural valve dysfunction (NSVD)
    - Autograft
    - Right ventricular outflow tract (RVOT)
  - Pacemaker implantation

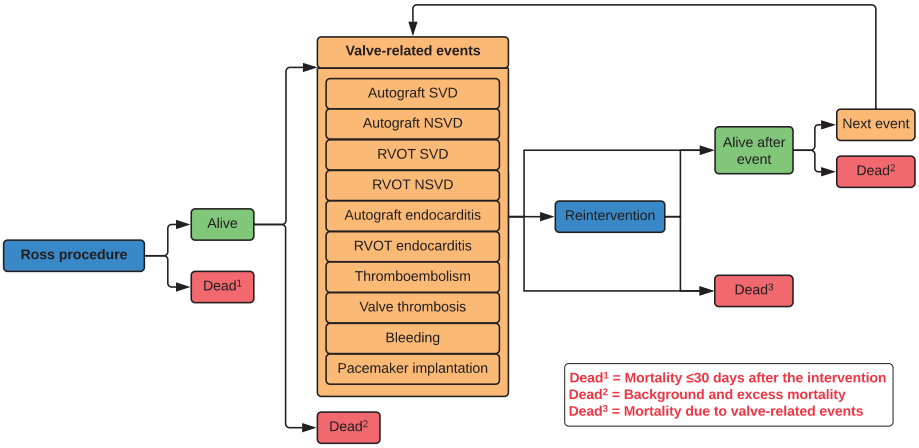
3. Statistical software used

Meta-analysis of baseline patient and study characteristics and event risks and linearized occurrence rates were performed in Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA). Published Kaplan-Meier curves were digitized using Engauge Digitizer (version 10.3, http://markummitchell.github.io/engauge-digitizer). Extrapolation of estimated individual patient time-to-event data from the digitized curves, meta-analysis thereof, microsimulation and meta-regression were performed in R statistical software (version 3.3.2, R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

4. Microsimulation model: concept

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.

4. Microsimulation model: schematic overview (each simulated patient is run through this hypothetical scenario)



5. Microsimulation model: estimation of excess mortality

For estimation of the hazard ratios of the additional excess mortality not directly resulting from valve-related events relative to background mortality, a microsimulation model containing only background mortality and mortality due to valve-related events (excluding early mortality) was run for 10,000 iterations at the mean age of the adult and pediatric subgroups separately. Subsequently, the hazard ratios were estimated by fitting the survival output of this microsimulation model to the survival observed in our meta-analysis of time-to-event data (excluding early mortality) using the least squares method.

Supplement 2. Individual study characteristics.

"-"=variable not reported. FUP=follow-up. Studies included only in the Kaplan-Meier meta-analysis due to overlapping study populations (Brown 2007, "All ages" and "Pediatric" groups; Frigiola 2010, "All awges" and "Pediatric" groups; Sievers 2010, "All ages", "Pediatric" and "Adult" groups; Brancaccio 2014, "All ages" and "Pediatric" groups) are not included in this overview.

ALL AGES				
	Study design	**Origin**	**Patients (N)**	**Inclusion period**
Sharoni 2000	-	Middle East	40	1996-1999
Sirvydis 2000	Prospective	EU	45	1993-1999
Solowiejczyk 2000	-	North America	40	1988-1996
Carr-White 2001	-	EU	144	1993-2000
Laudito 2001	Retrospective	North America	72	1993-2000
Oswalt 2001	Prospective	North America	191	1990-2000
Phillips 2001	-	North America	31	1993-1998
Xie 2001	-	North America	49	1991-1996
Schmid 2002	Retrospective	EU	51	1997-2002
Svensson 2002	-	EU	77	1995-1999
Fullerton 2003	-	North America	44	1997-2002
Lupinetti 2003	-	North America	78	1994-2001
Alphonso 2004	Retrospective	EU	60	1991-2002
Kouchoukos 2004	-	North America	119	1998-2002
Matalanis 2004	-	Oceania	31	1994-2002
Raja 2004	Retrospective	EU	38	1996-2003
Chotivatanapong 2005	-	Asia	30	1997-2002
Kumar 2005	-	Asia	153	1993-2003
Settepani 2005	Retrospective	EU	103	1991-2003
Pitsis 2006	-	EU	21	1998-2004
Wang 2006	Prospective	Oceania	30	1995-2005
Klieverik 2007	Prospective	EU	94	1988-2005
Pasquali 2007	Retrospective	North America	121	1995-2004
Salehi 2007	-	Middle East	80	2001-2004
Elkins 2008	Prospective	North America	487	1986-2002
Frigiola 2008	Retrospective	EU	110	1994-2007
Kadner 2008	Retrospective	EU	52	1993-2004
El Behery 2009	Retrospective	EU	41	1991-2003
Goldberg 2009	Retrospective	North America	32	2003-2007
Al Rashidi 2010	Prospective	EU	26	2003--
Alsoufi 2010	Retrospective	Middle East	227	1991-2004
Coskun 2010	Retrospective	EU	23	2000-2008
El-Hamamsy 2010	RCT	EU	108	1994-2001

Mean/median FUP	Mean/median age at surgery (range)	Technique		
		Total root replacement	Subcoronary	Inclusion
1.0	-(0.7-41.0)	-	-	-
2.5	11.5(4.0-45.0)	100.0%	0.0%	0.0%
2.0	8.3(0.0-19.0)	100.0%	0.0%	0.0%
4.0	31.0(0.2-64.0)	100.0%	0.0%	0.0%
3.5	9.1(0.0-39.6)	-	-	-
4.9	39.0(0.0-69.0)	100.0%	0.0%	0.0%
1.7	28.0(5.0-60.0)	-	-	-
3.0	36.0(16.0-66.0)	100.0%	0.0%	0.0%
3.0	43.2(-)	100.0%	0.0%	0.0%
-	44.0(17.0-66.0)	100.0%	0.0%	0.0%
3.2	49.0(19.0-71.0)	100.0%	0.0%	0.0%
3.4	10.7(0.2-22.3)	100.0%	0.0%	0.0%
5.8	15.0(0.5-67.0)	-	-	-
4.4	31.0(4.0-56.0)	100.0%	0.0%	0.0%
2.4	42.0(24.0-61.0)	100.0%	0.0%	0.0%
2.8	13.1(1.4-29.7)	100.0%	0.0%	0.0%
1.4	36.3(17.0-60.0)	100.0%	0.0%	0.0%
6.4	28.0(0.7-65.0)	100.0%	0.0%	0.0%
6.0	35.2(17.0-65.0)	100.0%	0.0%	0.0%
4.0	42.0(16.0-55.0)	81.0%	19.0%	0.0%
5.4	23.0(13.0-49.0)	100.0%	0.0%	0.0%
8.7	30.4(16.0-52.0)	93.6%	6.4%	0.0%
6.5	8.2(0.0-34.0)	-	-	-
1.4	27.6(11.0-56.0)	-	-	-
-	24.0(0.0-62.0)	83.6%	5.3%	11.1%
6.8	30.2(17.0-65.0)	100.0%	0.0%	0.0%
3.6	3.6(0.0-15.0)	100.0%	0.0%	0.0%
6.0	10.2(0.5-18.3)	95.1%	0.0%	4.9%
1.6	5.4(0.0-20.0)	-	-	-
2.9	37.0(31.0-41.0)	-	-	-
7.8	12.1(0.0-18.0)	100.0%	0.0%	0.0%
2.3	12.6(0.0-40.0)	-	-	-
10.2	38.0(19.0-66.0)	-	-	-

Supplement 2. (continued)

ALL AGES				
	Study design	**Origin**	**Patients (N)**	**Inclusion period**
Valeske 2010	Retrospective	EU	98	1996-2008
Brown 2011	Retrospective	North America	230	1994-2010
Clark 2011	Retrospective	North America	54	1992-2007
Kalfa 2011	Retrospective	EU	107	1993-2009
Kitamura 2011	-	Asia	21	-
Ryan 2011	Prospective	North America	160	1994-2008
Brinkman 2012	Prospective	North America	160	1994-2008
Charitos 2012	Retrospective/prospective	EU	263	-
Juthier 2012	Prospective	EU	336	1992-2010
Luciani 2012	Retrospective	EU	134	1994-2011
McBrien 2012	Retrospective	EU	101	1997-2010
Ruzmetov 2012	Retrospective	North America	106	1990-2011
Goda 2013	Retrospective	EU	33	1993-2010
Khan 2013	Retrospective	North America	68	1995-2011
Ruzmetov 2013	Retrospective	North America	78	1993-2011
Skillington 2013	-	Oceania	310	1992-2012
Stelzer 2013	Prospective	North America	530	1987-2013
Tanny 2013	Retrospective	Oceania	100	1995-2012
Andreas 2014	Retrospective	EU	246	1991-2011
Da Costa 2014	-	South America	414	1995-2013
David 2014	Prospective	North America	212	1990-2004
Kallio 2014	Retrospective	EU	51	1994-2009
Le Guillou 2014	Retrospective	EU	28	1997-2011
Lehoux 2014	Retrospective	North America	25	1997-2008
Lo Rito 2014	Retrospective	EU	140	1991-2011
Luciani 2014	Retrospective	EU	305	1990-2014
Ruzmetov 2014	Retrospective	North America	78	1993-2011
Xu 2014	Retrospective	Asia	58	1994-2009
Zebele 2014	Retrospective	EU	91	1998-2011
Bansal 2015	Retrospective	North America	305	1992-2012
Escarain 2015	Retrospective	South America	263	1995-2012
Jacobsen 2015	Retrospective	North America	36	1992-2014
Lukyanov 2015	-	EU	114	2002-2012
Mastrobuoni 2015	Prospective	EU	306	1991-2014
Nelson 2015	Retrospective	North America	240	1991-2013
Sievers 2015	Retrospective/Prospective	EU	1779	-

Mean/median FUP	Mean/median age at surgery (range)	Technique		
		Total root replacement	Subcoronary	Inclusion
5.0	11.0(0.1-25.0)	99.0%	1.0%	0.0%
7.8	42.4(20.0-68.0)	100.0%	0.0%	0.0%
6.4	13.5(0.5-35.0)	83.3%	0.0%	16.7%
5.7	22.0(0.2-67.0)	100.0%	0.0%	0.0%
9.9	22.0(6.0-47.0)	100.0%	0.0%	0.0%
5.4	42.0(-)	100.0%	0.0%	0.0%
10.1	-(-)	100.0%	0.0%	0.0%
6.9	8.0(-)	-	-	-
6.2	29.4(3.0-55.0)	80.1%	15.5%	-
10.8	25.9(0.1-49.0)	46.3%	21.6%	32.1%
4.7	24.8(0.1-53.0)	100.0%	-	-
7.8	17.9(0.1-40.0)	100.0%	0.0%	0.0%
8.8	9.9(0.0-17.0)	100.0%	0.0%	0.0%
6.7	5.9(0.0-17.0)	100.0%	0.0%	0.0%
8.8	11.1(0.0-18.0)	100.0%	0.0%	0.0%
9.4	39.3(16.0-63.0)	-	-	-
-	42.7(-)	100.0%	0.0%	0.0%
7.3	8.6(0.0-18.0)	91.0%	3.0%	6.0%
10.0	29.0(-)	100.0%	0.0%	0.0%
8.2	30.8(3.0-60.0)	86.0%	0.0%	14.0%
13.8	34.0(-)	50.9%	-	-
11.5	4.8(0.0-16.0)	-	-	-
6.4	42.0(19.0-57.0)	100.0%	0.0%	0.0%
7.3	7.3(-)	100.0%	0.0%	0.0%
10.8	9.9(0.2-35.4)	100.0%	0.0%	0.0%
8.4	9.4(0.0-18.0)	65.9%	5.6%	4.6%
9.9	11.1(0.0-18.0)	100.0%	0.0%	0.0%
8.2	28.3(5.0-56.0)	81.0%	19.0%	0.0%
20.0	20.0(-)	100.0%	0.0%	0.0%
8.2	13.1(0.0-70.3)	96.4%	3.6%	0.0%
7.5	42.0(15.0-67.0)	100.0%	0.0%	0.0%
2.2	14.0(11.0-31.0)	100.0%	0.0%	0.0%
3.9	-(0.0-18.0)	92.1%	12.3%	0.0%
10.6	41.7(-)	54.9%	2.3%	42.8%
10.7	-(0.0-18.0)	100.0%	0.0%	0.0%
8.3	44.7(-)	-	-	-

Supplement 2. (continued)

ALL AGES				
	Study design	**Origin**	**Patients (N)**	**Inclusion period**
Tierney 2005	Retrospective	North America	26	1989-2003
Boethig 2007	Retrospective	EU	109	1985-2005
Franke 2015	-	EU	136	2007-2013
Ruzmetov 2015	Retrospective	North America	72	1993-2012
Baird 2016	Retrospective	North America	50	2000-2014
Brown 2016	Retrospective	North America	115	1993-2015
Carrel 2016	Prospective	EU	22	2006--
Karaskov 2016	Retrospective	EU	741	1998-2014
Mazine 2016	Prospective	North America	208	1990-2014
Popelová 2016	-	EU	33	2005-2015
Zimmermann 2016	Retrospective	EU	76	1993-2011
Bouhout 2017	Retrospective	North America	200	2011-2016
Pardo González 2017	Prospective	EU	107	1997-2009
Martin 2017	Prospective	North America	310	1990-2014
Ratschiller 2017	Retrospective	EU	190	1991-2017
Schneider 2017	Retrospective	EU	154	1994-2016
Skoglund 2017	Retrospective	EU	77	--2015
Tran 2017	Retrospective	EU	75	1998-2012

Mean/median FUP	Mean/median age at surgery (range)	Technique		
		Total root replacement	Subcoronary	Inclusion
5.2	3.4(-)	-	-	-
5.0	31.5(0.0-69.5)	-	-	-
3.0	50.0(20.0-67.0)	100.0%	0.0%	0.0%
11.0	11.9(0.3-18.0)	-	-	-
4.4	4.5(-)	98.0%	2.0%	0.0%
7.8	11.4(0.1-18.0)	100.0%	0.0%	0.0%
5.0	-(-)	100.0%	0.0%	0.0%
5.8	47.4(18.0-67.0)	100.0%	0.0%	0.0%
13.6	37.3(16.0-63.0)	50.0%	-	-
-	-(-)	-	-	-
5.2	15.9(0.4-58.4)	100.0%	0.0%	0.0%
-	46.0(--65.0)	100.0%	0.0%	0.0%
11.0	30.0(3.0-54.0)	-	-	-
15.1	40.8(18.0--)	83.5%	5.8%	10.6%
12.0	28.0(0.0-61.7)	89.5%	0.0%	10.5%
10.0	12.0(19.0-48.0)	97.4%	1.3%	1.3%
15.9	22.7(-)	-	-	-
5.2	10.2(0.4-18.0)	100.0%	0.0%	0.0%

Supplement 2. (continued)

PEDIATRIC				
	Study design	**Origin**	**Patients (N)**	**Inclusion period**
Solowiejczyk 2000	-	North America	40	1988-1996
Pigula 2001	Retrospective	North America	34	1995-2000
Lupinetti 2003	-	North America	78	1994-2001
Hazekamp 2005	-	EU	53	1994-2003
Kalavrouziotis 2006	-	EU	35	1996-2004
Kadner 2008	Retrospective	EU	52	1993-2004
El Behery 2009	Retrospective	EU	41	1991-2003
Goldberg 2009	Retrospective	North America	32	2003-2007
Alsoufi 2010	Retrospective	Middle East	227	1991-2004
Valeske 2010	Retrospective	EU	98	1996-2008
Charitos 2012	Retrospective/prospective	EU	263	-
Oda 2012	Retrospective	Asia	38	1997-2011
Talwar 2012	Retrospective	Asia	36	1992-2009
Goda 2013	Retrospective	EU	33	1993-2010
Khan 2013	Retrospective	North America	68	1995-2011
Ruzmetov 2013	Retrospective	North America	78	1993-2011
Tanny 2013	Retrospective	Oceania	100	1995-2012
Andreas 2014	Retrospective	EU	70	1991-2011
Kallio 2014	Retrospective	EU	51	1994-2009
Lehoux 2014	Retrospective	North America	25	1997-2008
Lo Rito 2014	Retrospective	EU	140	1991-2011
Luciani 2014	Retrospective	EU	305	1990-2014
Ruzmetov 2014	Retrospective	North America	78	1993-2011
Lukyanov 2015	-	EU	114	2002-2012
Nelson 2015	Retrospective	North America	240	1991-2013
Piccardo 2009	Retrospective	EU	55	1993-2006
Tierney 2005	Retrospective	North America	26	1989-2003
Ruzmetov 2015	Retrospective	North America	72	1993-2012
Baird 2016	Retrospective	North America	50	2000-2014
Brown 2016	Retrospective	North America	115	1993-2015
Pardo González 2017	Prospective	EU	21	1997-2009
Tran 2017	Retrospective	EU	75	1998-2012

	Mean/median FUP	Mean/median age at surgery (range)	Technique		
			Total root replacement	Subcoronary	Inclusion
	2.0	8.3(0.0-19.0)	100.0%	0.0%	0.0%
	1.4	10.0(0.3-18.0)	100.0%	0.0%	0.0%
	3.4	10.7(0.2-22.3)	100.0%	0.0%	0.0%
	5.5	9.2(0.0-17.7)	100.0%	0.0%	0.0%
	4.1	10.6(0.0-18.0)	100.0%	0.0%	0.0%
	3.6	3.6(0.0-15.0)	100.0%	0.0%	0.0%
	6.0	10.2(0.5-18.3)	95.1%	0.0%	4.9%
	1.6	5.4(0.0-20.0)	-	-	-
	7.8	12.1(0.0-18.0)	100.0%	0.0%	0.0%
	5.0	11.0(0.1-25.0)	99.0%	1.0%	0.0%
	6.9	8.0(-)	-	-	-
	6.4	6.6(-)	100.0%	0.0%	0.0%
	7.9	11.3(0.8-11.0)	100.0%	0.0%	0.0%
	8.8	9.9(0.0-17.0)	100.0%	0.0%	0.0%
	6.7	5.9(0.0-17.0)	100.0%	0.0%	0.0%
	8.8	11.1(0.0-18.0)	100.0%	0.0%	0.0%
	7.3	8.6(0.0-18.0)	91.0%	3.0%	6.0%
	10.0	10.0(-)	100.0%	0.0%	0.0%
	11.5	4.8(0.0-16.0)	-	-	-
	7.3	7.3(-)	100.0%	0.0%	0.0%
	10.8	9.9(0.2-35.4)	100.0%	0.0%	0.0%
	8.4	9.4(0.0-18.0)	65.9%	5.6%	4.6%
	9.9	11.1(0.0-18.0)	100.0%	0.0%	0.0%
	3.9	-(0.0-18.0)	92.1%	12.3%	0.0%
	10.7	-(0.0-18.0)	100.0%	0.0%	0.0%
	5.5	10.0(0.3-18.0)	100.0%	0.0%	0.0%
	5.2	3.4(-)	-	-	-
	11.0	11.9(0.3-18.0)	-	-	-
	4.4	4.5(-)	98.0%	2.0%	0.0%
	7.8	11.4(0.1-18.0)	100.0%	0.0%	0.0%
	11.0	12.0(6.0-17.0)	-	-	-
	5.2	10.2(0.4-18.0)	100.0%	0.0%	0.0%

Supplement 2. (continued)

ADULT				
	Study design	**Origin**	**Patients (N)**	**Inclusion period**
Knott-Craig 2000	Retrospective	North America	145	1986-1999
Xie 2001	-	North America	49	1991-1996
Schmid 2002	Retrospective	EU	51	1997-2002
Svensson 2002	-	EU	77	1995-1999
Fullerton 2003	-	North America	44	1997-2002
Matalanis 2004	-	Oceania	31	1994-2002
Chotivatanapong 2005	-	Asia	30	1997-2002
Settepani 2005	Retrospective	EU	103	1991-2003
Pitsis 2006	-	EU	21	1998-2004
Klieverik 2007	Prospective	EU	94	1988-2005
Frigiola 2008	Retrospective	EU	110	1994-2007
Al Rashidi 2010	Prospective	EU	26	2003--
El-Hamamsy 2010	RCT	EU	108	1994-2001
Brown 2011	Retrospective	North America	230	1994-2010
Ryan 2011	Prospective	North America	160	1994-2008
Brinkman 2012	Prospective	North America	160	1994-2008
Skillington 2013	-	Oceania	310	1992-2012
Stelzer 2013	Prospective	North America	530	1987-2013
Andreas 2014	Retrospective	EU	176	1991-2011
David 2014	Prospective	North America	212	1990-2004
Le Guillou 2014	Retrospective	EU	28	1997-2011
Escarain 2015	Retrospective	South America	263	1995-2012
Jacobsen 2015	Retrospective	North America	36	1992-2014
Mastrobuoni 2015	Prospective	EU	306	1991-2014
Sievers 2015	Retrospective/Prospective	EU	1779	-
Franke 2015	-	EU	136	2007-2013
Carrel 2016	Prospective	EU	22	2006--
Karaskov 2016	Retrospective	EU	741	1998-2014
Mazine 2016	Prospective	North America	208	1990-2014
Popelová 2016	-	EU	33	2005-2015
Bouhout 2017	Retrospective	North America	200	2011-2016
Pardo González 2017	Prospective	EU	86	1997-2009
Martin 2017	Prospective	North America	310	1990-2014
Skoglund 2017	Retrospective	EU	77	--2015

	Mean/median FUP	Mean/median age at surgery (range)	Technique		
			Total root replacement	Subcoronary	Inclusion
	2.5	-(17.0-82.0)	100.0%	0.0%	0.0%
	3.0	36.0(16.0-66.0)	100.0%	0.0%	0.0%
	3.0	43.2(-)	100.0%	0.0%	0.0%
	-	44.0(17.0-66.0)	100.0%	0.0%	0.0%
	3.2	49.0(19.0-71.0)	100.0%	0.0%	0.0%
	2.4	42.0(24.0-61.0)	100.0%	0.0%	0.0%
	1.4	36.3(17.0-60.0)	100.0%	0.0%	0.0%
	6.0	35.2(17.0-65.0)	100.0%	0.0%	0.0%
	4.0	42.0(16.0-55.0)	81.0%	19.0%	0.0%
	8.7	30.4(16.0-52.0)	93.6%	6.4%	0.0%
	6.8	30.2(17.0-65.0)	100.0%	0.0%	0.0%
	2.9	37.0(31.0-41.0)	-	-	-
	10.2	38.0(19.0-66.0)	-	-	-
	7.8	42.4(20.0-68.0)	100.0%	0.0%	0.0%
	5.4	42.0(-)	100.0%	0.0%	0.0%
	10.1	-(-)	100.0%	0.0%	0.0%
	9.4	39.3(16.0-63.0)	-	-	-
	-	42.7(-)	100.0%	0.0%	0.0%
	10.0	36.0(-)	100.0%	0.0%	0.0%
	13.8	34.0(-)	50.9%	-	-
	6.4	42.0(19.0-57.0)	100.0%	0.0%	0.0%
	7.5	42.0(15.0-67.0)	100.0%	0.0%	0.0%
	2.2	14.0(11.0-31.0)	100.0%	0.0%	0.0%
	10.6	41.7(-)	54.9%	2.3%	42.8%
	8.3	44.7(-)	-	-	-
	3.0	50.0(20.0-67.0)	100.0%	0.0%	0.0%
	5.0	-(-)	100.0%	0.0%	0.0%
	5.8	47.4(18.0-67.0)	100.0%	0.0%	0.0%
	13.6	37.3(16.0-63.0)	50.0%	-	-
	-	-(-)	-	-	-
	-	46.0(--65.0)	100.0%	0.0%	0.0%
	11.0	34.0(18.0-54.0)	-	-	-
	15.1	40.8(18.0--)	83.5%	5.8%	10.6%
	15.9	22.7(-)	-	-	-

Supplement 3. Individual study outcome estimates.

[1]The reported p-values are those of the Cochran's Q test for heterogeneity. *zero events reported, for the purpose of the analyses it was assumed that 0.5 patient experienced that event. "-"=variable not reported. Yr=year. SUD=sudden unexplained death. RVOT=right ventricular outflow tract. Studies included only in the Kaplan-Meier meta-analysis due to overlapping study populations (Brown 2007, "All ages" and "Pediatric" groups; Frigiola 2010, "All ages" and "Pediatric" groups; Sievers 2010, "All ages", "Pediatric" and "Adult" groups; Brancaccio 2014, "All ages" and "Pediatric" groups) are not included in this overview.

ALL AGES			
	Early mortality (%)	**Late mortality (%/yr)**	-Cardiac (%/yr)
Sharoni 2000	1.25(0.08-19.64)*	1.25(0.08-19.64)*	1.25(0.08-19.64)*
Sirvydis 2000	8.89(3.49-22.65)	0.44(0.03-7.06)*	0.44(0.03-7.06)*
Solowiejczyk 2000	-	-	-
Carr-White 2001	0.35(0.02-5.52)*	0.69(0.26-1.84)	-
Laudito 2001	0.69(0.04-11.00)*	0.20(0.01-3.13)*	0.20(0.01-3.13)*
Oswalt 2001	5.24(2.86-9.57)	0.53(0.22-1.28)	-
Phillips 2001	9.68(3.30-28.37)	-	-
Xie 2001	4.08(1.05-15.86)	0.34(0.02-5.41)*	0.34(0.02-5.41)*
Schmid 2002	0.98(0.06-15.46)*	0.64(0.09-4.55)	0.32(0.02-5.13)*
Svensson 2002	3.90(1.28-11.81)	-	-
Fullerton 2003	6.82(2.29-20.33)	0.36(0.02-5.70)*	0.36(0.02-5.70)*
Lupinetti 2003	3.85(1.27-11.67)	0.19(0.01-3.03)*	0.19(0.01-3.03)*
Alphonso 2004	0.83(0.05-13.17)*	0.14(0.01-2.31)*	0.14(0.01-2.31)*
Kouchoukos 2004	1.68(0.43-6.64)	0.38(0.10-1.52)	0.38(0.10-1.52)
Matalanis 2004	3.23(0.47-22.18)	2.71(0.69-10.62)	-
Raja 2004	2.63(0.38-18.20)	0.95(0.14-6.69)	0.95(0.14-6.69)
Chotivatanapong 2005	13.33(5.35-33.20)	1.20(0.08-18.85)*	1.20(0.08-18.85)*
Kumar 2005	6.54(3.59-11.90)	0.87(0.44-1.74)	0.87(0.44-1.74)
Settepani 2005	0.49(0.03-7.71)*	0.32(0.08-1.29)	0.16(0.02-1.15)
Pitsis 2006	4.76(0.70-32.25)	0.60(0.04-9.44)*	0.60(0.04-9.44)*
Wang 2006	1.67(0.11-26.04)*	0.31(0.02-4.90)*	0.31(0.02-4.90)*
Klieverik 2007	3.19(1.05-9.72)	0.12(0.02-0.87)	0.12(0.02-0.87)
Pasquali 2007	2.48(0.81-7.58)	0.29(0.07-1.17)	0.29(0.07-1.17)
Salehi 2007	3.75(1.24-11.38)	0.44(0.03-6.99)*	0.44(0.03-6.99)*
Elkins 2008	3.90(2.51-6.06)	0.46(0.28-0.76)	0.25(0.12-0.49)
Frigiola 2008	0.45(0.03-7.22)*	0.13(0.02-0.94)	0.13(0.02-0.94)
Kadner 2008	9.62(4.18-22.12)	1.61(0.52-4.95)	0.27(0.02-4.28)*
El Behery 2009	4.88(1.26-18.85)	0.20(0.01-3.24)*	-
Goldberg 2009	15.63(6.98-34.95)	0.99(0.06-15.60)*	-
Al Rashidi 2010	1.92(0.12-29.93)*	0.66(0.04-10.45)*	0.66(0.04-10.45)*
Alsoufi 2010	3.08(1.49-6.39)	0.17(0.05-0.52)	-
Coskun 2010	4.35(0.64-29.57)	1.02(0.06-16.09)*	-

	-Valve-related (%/yr)	- SUD (%/yr)	**Reintervention (%/yr)**	-Autograft (%/yr)	-Allograft (%/yr)
	1.25(0.08-19.64)*	1.25(0.08-19.64)*	-	-	-
	0.44(0.03-7.06)*	0.44(0.03-7.06)*	0.44(0.03-7.06)*	0.44(0.03-7.06)*	0.44(0.03-7.06)*
	-	-	1.25(0.18-8.77)	0.63(0.04-9.91)*	1.25(0.18-8.77)
	-	-	-	-	0.69(0.26-1.84)
	0.20(0.01-3.13)*	0.20(0.01-3.13)*	-	2.75(1.32-5.70)	-
	0.05(0.00-0.85)*	0.05(0.00-0.85)*	1.60(0.97-2.64)	1.28(0.73-2.24)	0.32(0.10-0.99)
	-	-	-	-	-
	0.34(0.02-5.41)*	0.34(0.02-5.41)*	0.68(0.10-4.80)	0.34(0.02-5.41)*	0.68(0.10-4.80)
	0.32(0.02-5.13)*	0.32(0.02-5.13)*	0.64(0.09-4.55)	0.32(0.02-5.13)*	0.64(0.09-4.55)
	-	-	-	-	-
	0.36(0.02-5.70)*	0.36(0.02-5.70)*	0.72(0.10-5.05)	0.72(0.10-5.05)	0.36(0.02-5.70)*
	0.19(0.01-3.03)*	0.19(0.01-3.03)*	1.90(0.80-4.53)	1.52(0.57-4.02)	0.38(0.05-2.69)
	0.14(0.01-2.31)*	0.14(0.01-2.31)*	1.74(0.79-3.84)	1.16(0.44-3.07)	0.58(0.15-2.31)
	0.19(0.03-1.35)	0.10(0.01-1.52)*	2.86(1.74-4.72)	2.10(1.17-3.77)	0.76(0.29-2.03)
	0.68(0.04-10.72)*	0.68(0.04-10.72)*	2.71(0.69-10.62)	1.35(0.19-9.48)	0.68(0.04-10.72)*
	0.48(0.03-7.55)*	0.48(0.03-7.55)*	1.90(0.48-7.51)	0.48(0.03-7.55)*	1.90(0.48-7.51)
	1.20(0.08-18.85)*	1.20(0.08-18.85)*	-	-	-
	0.65(0.29-1.45)	-	1.09(0.59-2.02)	0.87(0.44-1.74)	0.05(0.00-0.87)*
	0.16(0.02-1.15)	0.08(0.01-1.29)*	0.97(0.44-2.15)	0.81(0.34-1.94)	0.16(0.02-1.15)
	0.60(0.04-9.44)*	0.60(0.04-9.44)*	2.38(0.61-9.36)	2.38(0.61-9.36)	0.60(0.04-9.44)*
	0.31(0.02-4.90)*	0.31(0.02-4.90)*	2.46(0.93-6.48)	1.85(0.60-5.66)	0.62(0.09-4.34)
	0.06(0.00-0.98)*	0.06(0.00-0.98)*	-	-	-
	0.07(0.00-1.17)*	0.07(0.00-1.17)*	4.67(3.33-6.55)	2.19(1.33-3.61)	2.19(1.33-3.61)
	0.44(0.03-6.99)*	0.44(0.03-6.99)*	1.76(0.45-6.95)	1.76(0.45-6.95)	0.44(0.03-6.99)*
	0.25(0.12-0.49)	0.18(0.08-0.41)	-	1.16(0.85-1.60)	1.01(0.72-1.42)
	0.13(0.02-0.94)	0.13(0.02-0.94)	-	1.06(0.53-2.12)	0.53(0.20-1.41)
	0.27(0.02-4.28)*	0.27(0.02-4.28)*	4.30(2.18-8.46)	0.54(0.08-3.79)	3.76(1.82-7.78)
	-	-	1.63(0.62-4.30)	0.20(0.01-3.24)*	1.63(0.62-4.30)
	-	-	-	-	-
	0.66(0.04-10.45)*	0.66(0.04-10.45)*	1.32(0.19-9.24)	1.32(0.19-9.24)	-
	-	-	4.86(3.95-5.97)	1.64(1.14-2.35)	1.64(1.14-2.35)
	-	-	-	-	-

Supplement 3. (continued)

ALL AGES			
	Early mortality (%)	**Late mortality (%/yr)**	-Cardiac (%/yr)
El-Hamamsy 2010	0.93(0.13-6.51)	0.27(0.09-0.84)	0.09(0.01-0.64)
Valeske 2010	2.04(0.52-8.05)	0.10(0.01-1.63)*	-
Brown 2011	0.87(0.22-3.46)	0.67(0.38-1.18)	0.17(0.05-0.52)
Clark 2011	0.93(0.06-14.61)*	0.14(0.01-2.31)*	0.14(0.01-2.31)*
Kalfa 2011	0.47(0.03-7.42)*	0.49(0.16-1.52)	0.08(0.01-1.31)*
Kitamura 2011	2.38(0.15-36.82)*	0.24(0.02-3.83)*	0.24(0.02-3.83)*
Ryan 2011	1.88(0.61-5.75)	0.58(0.24-1.39)	0.12(0.02-0.83)
Brinkman 2012	-	-	-
Charitos 2012	3.42(1.80-6.50)	-	-
Juthier 2012	3.27(1.83-5.85)	0.44(0.23-0.84)	0.10(0.02-0.39)
Luciani 2012	1.49(0.38-5.91)	0.14(0.03-0.55)	0.14(0.03-0.55)
McBrien 2012	0.50(0.03-7.86)*	0.21(0.03-1.49)	0.21(0.03-1.49)
Ruzmetov 2012	2.83(0.93-8.63)	0.73(0.33-1.61)	0.48(0.18-1.29)
Goda 2013	-	-	-
Khan 2013	2.94(0.75-11.52)	0.44(0.11-1.75)	-
Ruzmetov 2013	-	-	-
Skillington 2013	0.32(0.05-2.28)	0.17(0.07-0.41)	0.02(0.00-0.27)*
Stelzer 2013	1.13(0.51-2.51)	-	-
Tanny 2013	6.00(2.76-13.03)	0.55(0.21-1.46)	0.41(0.13-1.27)
Andreas 2014	1.63(0.62-4.30)	0.16(0.06-0.43)	0.02(0.00-0.32)*
Da Costa 2014	2.66(1.48-4.76)	0.60(0.39-0.94)	0.45(0.27-0.75)
David 2014	0.47(0.07-3.33)	0.31(0.16-0.59)	0.10(0.03-0.32)
Kallio 2014	9.80(4.26-22.54)	0.51(0.17-1.58)	0.51(0.17-1.58)
Le Guillou 2014	10.71(3.68-31.21)	3.35(1.52-7.35)	0.28(0.02-4.44)*
Lehoux 2014	-	-	-
Lo Rito 2014	2.86(1.09-7.51)	0.13(0.03-0.53)	0.13(0.03-0.53)
Luciani 2014	3.28(1.78-6.03)	0.47(0.27-0.82)	0.23(0.11-0.52)
Ruzmetov 2014	-	-	-
Xu 2014	3.45(0.88-13.46)	0.21(0.03-1.49)	0.21(0.03-1.49)
Zebele 2014	1.10(0.16-7.72)	0.16(0.05-0.51)	0.05(0.01-0.39)
Bansal 2015	3.61(2.02-6.44)	0.52(0.30-0.89)	-
Escarain 2015	2.66(1.28-5.53)	0.71(0.42-1.20)	0.30(0.14-0.68)
Jacobsen 2015	1.39(0.09-21.78)*	1.26(0.18-8.85)	1.26(0.18-8.85)
Lukyanov 2015	1.75(0.44-6.93)	-	-
Mastrobuoni 2015	2.29(1.10-4.76)	0.71(0.47-1.09)	0.10(0.03-0.32)
Nelson 2015	4.17(2.27-7.64)	0.66(0.41-1.06)	-
Sievers 2015	1.07(0.68-1.67)	0.68(0.56-0.83)	-

	-Valve-related (%/yr)	- SUD (%/yr)	**Reintervention (%/yr)**	-Autograft (%/yr)	-Allograft (%/yr)
	0.09(0.01-0.64)	0.09(0.01-0.64)	0.73(0.36-1.45)	0.09(0.01-0.64)	0.64(0.30-1.33)
	-	-	0.20(0.03-1.45)	0.20(0.03-1.45)	0.10(0.01-1.63)*
	-	0.28(0.12-0.67)	1.40(0.95-2.07)	1.12(0.73-1.74)	0.28(0.12-0.67)
	0.14(0.01-2.31)*	0.14(0.01-2.31)*	2.89(1.57-5.33)	0.29(0.04-2.05)	2.60(1.37-4.96)
	0.08(0.01-1.31)*	0.08(0.01-1.31)*	-	-	1.15(0.55-2.40)
	0.24(0.02-3.83)*	0.24(0.02-3.83)*	1.44(0.47-4.44)	0.24(0.02-3.83)*	0.96(0.24-3.82)
	0.06(0.00-0.93)*	0.06(0.00-0.93)*	1.75(1.06-2.88)	-	0.12(0.02-0.83)
	-	-	1.05(0.66-1.69)	1.05(0.66-1.69)	-
	-	-	3.63(2.81-4.69)	0.91(0.54-1.53)	2.72(2.02-3.67)
	0.02(0.00-0.39)*	0.02(0.00-0.39)*	2.29(1.73-3.04)	1.81(1.31-2.49)	0.49(0.26-0.91)
	0.14(0.03-0.55)	0.07(0.01-0.49)	1.93(1.34-2.79)	1.87(1.28-2.71)	0.07(0.01-0.49)
	0.21(0.03-1.49)	0.11(0.01-1.68)*	1.90(0.99-3.62)	1.26(0.57-2.80)	0.63(0.20-1.95)
	0.24(0.06-0.97)	0.24(0.06-0.97)	4.60(3.37-6.27)	2.18(1.38-3.44)	2.42(1.57-3.73)
	-	-	-	1.03(0.34-3.18)	-
	-	-	4.17(2.69-6.48)	0.66(0.21-2.03)	3.51(2.17-5.68)
	-	-	5.24(3.82-7.21)	-	2.33(1.44-3.78)
	0.02(0.00-0.27)*	0.02(0.00-0.27)*	0.51(0.31-0.85)	0.38(0.21-0.68)	0.17(0.07-0.41)
	-	-	-	-	-
	0.27(0.07-1.09)	0.14(0.02-0.97)	3.70(2.55-5.36)	1.23(0.64-2.36)	2.74(1.78-4.22)
	0.02(0.00-0.32)*	0.02(0.00-0.32)*	1.18(0.82-1.69)	0.45(0.25-0.81)	0.69(0.43-1.11)
	0.30(0.16-0.56)	0.18(0.08-0.40)	1.21(0.89-1.65)	0.67(0.44-1.01)	0.45(0.27-0.75)
	0.10(0.03-0.32)	0.10(0.03-0.32)	0.85(0.58-1.26)	0.51(0.31-0.85)	0.31(0.16-0.59)
	0.17(0.02-1.21)	0.09(0.01-1.36)*	3.58(2.35-5.45)	0.68(0.26-1.81)	2.05(1.17-3.58)
	0.28(0.02-4.44)*	0.28(0.02-4.44)*	2.23(0.85-5.88)	1.12(0.28-4.43)	0.56(0.08-3.94)
	-	-	2.19(0.83-5.78)	0.27(0.02-4.36)*	1.10(0.28-4.35)
	0.13(0.03-0.53)	0.03(0.00-0.53)*	1.72(1.17-2.52)	0.73(0.40-1.31)	0.99(0.60-1.64)
	-	-	2.93(2.34-3.66)	1.44(1.05-1.99)	1.44(1.05-1.99)
	-	-	-	3.37(2.31-4.91)	-
	0.21(0.03-1.49)	0.11(0.01-1.68)*	0.11(0.01-1.68)*	0.11(0.01-1.68)*	0.11(0.01-1.68)*
	-	-	0.88(0.54-1.43)	0.49(0.26-0.95)	0.38(0.18-0.81)
	-	-	-	1.84(1.38-2.45)	-
	0.30(0.14-0.68)	0.03(0.00-0.41)*	0.91(0.58-1.45)	0.66(0.38-1.13)	0.20(0.08-0.54)
	1.26(0.18-8.85)	1.26(0.18-8.85)	5.05(1.94-13.12)	3.79(1.25-11.49)	0.63(0.04-10.01)*
	-	-	-	-	-
	0.10(0.03-0.32)	0.03(0.00-0.24)	1.33(0.97-1.81)	1.23(0.89-1.70)	0.37(0.21-0.68)
	-	-	7.75(6.78-8.86)	2.69(2.13-3.39)	2.22(1.72-2.87)
	-	-	1.19(1.02-1.37)	0.72(0.59-0.87)	0.62(0.50-0.76)

Supplement 3. (continued)

ALL AGES			
	Early mortality (%)	**Late mortality (%/yr)**	-Cardiac (%/yr)
Tierney 2005	-	-	-
Boethig 2007	0.92(0.13-6.45)	0.36(0.09-1.45)	0.09(0.01-1.45)*
Franke 2015	0.74(0.10-5.18)	0.12(0.01-1.96)*	0.12(0.01-1.96)*
Ruzmetov 2015	1.39(0.20-9.73)	0.51(0.19-1.34)	-
Baird 2016	-	0.23(0.01-3.61)*	0.23(0.01-3.61)*
Brown 2016	0.87(0.12-6.12)	0.45(0.17-1.19)	0.22(0.06-0.89)
Carrel 2016	2.27(0.15-35.20)*	-	-
Karaskov 2016	2.97(1.97-4.48)	0.58(0.37-0.93)	0.45(0.27-0.77)
Mazine 2016	0.48(0.07-3.40)	0.42(0.24-0.75)	0.11(0.03-0.33)
Popelová 2016	1.52(0.10-23.72)*	-	-
Zimmermann 2016	-	0.13(0.01-2.02)*	0.13(0.01-2.02)*
Bouhout 2017	1.00(0.25-3.97)	-	-
Pardo González 2017	0.93(0.13-6.57)	0.17(0.04-0.68)	0.17(0.04-0.68)
Martin 2017	1.29(0.49-3.42)	0.60(0.41-0.87)	0.34(0.21-0.56)
Ratschiller 2017	2.11(0.80-5.55)	0.53(0.30-0.93)	-
Schneider 2017	5.19(2.65-10.20)	0.60(0.32-1.12)	0.42(0.20-0.88)
Skoglund 2017	0.65(0.04-10.29)*	0.08(0.01-0.58)	-
Tran 2017	0.67(0.04-10.56)*	0.13(0.01-2.05)*	0.13(0.01-2.05)*
Pooled estimate (95%CI)	2.87(2.39-3.45)	0.50(0.44-0.58)	0.29(0.24-0.35)
Heterogeneity	I^2=50.9%(p<0.001)	I^2=30.5%(p=0.009)	I^2=6.6%(p=0.335)
Number of studies	78	72	57

	-Valve-related (%/yr)	- SUD (%/yr)	**Reintervention (%/yr)**	-Autograft (%/yr)	-Allograft (%/yr)
	-	-	-	-	2.22(0.72-6.79)
	0.09(0.01-1.45)*	0.09(0.01-1.45)*	-	-	-
	0.12(0.01-1.96)*	0.12(0.01-1.96)*	0.98(0.37-2.61)	0.74(0.24-2.28)	0.25(0.03-1.74)
	-	-	-	2.78(1.84-4.19)	2.27(1.44-3.59)
	0.23(0.01-3.61)*	0.23(0.01-3.61)*	-	0.91(0.23-3.60)	4.98(2.80-8.86)
	0.22(0.06-0.89)	0.11(0.02-0.79)	3.57(2.54-5.01)	1.45(0.84-2.49)	1.90(1.18-3.03)
	-	-	0.91(0.13-6.40)	0.91(0.13-6.40)	0.45(0.03-7.22)*
	0.36(0.20-0.64)	0.26(0.13-0.52)	1.85(1.43-2.39)	1.20(0.87-1.65)	0.91(0.63-1.31)
	0.11(0.03-0.33)	0.07(0.02-0.28)	0.74(0.48-1.14)	0.49(0.29-0.83)	0.25(0.12-0.52)
	-	-	-	-	-
	0.13(0.01-2.02)*	0.13(0.01-2.02)*	-	1.52(0.69-3.36)	-
	-	-	-	-	-
	0.17(0.04-0.68)	0.17(0.04-0.68)	1.78(1.17-2.73)	0.93(0.52-1.68)	1.10(0.64-1.90)
	0.09(0.03-0.23)	0.02(0.00-0.15)	1.20(0.92-1.55)	0.68(0.48-0.97)	0.45(0.29-0.69)
	-	-	-	-	-
	0.30(0.13-0.72)	0.18(0.06-0.56)	-	1.56(1.07-2.29)	1.86(1.32-2.64)
	-	-	-	-	0.82(0.44-1.51)
	0.13(0.01-2.05)*	0.13(0.01-2.05)*	3.08(1.76-5.37)	0.77(0.25-2.37)	1.79(0.86-3.74)
	0.23(0.19-0.28)	0.17(0.13-0.21)	1.84(1.49-2.27)	1.10(0.94-1.29)	0.91(0.74-1.12)
	I^2=0.0%(p=0.821)	I^2=0.0%(p=0.926)	I^2=92.7%(p<0.001)	I^2=76.3%(p<0.001)	I^2=84.3%(p<0.001)
	56	56	60	68	67

Supplement 3. (continued)

ALL AGES (continued)			
	Endocarditis (%/yr)	-Autograft (%/yr)	-Allograft (%/yr)
Sharoni 2000	-	-	-
Sirvydis 2000	0.44(0.03-7.06)*	0.44(0.03-7.06)*	0.44(0.03-7.06)*
Solowiejczyk 2000	-	-	-
Carr-White 2001	-	-	-
Laudito 2001	-	-	-
Oswalt 2001	-	-	-
Phillips 2001	-	-	-
Xie 2001	-	-	-
Schmid 2002	-	-	-
Svensson 2002	-	-	-
Fullerton 2003	-	-	-
Lupinetti 2003	0.19(0.01-3.03)*	-	-
Alphonso 2004	-	-	-
Kouchoukos 2004	0.10(0.01-1.52)*	-	-
Matalanis 2004	0.68(0.04-10.72)*	-	-
Raja 2004	-	0.48(0.03-7.55)*	-
Chotivatanapong 2005	-	-	-
Kumar 2005	0.44(0.16-1.16)	0.44(0.16-1.16)	0.05(0.00-0.87)*
Settepani 2005	0.32(0.08-1.29)	0.16(0.02-1.15)	0.16(0.02-1.15)
Pitsis 2006	1.19(0.17-8.35)	1.19(0.17-8.35)	0.60(0.04-9.44)*
Wang 2006	0.62(0.09-4.34)	-	-
Klieverik 2007	-	-	-
Pasquali 2007	-	-	-
Salehi 2007	0.44(0.03-6.99)*	0.44(0.03-6.99)*	0.44(0.03-6.99)*
Elkins 2008	0.31(0.17-0.57)	0.15(0.06-0.37)	0.12(0.05-0.33)
Frigiola 2008	-	-	-
Kadner 2008	0.27(0.02-4.28)*	0.27(0.02-4.28)*	0.27(0.02-4.28)*
El Behery 2009	-	-	-
Goldberg 2009	-	-	-
Al Rashidi 2010	-	-	-
Alsoufi 2010	-	-	-
Coskun 2010	-	-	-
El-Hamamsy 2010	0.18(0.05-0.73)	0.05(0.00-0.73)*	0.18(0.05-0.73)
Valeske 2010	-	-	-
Brown 2011	0.17(0.05-0.52)	0.17(0.05-0.52)	-
Clark 2011	0.29(0.04-2.05)	0.29(0.04-2.05)	0.29(0.04-2.05)
Kalfa 2011	-	-	0.16(0.02-1.16)

	Thromboembolism (%/yr)	Valve thrombosis (%/yr)	Bleeding (%/yr)	Pacemaker implantation (%/yr)
	-	-	-	-
	0.44(0.03-7.06)*	-	0.44(0.03-7.06)*	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	0.36(0.02-5.70)*
	-	-	0.19(0.01-3.03)*	-
	-	-	-	-
	0.19(0.03-1.35)	-	-	-
	0.68(0.04-10.72)*	-	-	1.35(0.19-9.48)
	0.48(0.03-7.55)*	0.48(0.03-7.55)*	-	-
	-	-	11.99(5.27-27.29)	-
	0.05(0.00-0.87)*	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	0.06(0.00-0.98)*	0.06(0.00-0.98)*	-
	-	-	-	-
	0.44(0.03-6.99)*	-	-	-
	0.03(0.00-0.22)	-	-	-
	-	-	-	-
	0.27(0.02-4.28)*	-	-	0.27(0.02-4.28)*
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	0.10(0.01-1.63)*	0.10(0.01-1.63)*	-	-
	0.06(0.01-0.40)	0.03(0.00-0.45)*	0.03(0.00-0.45)*	-
	-	-	-	-
	-	-	-	-

Supplement 3. (continued)

ALL AGES (continued)			
	Endocarditis (%/yr)	-Autograft (%/yr)	-Allograft (%/yr)
Kitamura 2011	0.24(0.02-3.83)*	0.24(0.02-3.83)*	0.24(0.02-3.83)*
Ryan 2011	-	-	-
Brinkman 2012	-	-	-
Charitos 2012	-	-	-
Juthier 2012	0.15(0.05-0.45)	-	-
Luciani 2012	-	-	-
McBrien 2012	1.69(0.85-3.35)	1.26(0.57-2.80)	0.42(0.11-1.68)
Ruzmetov 2012	-	-	-
Goda 2013	-	-	-
Khan 2013	-	-	-
Ruzmetov 2013	-	-	-
Skillington 2013	0.14(0.05-0.37)	0.07(0.02-0.27)	0.10(0.03-0.32)
Stelzer 2013	-	-	-
Tanny 2013	-	-	-
Andreas 2014	0.37(0.19-0.70)	-	-
Da Costa 2014	0.24(0.12-0.48)	0.03(0.00-0.21)	0.21(0.10-0.44)
David 2014	0.14(0.05-0.36)	0.02(0.00-0.27)*	0.14(0.05-0.36)
Kallio 2014	-	-	-
Le Guillou 2014	1.12(0.28-4.43)	0.56(0.08-3.94)	0.56(0.08-3.94)
Lehoux 2014	-	-	-
Lo Rito 2014	-	-	-
Luciani 2014	0.20(0.08-0.47)	-	-
Ruzmetov 2014	-	-	-
Xu 2014	0.21(0.03-1.49)	0.11(0.01-1.68)*	0.21(0.03-1.49)
Zebele 2014	-	-	-
Bansal 2015	-	-	-
Escarain 2015	0.15(0.05-0.47)	0.10(0.03-0.41)	0.10(0.03-0.41)
Jacobsen 2015	-	-	-
Lukyanov 2015	-	-	-
Mastrobuoni 2015	0.10(0.03-0.32)	0.07(0.02-0.27)	0.07(0.02-0.27)
Nelson 2015	-	-	-
Sievers 2015	-	-	-
Tierney 2005	-	-	-
Boethig 2007	-	-	-
Franke 2015	0.74(0.24-2.28)	0.74(0.24-2.28)	0.12(0.01-1.96)*
Ruzmetov 2015	-	-	-
Baird 2016	-	-	-

Thromboembolism (%/yr)	Valve thrombosis (%/yr)	Bleeding (%/yr)	Pacemaker implantation (%/yr)
0.24(0.02-3.83)*	0.24(0.02-3.83)*	-	-
-	-	-	-
-	-	-	-
-	-	-	-
-	-	-	-
-	-	-	-
-	-	-	0.42(0.11-1.68)
-	-	-	0.36(0.12-1.12)
-	-	-	-
-	-	-	0.22(0.03-1.55)
-	-	-	0.29(0.07-1.16)
-	-	-	-
-	-	-	-
-	-	-	0.55(0.21-1.46)
0.04(0.01-0.29)	-	-	0.12(0.04-0.38)
0.24(0.12-0.48)	-	0.06(0.02-0.24)	-
0.14(0.05-0.36)	-	0.02(0.00-0.27)*	-
-	-	-	-
-	-	-	-
-	-	-	-
-	-	-	-
0.08(0.02-0.31)	-	0.02(0.00-0.31)*	0.20(0.08-0.47)
-	-	-	-
0.11(0.01-1.68)*	0.11(0.01-1.68)*	0.11(0.01-1.68)*	-
-	-	-	-
-	-	-	-
0.03(0.00-0.41)*	0.03(0.00-0.41)*	0.03(0.00-0.41)*	-
-	-	-	-
-	-	-	-
-	0.02(0.00-0.27)*	0.14(0.05-0.36)	-
-	-	-	-
-	-	-	-
-	-	-	-
-	-	-	-
0.12(0.01-1.96)*	0.12(0.01-1.96)*	0.12(0.01-1.96)*	0.12(0.01-1.96)*
-	-	-	-
-	-	-	-

Supplement 3. (continued)

ALL AGES (continued)			
	Endocarditis (%/yr)	-Autograft (%/yr)	-Allograft (%/yr)
Brown 2016	0.22(0.06-0.89)	0.11(0.02-0.79)	0.11(0.02-0.79)
Carrel 2016	-	-	-
Karaskov 2016	0.81(0.55-1.20)	0.71(0.47-1.08)	0.10(0.03-0.30)
Mazine 2016	0.25(0.12-0.52)	0.07(0.02-0.28)	0.18(0.07-0.42)
Popelová 2016	-	-	-
Zimmermann 2016	-	-	-
Bouhout 2017	-	-	-
Pardo González 2017	-	-	-
Martin 2017	0.06(0.02-0.20)	-	-
Ratschiller 2017	-	-	-
Schneider 2017	-	0.03(0.00-0.48)*	0.24(0.09-0.64)
Skoglund 2017	-	-	-
Tran 2017	-	-	-
Pooled estimate (95%CI)	0.29(0.21-0.41)	0.21(0.13-0.35)	0.17(0.13-0.22)
Heterogeneity	I^2=61.2%(p<0.001)	I^2=64.3%(p<0.001)	I^2=0.0%(p=0.977)
Number of studies	31	25	24

	Thromboembolism (%/yr)	Valve thrombosis (%/yr)	Bleeding (%/yr)	Pacemaker implantation (%/yr)
	-	-	-	0.33(0.11-1.04)
	-	-	-	-
	0.23(0.11-0.48)	0.03(0.00-0.23)	0.10(0.03-0.30)	-
	0.18(0.07-0.42)	0.02(0.00-0.28)*	0.02(0.00-0.28)*	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	0.12(0.03-0.48)	0.03(0.00-0.48)*	0.03(0.00-0.48)*	-
	-	-	-	-
	-	-	-	-
	0.16(0.12-0.22)	0.06(0.03-0.12)	0.09(0.02-0.36)	0.30(0.20-0.44)
	I^2=0.0%(p=0.793)	I^2=0.0%(p=0.840)	I^2=87.4%(p<0.001)	I^2=0.0%(p=0.712)
	21	12	15	12

Supplement 3. (continued)

PEDIATRIC			
	Early mortality (%)	**Late mortality (%/yr)**	-Cardiac (%/yr)
Solowiejczyk 2000	-	-	-
Pigula 2001	1.47(0.09-23.04)*	1.04(0.07-16.32)*	1.04(0.07-16.32)*
Lupinetti 2003	3.85(1.27-11.67)	0.19(0.01-3.03)*	0.19(0.01-3.03)*
Hazekamp 2005	5.66(1.89-16.99)	1.03(0.33-3.17)	1.03(0.33-3.17)
Kalavrouziotis 2006	1.43(0.09-22.39)*	0.70(0.10-4.91)	0.70(0.10-4.91)
Kadner 2008	9.62(4.18-22.12)	1.61(0.52-4.95)	0.27(0.02-4.28)*
El Behery 2009	4.88(1.26-18.85)	0.20(0.01-3.24)*	-
Goldberg 2009	15.63(6.98-34.95)	0.99(0.06-15.60)*	-
Alsoufi 2010	3.08(1.49-6.39)	0.17(0.05-0.52)	-
Valeske 2010	2.04(0.52-8.05)	0.10(0.01-1.63)*	-
Charitos 2012	3.42(1.80-6.50)	-	-
Oda 2012	5.26(1.37-20.28)	0.21(0.01-3.28)*	0.21(0.01-3.28)*
Talwar 2012	2.78(0.40-19.19)	1.40(0.53-3.71)	1.40(0.53-3.71)
Goda 2013	-	-	-
Khan 2013	2.94(0.75-11.52)	0.44(0.11-1.75)	-
Ruzmetov 2013	-	-	-
Tanny 2013	6.00(2.76-13.03)	0.55(0.21-1.46)	0.41(0.13-1.27)
Andreas 2014	-	-	-
Kallio 2014	9.80(4.26-22.54)	0.51(0.17-1.58)	0.51(0.17-1.58)
Lehoux 2014	-	-	-
Lo Rito 2014	2.86(1.09-7.51)	0.13(0.03-0.53)	0.13(0.03-0.53)
Luciani 2014	3.28(1.78-6.03)	0.47(0.27-0.82)	0.23(0.11-0.52)
Ruzmetov 2014	-	-	-
Lukyanov 2015	1.75(0.44-6.93)	-	-
Nelson 2015	4.17(2.27-7.64)	0.66(0.41-1.06)	-
Piccardo 2009	1.82(0.26-12.68)	0.66(0.17-2.63)	0.33(0.05-2.34)
Tierney 2005	-	-	-
Ruzmetov 2015	1.39(0.20-9.73)	0.51(0.19-1.34)	-
Baird 2016	-	0.23(0.01-3.61)*	0.23(0.01-3.61)*
Brown 2016	0.87(0.12-6.12)	0.45(0.17-1.19)	0.22(0.06-0.89)
Pardo González 2017	4.76(0.70-32.25)	-	-
Tran 2017	0.67(0.04-10.56)*	0.13(0.01-2.05)*	0.13(0.01-2.05)*
Pooled estimate (95%CI)	4.19(3.21-5.46)	0.54(0.42-0.70)	0.41(0.27-0.63)
Heterogeneity	I^2=27.9%(p=0.102)	I^2=7.3%(p=0.363)	I^2=14.0%(p=0.296)
Number of studies	24	22	15

	-Valve-related (%/yr)	- SUD (%/yr)	**Reintervention (%/yr)**	-Autograft (%/yr)	-Allograft (%/yr)
	-	-	1.25(0.18-8.77)	0.63(0.04-9.91)*	1.25(0.18-8.77)
	1.04(0.07-16.32)*	1.04(0.07-16.32)*	4.14(1.07-16.09)	1.04(0.07-16.32)*	1.04(0.07-16.32)*
	0.19(0.01-3.03)*	0.19(0.01-3.03)*	1.90(0.80-4.53)	1.52(0.57-4.02)	0.38(0.05-2.69)
	1.03(0.33-3.17)	0.34(0.05-2.43)	2.74(1.39-5.44)	1.72(0.72-4.09)	1.03(0.33-3.17)
	0.70(0.10-4.91)	0.70(0.10-4.91)	1.39(0.35-5.52)	0.35(0.02-5.54)*	1.39(0.35-5.52)
	0.27(0.02-4.28)*	0.27(0.02-4.28)*	4.30(2.18-8.46)	0.54(0.08-3.79)	3.76(1.82-7.78)
	-	-	1.63(0.62-4.30)	0.20(0.01-3.24)*	1.63(0.62-4.30)
	-	-	-	-	-
	-	-	4.86(3.95-5.97)	1.64(1.14-2.35)	1.64(1.14-2.35)
	-	-	0.20(0.03-1.45)	0.20(0.03-1.45)	0.10(0.01-1.63)*
	-	-	3.63(2.81-4.69)	0.91(0.54-1.53)	2.72(2.02-3.67)
	0.21(0.01-3.28)*	0.21(0.01-3.28)*	1.23(0.40-3.80)	0.21(0.01-3.28)*	1.23(0.40-3.80)
	0.70(0.18-2.79)	0.18(0.01-2.80)*	2.46(1.18-5.11)	1.75(0.74-4.18)	0.70(0.18-2.79)
	-	-	-	1.03(0.34-3.18)	-
	-	-	4.17(2.69-6.48)	0.66(0.21-2.03)	3.51(2.17-5.68)
	-	-	5.24(3.82-7.21)	-	2.33(1.44-3.78)
	0.27(0.07-1.09)	0.14(0.02-0.97)	3.70(2.55-5.36)	1.23(0.64-2.36)	2.74(1.78-4.22)
	-	-	-	-	-
	0.17(0.02-1.21)	0.09(0.01-1.36)*	3.58(2.35-5.45)	0.68(0.26-1.81)	2.05(1.17-3.58)
	-	-	2.19(0.83-5.78)	0.27(0.02-4.36)*	1.10(0.28-4.35)
	0.13(0.03-0.53)	0.03(0.00-0.53)*	1.72(1.17-2.52)	0.73(0.40-1.31)	0.99(0.60-1.64)
	-	-	2.93(2.34-3.66)	1.44(1.05-1.99)	1.44(1.05-1.99)
	-	-	-	3.37(2.31-4.91)	-
	-	-	-	-	-
	-	-	7.75(6.78-8.86)	2.69(2.13-3.39)	2.22(1.72-2.87)
	0.33(0.05-2.34)	0.17(0.01-2.64)*	1.65(0.69-3.94)	0.66(0.17-2.63)	0.99(0.32-3.06)
	-	-	-	-	2.22(0.72-6.79)
	-	-	-	2.78(1.84-4.19)	2.27(1.44-3.59)
	0.23(0.01-3.61)*	0.23(0.01-3.61)*	-	0.91(0.23-3.60)	4.98(2.80-8.86)
	0.22(0.06-0.89)	0.11(0.02-0.79)	3.57(2.54-5.01)	1.45(0.84-2.49)	1.90(1.18-3.03)
	-	-	-	-	-
	0.13(0.01-2.05)*	0.13(0.01-2.05)*	3.08(1.76-5.37)	0.77(0.25-2.37)	1.79(0.86-3.74)
	0.36(0.22-0.57)	0.20(0.11-0.39)	3.04(2.39-3.87)	1.28(0.99-1.66)	1.97(1.64-2.36)
	I^2=0.0%(p=0.736)	I^2=0.0%(p=0.951)	I^2=85.5%(p<0.001)	I^2=66.1%(p<0.001)	I^2=52.1%(p=0.001)
	14	14	23	26	26

Supplement 3. (continued)

PEDIATRIC (continued)			
	Endocarditis (%/yr)	-Autograft (%/yr)	-Allograft (%/yr)
Solowiejczyk 2000	-	-	-
Pigula 2001	-	-	-
Lupinetti 2003	0.19(0.01-3.03)*	-	-
Hazekamp 2005	-	-	-
Kalavrouziotis 2006	-	-	-
Kadner 2008	0.27(0.02-4.28)*	0.27(0.02-4.28)*	0.27(0.02-4.28)*
El Behery 2009	-	-	-
Goldberg 2009	-	-	-
Alsoufi 2010	-	-	-
Valeske 2010	-	-	-
Charitos 2012	-	-	-
Oda 2012	-	-	-
Talwar 2012	0.70(0.18-2.79)	-	-
Goda 2013	-	-	-
Khan 2013	-	-	-
Ruzmetov 2013	-	-	-
Tanny 2013	-	-	-
Andreas 2014	-	-	-
Kallio 2014	-	-	-
Lehoux 2014	-	-	-
Lo Rito 2014	-	-	-
Luciani 2014	0.20(0.08-0.47)	-	-
Ruzmetov 2014	-	-	-
Lukyanov 2015	-	-	-
Nelson 2015	-	-	-
Piccardo 2009	0.33(0.05-2.34)	0.17(0.01-2.64)*	0.33(0.05-2.34)
Tierney 2005	-	-	-
Ruzmetov 2015	-	-	-
Baird 2016	-	-	-
Brown 2016	0.22(0.06-0.89)	0.11(0.02-0.79)	0.11(0.02-0.79)
Pardo González 2017	-	-	-
Tran 2017	-	-	-
Pooled estimate (95%CI)	0.27(0.15-0.48)	0.15(0.04-0.61)	0.21(0.06-0.71)
Heterogeneity	I^2=0.0%(p=0.770)	I^2=0.0%(p=0.877)	I^2=0.0%(p=0.727)
Number of studies	6	3	3

	Thromboembolism (%/yr)	Valve thrombosis (%/yr)	Bleeding (%/yr)	Pacemaker implantation (%/yr)
	-	-	-	-
	-	-	-	2.07(0.30-14.41)
	-	-	0.19(0.01-3.03)*	-
	-	-	-	-
	-	-	-	-
	0.27(0.02-4.28)*	-	-	0.27(0.02-4.28)*
	-	-	-	-
	-	-	-	-
	-	-	-	-
	0.10(0.01-1.63)*	0.10(0.01-1.63)*	-	-
	-	-	-	-
	-	-	-	-
	0.18(0.01-2.80)*	0.18(0.01-2.80)*	0.18(0.01-2.80)*	-
	-	-	-	-
	-	-	-	0.22(0.03-1.55)
	-	-	-	0.29(0.07-1.16)
	-	-	-	0.55(0.21-1.46)
	-	-	-	0.29(0.07-1.14)
	-	-	-	-
	-	-	-	-
	-	-	-	-
	0.08(0.02-0.31)	-	0.02(0.00-0.31)*	0.20(0.08-0.47)
	-	-	-	-
	-	-	-	-
	-	-	-	-
	0.17(0.01-2.64)*	0.17(0.01-2.64)*	0.17(0.01-2.64)*	0.17(0.01-2.64)*
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	0.33(0.11-1.04)
	-	-	-	-
	-	-	-	-
	0.11(0.04-0.30)	0.14(0.03-0.71)	0.10(0.03-0.41)	0.33(0.21-0.51)
	I^2=0.0%(p=0.935)	I^2=0.0%(p=0.957)	I^2=0.0%(p=0.609)	I^2=0.0%(p=0.607)
	5	3	4	9

Supplement 3. (continued)

ADULT			
	Early mortality (%)	**Late mortality (%/yr)**	-Cardiac (%/yr)
Knott-Craig 2000	-	1.66(0.75-3.66)	-
Xie 2001	4.08(1.05-15.86)	0.34(0.02-5.41)*	0.34(0.02-5.41)*
Schmid 2002	0.98(0.06-15.46)*	0.64(0.09-4.55)	0.32(0.02-5.13)*
Svensson 2002	3.90(1.28-11.81)	-	-
Fullerton 2003	6.82(2.29-20.33)	0.36(0.02-5.70)*	0.36(0.02-5.70)*
Matalanis 2004	3.23(0.47-22.18)	2.71(0.69-10.62)	-
Chotivatanapong 2005	13.33(5.35-33.20)	1.20(0.08-18.85)*	1.20(0.08-18.85)*
Settepani 2005	0.49(0.03-7.71)*	0.32(0.08-1.29)	0.16(0.02-1.15)
Pitsis 2006	4.76(0.70-32.25)	0.60(0.04-9.44)*	0.60(0.04-9.44)*
Klieverik 2007	3.19(1.05-9.72)	0.12(0.02-0.87)	0.12(0.02-0.87)
Frigiola 2008	0.45(0.03-7.22)*	0.13(0.02-0.94)	0.13(0.02-0.94)
Al Rashidi 2010	1.92(0.12-29.93)*	0.66(0.04-10.45)*	0.66(0.04-10.45)*
El-Hamamsy 2010	0.93(0.13-6.51)	0.27(0.09-0.84)	0.09(0.01-0.64)
Brown 2011	0.87(0.22-3.46)	0.67(0.38-1.18)	0.17(0.05-0.52)
Ryan 2011	1.88(0.61-5.75)	0.58(0.24-1.39)	0.12(0.02-0.83)
Brinkman 2012	-	-	-
Skillington 2013	0.32(0.05-2.28)	0.17(0.07-0.41)	0.02(0.00-0.27)*
Stelzer 2013	1.13(0.51-2.51)	-	-
Andreas 2014	-	-	-
David 2014	0.47(0.07-3.33)	0.31(0.16-0.59)	0.10(0.03-0.32)
Le Guillou 2014	10.71(3.68-31.21)	3.35(1.52-7.35)	0.28(0.02-4.44)*
Escarain 2015	2.66(1.28-5.53)	0.71(0.42-1.20)	0.30(0.14-0.68)
Jacobsen 2015	1.39(0.09-21.78)*	1.26(0.18-8.85)	1.26(0.18-8.85)
Mastrobuoni 2015	2.29(1.10-4.76)	0.71(0.47-1.09)	0.10(0.03-0.32)
Sievers 2015	1.07(0.68-1.67)	0.68(0.56-0.83)	-
Franke 2015	0.74(0.10-5.18)	0.12(0.01-1.96)*	0.12(0.01-1.96)*
Carrel 2016	2.27(0.15-35.20)*	-	-
Karaskov 2016	2.97(1.97-4.48)	0.58(0.37-0.93)	0.45(0.27-0.77)
Mazine 2016	0.48(0.07-3.40)	0.42(0.24-0.75)	0.11(0.03-0.33)
Popelová 2016	1.52(0.10-23.72)*	-	-
Bouhout 2017	1.00(0.25-3.97)	-	-
Pardo González 2017	0.58(0.04-9.22)*	-	-
Martin 2017	1.29(0.49-3.42)	0.60(0.41-0.87)	0.34(0.21-0.56)
Skoglund 2017	0.65(0.04-10.29)*	0.08(0.01-0.58)	-
Pooled estimate (95%CI)	2.01(1.44-2.82)	0.59(0.46-0.76)	0.24(0.17-0.33)
Heterogeneity	I^2=53.6%(p<0.001)	I^2=57.3%(p<0.001)	I^2=17.5%(p=0.227)
Number of studies	31	26	22

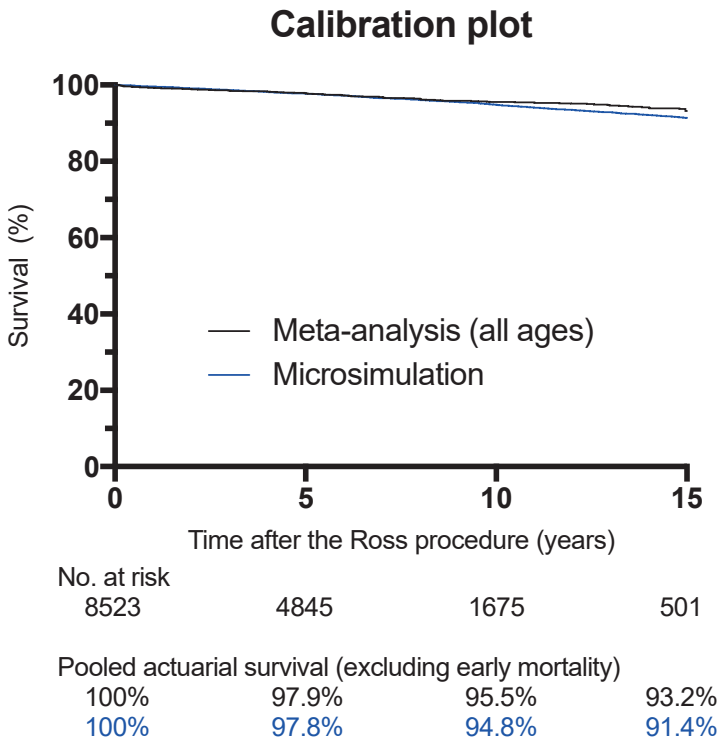
	-Valve-related (%/yr)	- SUD (%/yr)	**Reintervention (%/yr)**	-Autograft (%/yr)	-Allograft (%/yr)
	0.83(0.27-2.55)	-	2.21(1.11-4.38)	0.83(0.27-2.55)	1.38(0.58-3.29)
	0.34(0.02-5.41)*	0.34(0.02-5.41)*	0.68(0.10-4.80)	0.34(0.02-5.41)*	0.68(0.10-4.80)
	0.32(0.02-5.13)*	0.32(0.02-5.13)*	0.64(0.09-4.55)	0.32(0.02-5.13)*	0.64(0.09-4.55)
	-	-	-	-	-
	0.36(0.02-5.70)*	0.36(0.02-5.70)*	0.72(0.10-5.05)	0.72(0.10-5.05)	0.36(0.02-5.70)*
	0.68(0.04-10.72)*	0.68(0.04-10.72)*	2.71(0.69-10.62)	1.35(0.19-9.48)	0.68(0.04-10.72)*
	1.20(0.08-18.85)*	1.20(0.08-18.85)*	-	-	-
	0.16(0.02-1.15)	0.08(0.01-1.29)*	0.97(0.44-2.15)	0.81(0.34-1.94)	0.16(0.02-1.15)
	0.60(0.04-9.44)*	0.60(0.04-9.44)*	2.38(0.61-9.36)	2.38(0.61-9.36)	0.60(0.04-9.44)*
	0.06(0.00-0.98)*	0.06(0.00-0.98)*	-	-	-
	0.13(0.02-0.94)	0.13(0.02-0.94)	-	1.06(0.53-2.12)	0.53(0.20-1.41)
	0.66(0.04-10.45)*	0.66(0.04-10.45)*	1.32(0.19-9.24)	1.32(0.19-9.24)	-
	0.09(0.01-0.64)	0.09(0.01-0.64)	0.73(0.36-1.45)	0.09(0.01-0.64)	0.64(0.30-1.33)
	-	0.28(0.12-0.67)	1.40(0.95-2.07)	1.12(0.73-1.74)	0.28(0.12-0.67)
	0.06(0.00-0.93)*	0.06(0.00-0.93)*	1.75(1.06-2.88)	-	0.12(0.02-0.83)
	-	-	1.05(0.66-1.69)	1.05(0.66-1.69)	-
	0.02(0.00-0.27)*	0.02(0.00-0.27)*	0.51(0.31-0.85)	0.38(0.21-0.68)	0.17(0.07-0.41)
	-	-	-	-	-
	-	-	-	-	-
	0.10(0.03-0.32)	0.10(0.03-0.32)	0.85(0.58-1.26)	0.51(0.31-0.85)	0.31(0.16-0.59)
	0.28(0.02-4.44)*	0.28(0.02-4.44)*	2.23(0.85-5.88)	1.12(0.28-4.43)	0.56(0.08-3.94)
	0.30(0.14-0.68)	0.03(0.00-0.41)*	0.91(0.58-1.45)	0.66(0.38-1.13)	0.20(0.08-0.54)
	1.26(0.18-8.85)	1.26(0.18-8.85)	5.05(1.94-13.12)	3.79(1.25-11.49)	0.63(0.04-10.01)*
	0.10(0.03-0.32)	0.03(0.00-0.24)	1.33(0.97-1.81)	1.23(0.89-1.70)	0.37(0.21-0.68)
	-	-	1.19(1.02-1.37)	0.72(0.59-0.87)	0.62(0.50-0.76)
	0.12(0.01-1.96)*	0.12(0.01-1.96)*	0.98(0.37-2.61)	0.74(0.24-2.28)	0.25(0.03-1.74)
	-	-	0.91(0.13-6.40)	0.91(0.13-6.40)	0.45(0.03-7.22)*
	0.36(0.20-0.64)	0.26(0.13-0.52)	1.85(1.43-2.39)	1.20(0.87-1.65)	0.91(0.63-1.31)
	0.11(0.03-0.33)	0.07(0.02-0.28)	0.74(0.48-1.14)	0.49(0.29-0.83)	0.25(0.12-0.52)
	-	-	-	-	-
	-	-	-	-	-
	-	-	-	-	-
	0.09(0.03-0.23)	0.02(0.00-0.15)	1.20(0.92-1.55)	0.68(0.48-0.97)	0.45(0.29-0.69)
	-	-	-	-	0.82(0.44-1.51)
	0.21(0.14-0.32)	0.16(0.10-0.25)	1.20(1.01-1.42)	0.83(0.68-1.01)	0.47(0.37-0.59)
	I^2=26.8%(p=0.117)	I^2=20.7%(p=0.185)	I^2=57.0%(p<0.001)	I^2=52.2%(p=0.002)	I^2=45.5%(p=0.009)
	23	23	24	24	24

Supplement 3. (continued)

ADULT (continued)			
	Endocarditis (%/yr)	-Autograft (%/yr)	-Allograft (%/yr)
Knott-Craig 2000	0.28(0.04-1.95)	-	-
Xie 2001	-	-	-
Schmid 2002	-	-	-
Svensson 2002	-	-	-
Fullerton 2003	-	-	-
Matalanis 2004	0.68(0.04-10.72)*	-	-
Chotivatanapong 2005	-	-	-
Settepani 2005	0.32(0.08-1.29)	0.16(0.02-1.15)	0.16(0.02-1.15)
Pitsis 2006	1.19(0.17-8.35)	1.19(0.17-8.35)	0.60(0.04-9.44)*
Klieverik 2007	-	-	-
Frigiola 2008	-	-	-
Al Rashidi 2010	-	-	-
El-Hamamsy 2010	0.18(0.05-0.73)	0.05(0.00-0.73)*	0.18(0.05-0.73)
Brown 2011	0.17(0.05-0.52)	0.17(0.05-0.52)	-
Ryan 2011	-	-	-
Brinkman 2012	-	-	-
Skillington 2013	0.14(0.05-0.37)	0.07(0.02-0.27)	0.10(0.03-0.32)
Stelzer 2013	-	-	-
Andreas 2014	-	-	-
David 2014	0.14(0.05-0.36)	0.02(0.00-0.27)*	0.14(0.05-0.36)
Le Guillou 2014	1.12(0.28-4.43)	0.56(0.08-3.94)	0.56(0.08-3.94)
Escarain 2015	0.15(0.05-0.47)	0.10(0.03-0.41)	0.10(0.03-0.41)
Jacobsen 2015	-	-	-
Mastrobuoni 2015	0.10(0.03-0.32)	0.07(0.02-0.27)	0.07(0.02-0.27)
Sievers 2015	-	-	-
Franke 2015	0.74(0.24-2.28)	0.74(0.24-2.28)	0.12(0.01-1.96)*
Carrel 2016	-	-	-
Karaskov 2016	0.81(0.55-1.20)	0.71(0.47-1.08)	0.10(0.03-0.30)
Mazine 2016	0.25(0.12-0.52)	0.07(0.02-0.28)	0.18(0.07-0.42)
Popelová 2016	-	-	-
Bouhout 2017	-	-	-
Pardo González 2017	-	-	-
Martin 2017	0.06(0.02-0.20)	-	-
Skoglund 2017	-	-	-
Pooled estimate (95%CI)	0.27(0.16-0.45)	0.18(0.09-0.39)	0.14(0.09-0.21)
Heterogeneity	I^2=71.8%(p<0.001)	I^2=74.0%(p<0.001)	I^2=0.0%(p=0.867)
Number of studies	15	12	11

	Thromboembolism (%/yr)	Valve thrombosis (%/yr)	Bleeding (%/yr)	Pacemaker implantation (%/yr)
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	0.36(0.02-5.70)*
	0.68(0.04-10.72)*	-	-	1.35(0.19-9.48)
	-	-	11.99(5.27-27.29)	-
	-	-	-	-
	-	-	-	-
	-	0.06(0.00-0.98)*	0.06(0.00-0.98)*	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	0.06(0.01-0.40)	0.03(0.00-0.45)*	0.03(0.00-0.45)*	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	0.06(0.01-0.40)
	0.14(0.05-0.36)	-	0.02(0.00-0.27)*	-
	-	-	-	-
	0.03(0.00-0.41)*	0.03(0.00-0.41)*	0.03(0.00-0.41)*	-
	-	-	-	-
	-	0.02(0.00-0.27)*	0.14(0.05-0.36)	-
	-	-	-	-
	0.12(0.01-1.96)*	0.12(0.01-1.96)*	0.12(0.01-1.96)*	0.12(0.01-1.96)*
	-	-	-	-
	0.23(0.11-0.48)	0.03(0.00-0.23)	0.10(0.03-0.30)	-
	0.18(0.07-0.42)	0.02(0.00-0.28)*	0.02(0.00-0.28)*	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
	0.17(0.11-0.27)	0.03(0.01-0.09)	0.10(0.01-0.67)	0.25(0.05-1.17)
	I^2=0.0%(p=0.565)	I^2=0.0%(p=0.958)	I^2=91.6%(p<0.001)	I^2=44.5%(p=0.144)
	7	7	9	4

Supplement 4. Calibration plot of the microsimulation model. Microsimulation-based actuarial survival is plotted against observed pooled Kaplan-Meier survival rates in the all ages group (age- and sex-matched), excluding early mortality.



Supplement 5. Least squares regression of modeled survival vs. observed survival for estimation of excess mortality not directly related to valve-related events.

Hazard ratio[1]	Sum of squared residuals[2]		
	All ages	**Pediatric**	**Adult**
1.00	**359.3**	**173.8**	**7063.2**
1.05	417.2	208.4	8085.1
1.10	822.8	204.7	8605.5
1.20	1280.9	259.8	12633.2

Bold print indicates the selected model.

[1]Hazard ratio of background mortality + excess mortality relative to background mortality.

[2]Sum of squared residuals between microsimulation-based survival and survival observed in our meta-analysis of Kaplan-Meier freedom from all-cause mortality.

Supplement 6. Univariable random effects meta-regression of natural log-transformed outcome measures.

	Early mortality		Late mortality	
	β (95%CI)	p-value	β (95%CI)	p-value
Study design (prospective/RCT)	-0.36(-0.86 - 0.14)	0.155	0.03(-0.35 - 0.41)	0.878
Median year of surgery	-0.04(-0.09 - 0.01)	0.105	0.03(-0.02 - 0.07)	0.303
Mean follow-up (/year increase)	**-0.10(-0.15 - -0.04)**	**<0.001**	**-0.05(-0.09 - -0.01)**	**0.012**
Mean age at surgery (/year increase)	**-0.02(-0.03 - -0.01)**	**0.003**	**0.01(0.00 - 0.02)**	**0.039**
Male	-1.47(-4.38 - 1.44)	0.323	0.08(-2.17 - 2.34)	0.942
Urgent	2.23(-0.62 - 5.08)	0.125	**3.71(1.77 - 5.65)**	**<0.001**
Preoperative NYHA/Ross class				
I/II	**-1.59(-3.03 - -0.14)**	**0.031**	-1.35(-2.73 - 0.02)	0.053
III/IV	**1.59(0.15 - 3.03)**	**0.031**	1.36(-0.02 - 2.74)	0.053
Hemodynamics				
Aortic stenosis	-0.70(-1.86 - 0.47)	0.243	0.40(-0.37 - 1.18)	0.308
Aortic regurgitation	0.06(-1.46 - 1.58)	0.940	-0.35(-1.43 - 0.73)	0.527
Combined	0.60(-0.44 - 1.63)	0.258	0.00(-0.70 - 0.69)	0.998
Bicuspid AV	-0.94(-2.23 - 0.35)	0.155	-0.24(-1.17 - 0.69)	0.611
Etiology				
Congenital	0.08(-0.49 - 0.65)	0.788	-0.11(-0.62 - 0.40)	0.668
Degenerative/calcification	**-3.10(-5.94 - -0.26)**	**0.033**	0.27(-1.55 - 2.09)	0.771
Rheumatic	0.58(-1.04 - 2.19)	0.485	0.46(-0.53 - 1.45)	0.362
Endocarditis	**1.50(0.52 - 2.48)**	**0.003**	**1.75(0.95 - 2.55)**	**<0.001**
Other/unknown	-0.42(-2.08 - 1.24)	0.618	-0.07(-1.09 - 0.96)	0.895
Previous cardiac intervention	0.44(-0.20 - 1.08)	0.180	-0.22(-0.70 - 0.26)	0.372
AV intervention	0.40(-0.37 - 1.17)	0.309	0.07(-0.57 - 0.71)	0.830
Percutaneous	0.17(-1.22 - 1.56)	0.815	0.62(-0.47 - 1.72)	0.266
AV surgery	0.59(-1.00 - 2.18)	0.466	-0.04(-1.55 - 1.46)	0.955
AVR	-3.02(-9.76 - 3.72)	0.380	0.25(-6.87 - 7.37)	0.946
Technique				
Total root replacement	1.21(-0.14 - 2.56)	0.078	0.59(-0.34 - 1.52)	0.216
Subcoronary	-0.77(-4.39 - 2.85)	0.678	-3.40(-7.09 - 0.28)	0.070
Inclusion cylinder	-1.19(-3.21 - 0.83)	0.247	0.03(-1.59 - 1.64)	0.973
RVOT conduit				
Allograft	**-1.18(-2.02 - -0.35)**	**0.005**	-0.59(-1.42 - 0.24)	0.167
Bioprosthesis	0.65(-0.44 - 1.74)	0.240	0.56(-0.33 - 1.44)	0.216
Concomitant procedures	-0.26(-2.42 - 1.89)	0.810	0.08(-1.58 - 1.73)	0.929
CABG	0.05(-2.85 - 2.95)	0.973	-1.67(-4.60 - 1.26)	0.264
Ascending aortic surgery	**-3.78(-5.87 - -1.68)**	**<0.001**	-2.06(-4.44 - 0.32)	0.090
Annular enlargement procedure	0.99(-0.66 - 2.64)	0.239	-0.41(-2.03 - 1.21)	0.617
Other valve repair or replacement	**4.99(0.46 - 9.52)**	**0.031**	-1.65(-6.16 - 2.86)	0.473
Other	1.49(-1.53 - 4.50)	0.334	0.54(-1.92 - 3.01)	0.667

*Could not be assessed due to insufficient sample size. CI=confidence interval. RCT=randomized controlled trial. NYHA=New York Heart Association. AV=aortic valve. AVR=aortic valve replacement. RVOT=right ventricular outflow tract. CABG=coronary artery bypass grafting

Reintervention		Endocarditis		Bleeding	
β (95%CI)	p-value	β (95%CI)	p-value	β (95%CI)	p-value
-0.38(-0.95 - 0.20)	0.197	-0.50(-1.31 - 0.31)	0.225	-1.59(-4.42 - 1.24)	0.270
0.02(-0.06 - 0.09)	0.636	0.06(-0.03 - 0.16)	0.179	-0.10(-0.44 - 0.24)	0.570
-0.04(-0.10 - 0.02)	0.242	**-0.17(-0.25 - -0.09)**	**<0.001**	**-0.39(-0.62 - -0.15)**	**0.001**
-0.03(-0.04 - -0.02)	**<0.001**	0.00(-0.03 - 0.03)	0.814	0.00(-0.10 - 0.11)	0.940
-1.00(-4.58 - 2.58)	0.585	2.51(-3.89 - 8.90)	0.442	*	
1.06(-2.26 - 4.37)	0.532	3.63(-0.26 - 7.52)	0.067	*	
-0.55(-1.55 - 0.45)	0.283	-1.72(-3.59 - 0.15)	0.071	-6.55(-13.90 - 0.81)	0.081
0.57(-0.45 - 1.58)	0.272	1.76(-0.09 - 3.61)	0.063	6.87(-0.17 - 13.90)	0.056
-1.02(-2.18 - 0.13)	0.082	-1.08(-3.29 - 1.13)	0.339	0.75(-2.60 - 4.10)	0.660
-0.92(-2.48 - 0.64)	0.248	-1.79(-4.87 - 1.28)	0.253	-2.35(-9.80 - 5.11)	0.537
1.39(0.31 - 2.46)	**0.011**	1.30(-0.83 - 3.43)	0.231	2.41(-2.53 - 7.34)	0.339
-0.01(-1.82 - 1.80)	0.992	**-2.17(-3.63 - -0.70)**	**0.004**	-2.42(-6.87 - 2.03)	0.286
0.29(-1.09 - 1.66)	0.683	-0.22(-1.60 - 1.16)	0.754	-0.23(-2.27 - 1.81)	0.822
-1.05(-6.03 - 3.93)	0.681	-1.08(-6.30 - 4.14)	0.685	6.38(-4.26 - 17.02)	0.240
0.50(-1.73 - 2.72)	0.661	1.99(-0.36 - 4.34)	0.096	1.61(-14.60 - 17.83)	0.845
0.21(-1.45 - 1.88)	0.800	1.87(-0.13 - 3.88)	0.067	**6.26(5.00 - 7.51)**	**<0.001**
-1.48(-5.13 - 2.16)	0.425	-0.14(-5.09 - 4.80)	0.955	-1.49(-4.79 - 1.81)	0.377
0.76(0.16 - 1.37)	**0.014**	1.22(-0.97 - 3.40)	0.275	0.92(-1.80 - 3.65)	0.506
1.53(0.77 - 2.29)	**<0.001**	-0.30(-2.80 - 2.19)	0.812	-1.64(-5.42 - 2.14)	0.394
1.43(0.19 - 2.67)	**0.024**	-1.59(-6.28 - 3.10)	0.507	-4.14(-12.42 - 4.14)	0.327
1.77(-0.06 - 3.59)	0.057	-1.75(-5.84 - 2.33)	0.400	-1.47(-7.66 - 4.72)	0.642
-0.81(-10.40 - 8.79)	0.869	-3.82(-19.14 - 11.49)	0.625	-10.18(-32.97 - 12.61)	0.381
0.90(-0.49 - 2.29)	0.205	**2.34(0.65 - 4.03)**	**0.007**	3.57(-3.42 - 10.55)	0.317
-0.82(-5.49 - 3.85)	0.729	-2.76(-9.19 - 3.67)	0.399	-5.12(-33.98 - 23.74)	0.728
-0.59(-3.11 - 1.93)	0.647	**-3.64(-6.59 - -0.68)**	**0.016**	-0.61(-13.18 - 11.96)	0.924
-0.18(-1.58 - 1.23)	0.804	-1.23(-3.08 - 0.62)	0.194	*	
0.18(-1.24 - 1.61)	0.801	**1.55(0.56 - 2.54)**	**0.002**	*	
1.43(-1.07 - 3.92)	0.263	-2.60(-6.68 - 1.48)	0.212	-4.39(-10.92 - 2.14)	0.188
0.78(-2.79 - 4.34)	0.670	-7.92(-28.65 - 12.80)	0.454	-7.35(-82.81 - 68.12)	0.849
-2.71(-5.93 - 0.52)	0.100	-2.29(-6.52 - 1.93)	0.288	-7.66(-27.55 - 12.23)	0.450
3.03(1.40 - 4.66)	**<0.001**	-1.10(-7.87 - 5.66)	0.750	-5.17(-22.27 - 11.94)	0.554
5.42(-1.81 - 12.65)	0.142	-13.69(-33.33 - 5.96)	0.172	**28.30(22.63 - 33.97)**	**<0.001**
2.52(-0.89 - 5.93)	0.147	2.18(-6.21 - 10.58)	0.610	-5.71(-34.03 - 22.60)	0.693

Supplement 7. References of the included studies.[1-99]

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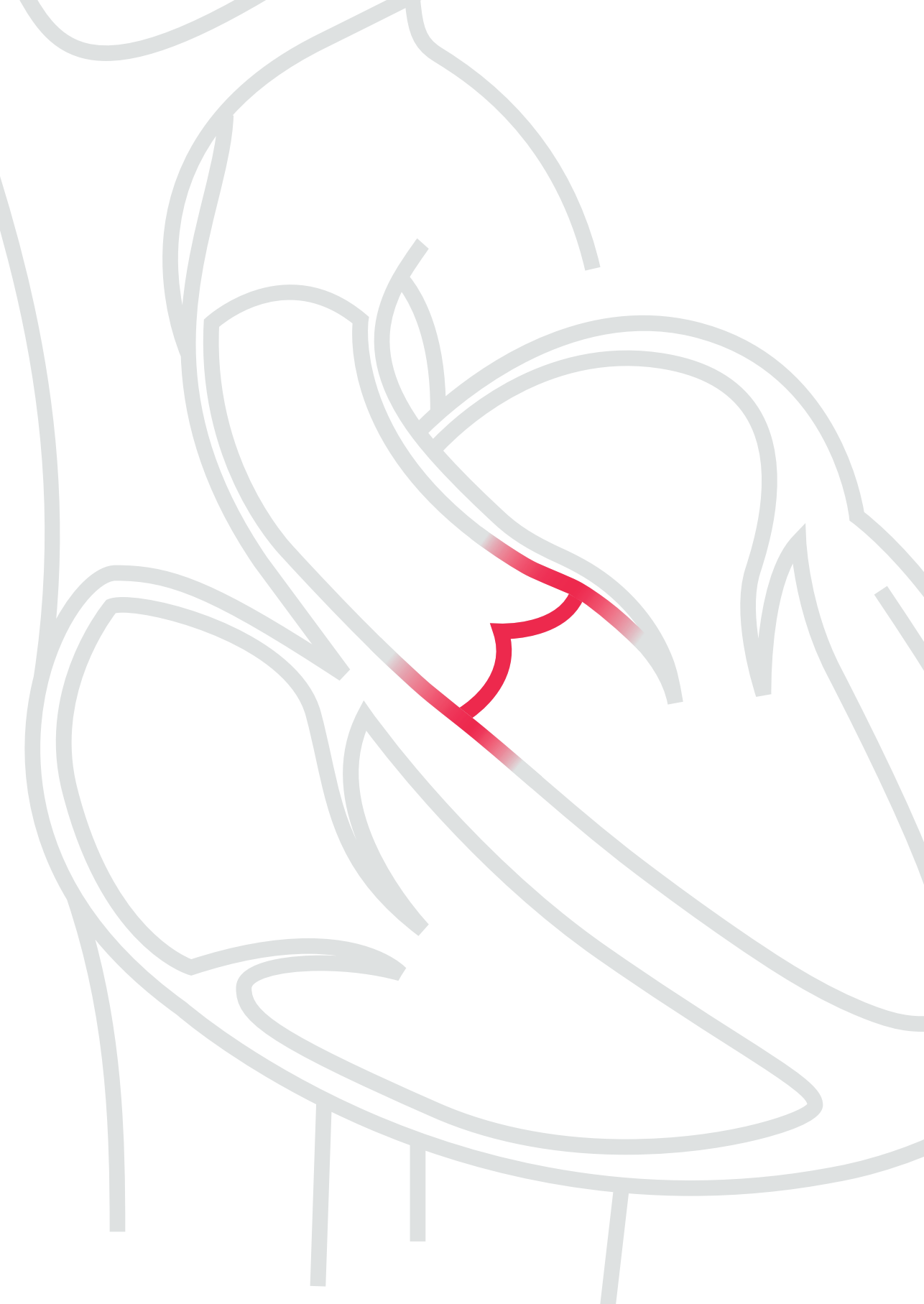

6

Bioprosthetic aortic valve replacement in nonelderly adults: a systematic review, meta-analysis, and microsimulation

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ABSTRACT

Background

To support decision-making in aortic valve replacement in nonelderly adults, we aim to provide a comprehensive overview of reported outcome after bioprosthetic aortic valve replacement and to translate this to age-specific patient outcome estimates.

Methods

A systematic review was conducted for papers reporting clinical outcome after aortic valve replacement with currently available bioprostheses in patients with a mean age <55 years, published between January 1, 2000, and January 9, 2016. Pooled reported event rates and time-to-event data were pooled and entered into a microsimulation model to calculate life expectancy and lifetime event risk for the ages of 25, 35, 45, and 55 years at surgery.

Results

Nineteen publications were included, encompassing a total of 2686 patients with 21 117 patient-years of follow-up (pooled mean follow-up: 7.9±4.2 years). Pooled mean age at surgery was 50.7±11.0 years. Pooled early mortality risk was 3.30% (95% CI, 2.39-4.55), late mortality rate was 2.39%/y (95% CI, 1.13-2.94), reintervention 1.82%/y (95% CI, 1.31-2.52), structural valve deterioration 1.59%/y (95% CI, 1.21-2.10), thromboembolism 0.53%/y (95% CI, 0.42-0.67), bleeding 0.22%/y (95% CI, 0.16-0.32), endocarditis 0.48%/y (95% CI, 0.37-0.62), and 20-year pooled actuarial survival was 58.7% and freedom from reintervention was 29.0%. Median time to structural valve deterioration was 17.3 years and median time to all-cause first reintervention was 16.9 years. For a 45-year-old adult, for example, this translated to a microsimulation-based estimated life expectancy of 21 years (general population: 32 years) and lifetime risk of reintervention of 78%, structural valve deterioration 71%, thromboembolism 12%, bleeding 5%, and endocarditis 9%.

Conclusions

Aortic valve replacement with bioprostheses in young adults is associated with high structural valve deterioration and reintervention rates and low, though not absent, hazards of thromboembolism and bleeding. Foremostly, most patients will require one or more reinterventions during their lifetime and survival is impaired in comparison with the age- and sex-matched general population. Prosthesis durability remains the main concern in nonelderly patients.

INTRODUCTION

When valve repair is not possible, surgical aortic valve replacement (AVR) is the most widely used treatment for aortic valve disease in nonelderly adults. Two types of valve substitutes are available for AVR: mechanical and biological valves. Mechanical valves are often recommended in nonelderly adults because of the lower, though not absent, rate of reoperation compared with biological valves. They do, however, require lifelong anticoagulation because of 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 International Normalized Ratio regulation, valve sound and, in women of childbearing age, the potential hazards of anticoagulation during pregnancy. Biological alternatives, such as bioprostheses (ie, xenografts) and the Ross procedure, 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.

Improvements in the design of bioprostheses with hypothesized durability benefits, enthusiasm for the prospect of transcatheter valve-in-valve implantation as an option for reintervention and the increasing role of shared decision-making in valve selection has led to an increase in the use of bioprostheses in increasingly younger patients. However, reports on long-term outcome after bioprosthetic AVR in nonelderly adults are scattered. This makes it difficult to draw inferences on what patients can expect after bioprosthetic AVR, information essential in guiding decision-making. Furthermore, with growing interest in transcatheter aortic valve implantation (TAVI) as a primary intervention in increasingly younger and lower-risk patients, there is an urgent need for insight into long-term outcome of the golden standard in nonelderly adult patients (surgical AVR) as a benchmark.

In this light, this systematic review and meta-analysis aims to provide a comprehensive overview of reported outcome and calculates microsimulation-based agespecific estimates of life expectancy and lifetime risk of valve-related events.

METHODS

Search strategy and selection of studies

This systematic review was conducted according to the PRISMA guidelines[2] and registered in the PROSPERO registry (CRD42017079929). The data, analytic methods, and

study materials will be made available to other researchers for the purposes of reproducing the results or replicating the procedure on request to the corresponding author.

On September 1, 2016, Embase, MEDLINE, Cochrane Central, and Google Scholar databases were searched by a biomedical information specialist using keywords about AVR with bioprostheses (Supplement 1).

All studies were screened by 2 independent reviewers (J.R.G. Etnel and S.A. Huygens). Observational studies and randomized controlled trials reporting clinical outcome after AVR with currently available bioprostheses (ie, xenografts) in patients with a mean age ≥18 and ≤55 years published in English after January 1, 2000, were considered for inclusion. Studies limited to patients with preexisting comorbidities (dysfunction of extracardiac organ systems) or a history of previous AVR were excluded. Studies with a study size <20 patients or focusing only on certain prosthesis sizes were also excluded. In case of multiple publications on overlapping study populations, the publication with the greatest total follow-up in patient-years and overall completeness of data was included for each outcome of interest separately. In case of disagreement between the reviewers, a consensus was negotiated.

Data extraction

Microsoft Office Excel 2010 (Microsoft Corp, Redmond, WA) was used for data extraction. Data were extracted independently by 2 reviewers (P. Grashuis and B. Pekbay). After data extraction, each reviewer verified the other reviewer's data entries and data entries were also verified by a third reviewer (J.R.G. Etnel). Recorded study characteristics, baseline patient and operative characteristics and outcome events are listed in Supplement 1.

Morbidity and mortality were documented according to the 2008 guidelines by Akins et al.[3] 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. Structural valve deterioration was defined as dysfunction or deterioration intrinsic to the operated valve (exclusive of infection or thrombosis), as determined by reoperation, autopsy, or clinical investigation (including periodic echocardiographic surveillance). If the total follow-up duration in patient-years was not reported, it was calculated by multiplying the number of patients with the mean follow-up duration of that study.

Statistical analyses

Statistical software used is listed in Supplement 1.

Continuous variables are presented as mean±SD. 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 risks of mortality and linearized occurrence rates of late morbidity and mortality were calculated for each individual study and pooled with the use of inverse variance weighting in a random-effects model according to the DerSimonian and Laird method. Outcomes were pooled 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, it was assumed that 0.5 patient experienced that event for the purpose of inverse variance weighting. The Cochran Q statistic and I^2 statistic were used to assess heterogeneity between studies. Potential causes of heterogeneity were explored by investigating the effect of all baseline patient characteristics and operative details listed in Table 1 as well as study design (retrospective versus prospective/randomized controlled trial) and pooled median year of surgery by means of univariable random-effects meta-regression. The influence of potential publication bias on pooled outcome was investigated by conducting sensitivity analyses by temporarily excluding the smallest quartile (by sample size) of included studies in all ages group.

Kaplan-Meier meta-analysis

Pooled Kaplan-Meier time-to-event meta-analysis was conducted by extrapolating and pooling estimates of individual patient time-to-event data from published Kaplan-Meier curves. Published Kaplan-Meier curves were digitized and an estimate of the individual patient time-to-event data was then extrapolated from the digitized curve coordinates, assuming a constant rate of censorship between each time point at which the number of patients at risk was specified.[4] If there were no Kaplan-Meier curves available, but time points of each event were reported or there were no events, the individual patient time-to-event data was manually reconstructed up to a maximum follow-up of the mean follow-up + 2 SDs, under the same assumption of a constant rate of censorship. Reconstructed individual patient time-to-event data of each study were then combined.

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.[5-7]

Table 1. Pooled baseline patient characteristics and operative details

	Pooled Estimate	No. Of Studies
Mean age, y	50.7±11.0	17
Male	53.1% (0.2-84.5)	16
Mean follow-up, y	7.9±4.2	0
Emergency	5.9% (0.0-20.6)	5
Preoperative NYHA class		
I/II	56.1% (24.8-79.5)	11
III/IV	43.9% (20.5-81.0)	11
Hemodynamics		
Aortic stenosis	41.2% (19.6-77.1)	9
Aortic regurgitation	39.6% (24.6-51.8)	10
Combined	19.2% (11.9-49.1)	8
Atrial fibrillation	6.1% (0.7-18.9)	8
Bicuspid AV	14.7% (13.8-18.9)	2
Cause		
Congenital	10.7% (0.0-61.9)	7
Degenerative/calcification	36.1% (6.9-84.5)	6
Rheumatic	30.4% (1.6-88.9)	8
Endocarditis	13.2% (0.0-11.3)	13
Other/Unknown	9.6% (0.0-30.4)	6
Previous cardiac intervention	8.0% (0.0-13.0)	8
AV intervention	4.9% (0.0-9.8)	5
AVR	2.7% (0.0-9.8)	4
Prosthesis		
Porcine	52.0% (0.0-100.0)	18
Bovine pericardial	47.9% (0.0-100.0)	18
Stented	78.2% (0.0-100.0)	18
Stentless	21.7% (0.0-100.0)	18
Concomitant procedures		
CABG	11.8% (0.0-27.0)	16
Ascending aortic surgery	8.2% (0.0-17.5)	9
Annular enlargement procedure	7.5% (0.0-19.7)	6
Other valve repair or replacement	11.9% (0.0-26.9)	12
Other	7.3% (0.0-21.1)	8

Data presented as mean±SD or percentage (range). The number of studies represents the number of studies in which each respective variable was reported. AV indicates aortic valve; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; and NYHA, New York Heart Association.

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 rate of structural valve deterioration was modeled by fitting a Weibull distribution to our pooled time-to-event data, for bleeding a log-normal distribution was used, and for thromboembolism and endocarditis a gamma distribution. The occurrence rates of all other events were assumed to be linear. Additional excess mortality not directly resulting from valve-related events was estimated separately for the age groups 20 to 40, 40 to 50, and 50 to 60 years, based on previously published age-specific survival after bioprosthetic AVR, using the least squares method (details in Supplement 1).[8,9] The background mortality of the general population was obtained for the pooled median year of intervention among included studies (1998, assuming a constant incidence rate over time in each study) and for the regions that the majority of the included study population originated from (North America, 41% of patients and Europe, 30% of patients).[10,11]

To obtain estimates of life expectancy and lifetime risk of valve-related morbidity, taking into account both first-order uncertainty (random variability in outcomes between identical patients) and second-order uncertainty (uncertainty in the input parameter estimates), probabilistic sensitivity analysis was conducted. The microsimulation model was run iteratively for 500 simulations with a sample size of 1000 patients per simulation (these amounts were based on the method described by O'Hagan et al[12]). In each of the 500 simulations, the values of the input parameters were randomly drawn from distributions corresponding with each parameter's point estimate and variance, obtained from the meta-analysis as described above. This yielded a complete set of outcome estimates for each of the 500 simulated patient populations. For each outcome measure, the mean of outcome estimates across all 500 simulated populations was considered the point estimate of outcome, and the 2.5th and 97.5th percentile were considered the lower and upper limits of the 95% credible interval, respectively. To obtain age-specific estimates, this process was repeated separately for the specific ages 25, 35, 45, and 55 years and at the male/female ratio obtained from our meta-analysis (53.1% male).

For the purposes of internal validation, the model was additionally run for 10 000 iterations at the pooled mean age (50.7 years) and pooled male/female ratio (53.1% male) from our meta-analysis. The actuarial survival curve obtained from this model was then plotted against the pooled overall survival curve observed in our Kaplan-Meier meta-analysis, excluding early mortality.

Software

Meta-analysis of baseline patient and study characteristics and event risks and linearized occurrence rates were performed in Microsoft Office Excel 2011 (Microsoft Corp, Redmond, WA). Published Kaplan-Meier curves were digitized using Engauge Digitizer (version 10.3, http://markummitchell. github.io/engauge-digitizer). Extrapolation of estimated individual patient time-to-event data from the digitized curves, meta-analysis thereof, microsimulation and metaregression were performed in R statistical software (version 3.3.2, R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The systematic literature search identified 4105 publications, of which 19 were included in the meta-analysis, encompassing a total of 2686 patients with 21 117 patient-years of follow-up (pooled mean follow- up: 7.9±4.2 years; Figure 1).[13-31] Supplement 2 represents the characteristics of the included studies.

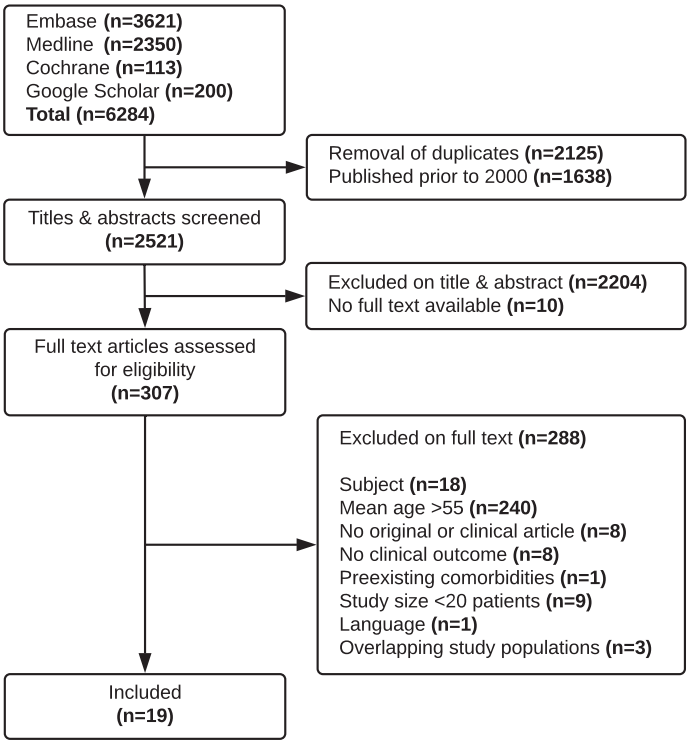

Figure 1. Flowchart of study selection.

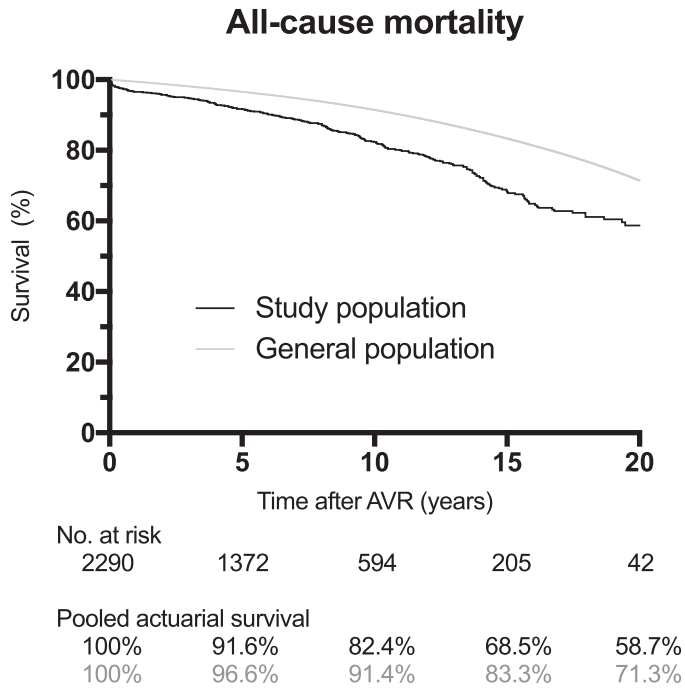

Figure 2. Pooled Kaplan-Meier freedom from all-cause mortality of the study population compared with the age- and sex-matched general population.
AVR indicates aortic valve replacement.

Pooled baseline patient characteristics are shown in Table 1.

Pooled risks of early mortality 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). Early morbidity, with the exception of reexploration for bleeding and thromboembolism, as well as late pacemaker implantation were not reported consistently across >1 study and could thus not be included in the analyses. Pooled Kaplan-Meier curves of freedom from all-cause mortality and morbidity are shown in Figures 2 through 5. Median time to structural valve deterioration was 17.3 years, and median time to all-cause first reintervention was 16.9 years.

Microsimulation-based age-specific estimates of lifetime risk of valve-related morbidity and life expectancy are shown in Figures 6 and 7, respectively. The microsimulation model calibrated well with the pooled mortality observed in our meta-analysis (Supplement 4).

Excess mortality not directly related to valve-related events was considerable; for patients aged 20 to 40 years at surgery the hazard ratio for background + excess mortality

Table 2. Pooled Outcome Estimates

	Pooled Estimate (95%CI)	Heterogeneity	No. Of Studies
Early outcome			
Early mortality (%)	3.30 (2.39-4.55)	I^2=41.7% (*P*=0.051)	14
Reexploration for bleeding (%)	4.08 (1.96-8.51)	I^2=71.4% (*P*=0.007)	5
Thromboembolism (%)	1.60 (0.89-2.87)	I^2=0.0% (*P*=0.930)	4
Late outcome			
Late mortality (%/y)	2.39 (1.13-2.94)	I^2=75.0% (*P*<0.001)	15
Cardiac (%/y)	0.96 (0.71-1.29)	I^2=52.4% (*P*=0.017)	12
Valve-related (%/y)	0.60 (0.37-0.98)	I^2=55.5% (*P*=0.017)	10
SUD (%/y)	0.30 (0.12-0.76)	I^2=66.0% (*P*=0.004)	8
Reintervention (%/y)	1.82 (1.31-2.52)	I^2=88.9% (*P*<0.001)	17
SVD (%/y)	1.59 (1.21-2.10)	I^2=74.4% (*P*<0.001)	15
NSVD (%/y)	0.24 (0.10-0.58)	I^2=0.0% (*P*=0.749)	2
Endocarditis (%/y)	0.48 (0.37-0.62)	I^2=0.0% (*P*=0.535)	9
Thromboembolism (%/y)	0.53 (0.42-0.67)	I^2=7.5% (*P*=0.372)	12
Valve thrombosis (%/y)	0.07 (0.02-0.20)	I^2=0.0% (*P*=0.545)	5
Bleeding (%/y)	0.22 (0.16-0.32)	I^2=0.0% (*P*=0.619)	10

Data presented as percentage (95% CI) or linearized occurrence rate (95% CI). The number of studies represents the number of studies in which each respective variable was reported. NSVD indicates nonstructural valve dysfunction; SUD, sudden unexplained death; and SVD, structural valve degeneration.

versus background mortality was 3.6, for 40- to 50-year-olds hazard ratio=2.7, and for 50- to 60-year-olds hazard ratio=1.7 (Supplement 5). For a 25-year-old, life expectancy (32.5 years) was 64.1% of that in the age- and sex-matched general population (50.7 years), for a 35-year-old 61.6% (25.5 versus 41.3 years), 45-year-old 64.9% (21.0 versus 32.3 years), and 55-year-old 75.0% (23.9 versus 23.9 years).

Sensitivity analyses showed that any eventual publication bias did not substantially influence our pooled outcomes, as pooled outcomes remained largely unchanged after temporary exclusion of the smallest quartile of studies by sample size (before versus after exclusion: early mortality [3.30% versus 3.13%], late mortality [2.39%/y versus 2.31%/y], reintervention [1.82%/y versus 1.66%/y], structural valve deterioration [1.59%/y versus 1.25%/y], endocarditis [0.48%/y versus 0.48%/y], thromboembolism [0.53%/y versus 0.50%/y], and bleeding [0.22%/y versus 0.20%/y]).

Sensitivity analysis including only studies with a mean age ≤50 years (n=9; Supplement 6), compared with our main analyses of all studies with a mean age of ≤55 years (n=19), revealed higher early mortality (4.59% versus 3.30%, respectively), lower late mortality (1.61%/y versus 2.39%/y) and comparable rates of reintervention (1.69%/y versus

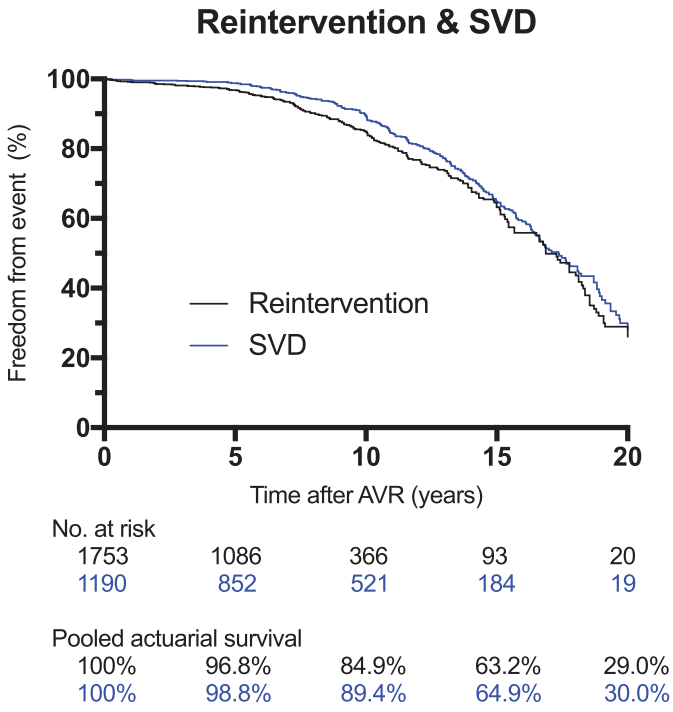

Figure 3. Pooled Kaplan-Meier freedom from reintervention and struc-tural valve deterioration (SVD). AVR indicates aortic valve replacement.

1.82%/y), structural valve deterioration (1.28%/y versus 1.59%/y), endocarditis (0.43%/y versus 0.48%/y), thromboembolism (0.50%/y versus 0.53%/y), and bleeding (0.19%/y versus 0.22%/y). Studies with a lower mean age had an earlier median year of surgery (Pearson r=0.60), more rheumatic cause (Pearson r=−0.89), higher preoperative New York Heart Association class (Pearson r=−0.66), more concomitant annular enlargement procedures (Pearson r=−0.78).

Heterogeneity

There was substantial heterogeneity in reexploration for bleeding, late mortality, reintervention, and structural valve deterioration.

Univariable random-effects meta-regression (Supplement 7) showed that studies reporting higher late mortality rates included cohorts with a higher mean age (P=0.006), a higher proportion of congenital cause (P=0.001; moderate correlation with higher proportion of prior surgery, Pearson r=0.44), more frequent use of bovine pericardial prostheses as opposed to porcine prostheses (P=0.048; moderate correlation with higher age, Pearson r=0.48), and less frequent annular enlargement procedures (P<0.001).

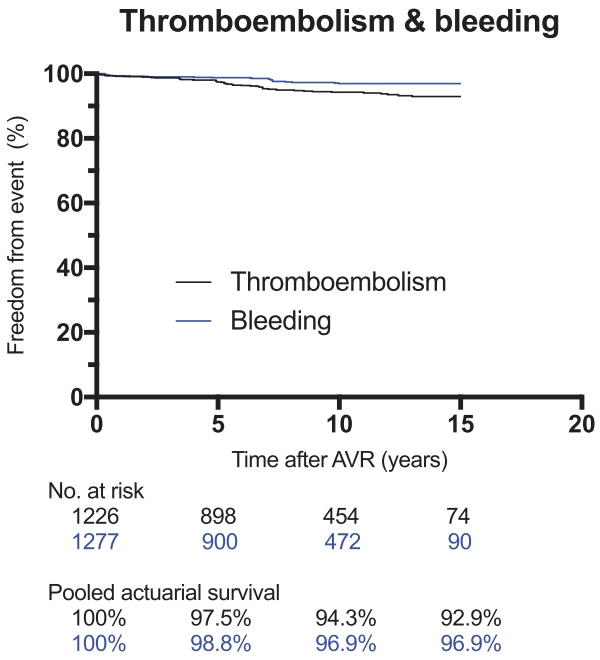

Figure 4. Pooled Kaplan-Meier freedom from thromboembolism and bleeding. AVR indicates aortic valve replacement.

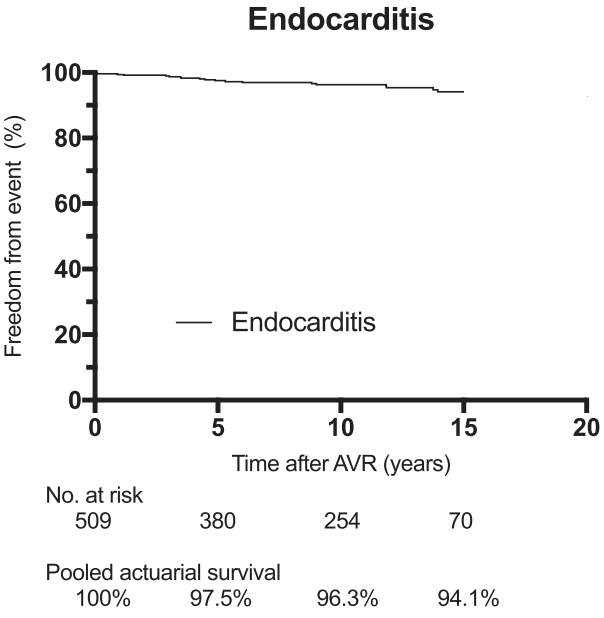

Figure 5. Pooled Kaplan-Meier freedom from endocarditis. AVR indicates aortic valve replacement.

Studies reporting higher late reintervention rates included cohorts with a lower proportion of rheumatic cause (P=0.014).

Studies reporting higher rates of structural valve deterioration included cohorts with an earlier year of surgery (P=0.03), longer mean follow-up (P=0.007), a higher proportion of degenerative/calcific cause (P=0.037), and lower preoperative New York Heart Association class (P=0.012; strong correlation with higher proportion of degenerative/calcific cause, Pearson r=−0.92).

Differences in study design, sex, urgency, hemodynamics, and previous interventions were not associated with heterogeneity in any of these outcome measures.

No associations were found between study/baseline patient characteristics and reexploration for bleeding, although limited sample size did not allow for inclusion of all covariates in the analysis.

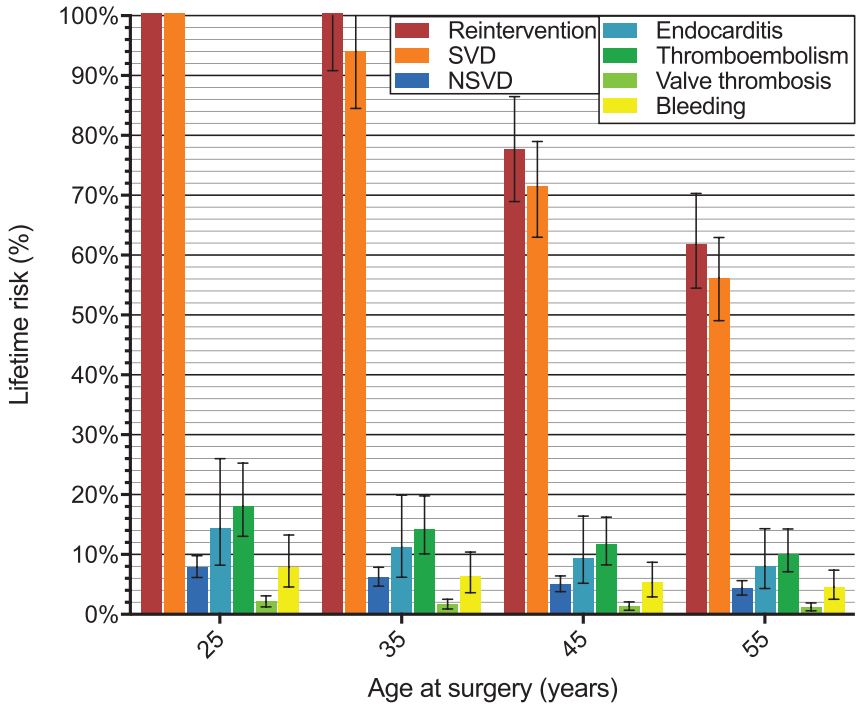

Figure 6. Microsimulation-based age-specific lifetime risks of valve-related morbidity bioprosthetic aortic valve replacement (AVR).
Error bars represent 95% credible intervals. NSVD indicates non-SVD; and SVD, structural valve deterioration.

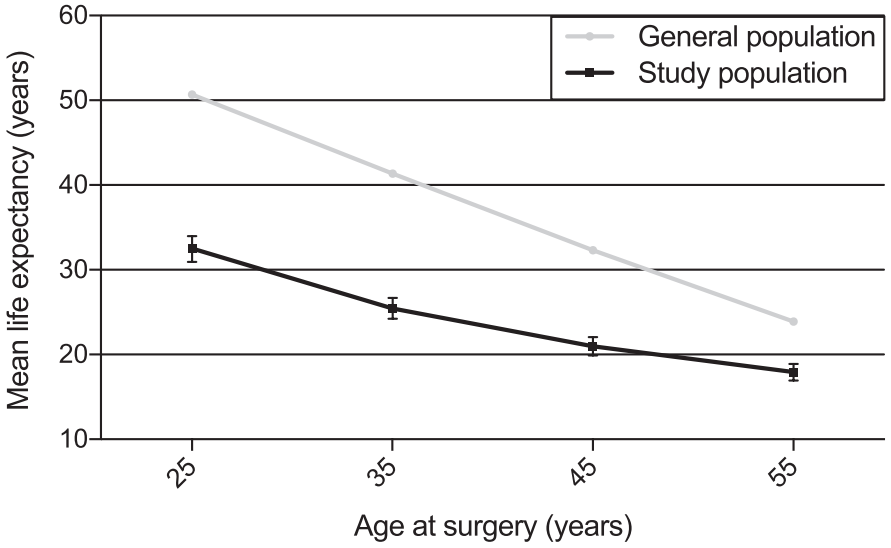

Figure 7. Microsimulation-based age-specific mean life expectancy after bioprosthetic AVR compared with the age- and sex-matched general population.
Error bars represent 95% credible intervals.

DISCUSSION

This study shows that AVR with bioprostheses in young adults is associated with high rates of structural valve deterioration and reintervention, with almost all patients aged 20 to 40 years at surgery projected to undergo one or more reinterventions during their lifetime and ≈60% to 75% of patients aged 40 to 60 years at surgery. Although early mortality is low, long-term survival is impaired, with a life expectancy of ≈60% to 75% of the life expectancy in the age- and sex-matched general population. Thromboembolism and bleeding rates are lower than after mechanical AVR, but not zero, with a lifetime thromboembolism risk of ≈10% to 20% and bleeding risk of 5% to 10%, depending on age at surgery.

Mortality

Our results show that bioprosthetic AVR in young adults is associated with low early mortality (3.30%), although late mortality is high (2.39%/y) and thus life expectancy is impaired compared with the general population. This late mortality is higher than the late mortality previously reported for the Ross procedure (0.64%/y) and mechanical AVR (1.55%/y) in young adults.[1,32]

This may be explained in part by bioprosthetic AVR having the highest overall reintervention rates of the 3 in combination with higher thromboembolism and bleeding rates than after the Ross procedure, with a subsequently higher valve-related mortality.

Besides higher valve-related mortality, excess mortality not directly related to valve-related events is also higher than after the Ross procedure.[33] The less favorable hemodynamics of bioprostheses may play a role in this observed difference.[34] Differences in preoperative patient characteristics should also be taken into account. Compared with adults undergoing the Ross procedure, bioprosthetic AVR patients are on average slightly older, more frequently have degenerative and rheumatic valve disease, and more frequently undergo concomitant procedures, but on the contrary, also have had less prior surgery, and undergo less concomitant aortic surgery.[33]

Comparison of our findings with mortality after aortic valve repair is difficult, because of a sparsity of available outcome data, disparity in indications and a lack of standardization in data reporting.[35] Collaborative initiatives, such as the AVIATOR registry, may shed more light on whether the benefits of native valve-preservation translate to a survival advantage.[35]

Structural valve deterioration and reintervention

The most important drawback of bioprostheses is their susceptibility to structural valve deterioration over time, particularly in younger patients.[19,27,28,36] This is reflected by our findings of structural valve deterioration rates of 1.59%/y, considerably higher than previously reported for middle-aged and elderly patients (0.60%/y).[37] This translates to all patients younger than 40 years of age at surgery projected to undergo one or more reinterventions during their lifetime and ≈60% to 75% of patients aged 40 to 60 years. Overall reintervention rates are higher than after the Ross procedure, even after taking right ventricular outflow tract reinterventions associated with the Ross procedure into account.[32] The reintervention rate is also higher than previously reported for aortic valve repair in selected patients and for mechanical AVR.[1,35]

The exact mechanism of the age-related nature of structural valve deterioration is not yet fully understood. Increased immune competence, more active calcium metabolism and hemodynamics have all been previously proposed to play a role, however, definitive evidence is lacking.[36,38,39] In light of the increasingly recognized relationship between hemodynamics and valve durability, technical considerations aimed at avoiding patient-prosthesis mismatch may prove useful in improving outcome.[36]

Many improvements in the design of modern bioprostheses have been proposed to improve durability and hemodynamics, however, clinical evidence of the hypothesized benefits provided by these modifications is inconclusive.[40-42]

Valve-in-valve TAVI is emerging as a prospective option for reintervention of failing bioprostheses in high-risk elderly patients although there are considerable risks of device malposition, high gradients, arrhythmias, and coronary obstruction.[43] However, its effectiveness in younger, lower-risk patients, the feasibility of multiple sequential valve-in-valve TAVIs and medium-to-long-term outcome remain to be investigated.

Thromboembolism and bleeding

Our study shows that thromboembolism (0.53%/y) and bleeding (0.22%/y) rates are far lower than reported for mechanical AVR in young adults (0.90%/y and 0.85%/y, respectively).[1] However, these risks are not zero. We found thromboembolism and bleeding rates higher than in the general population and higher than reported after the Ross procedure (thromboembolism and bleeding combined 0.36%/y) and aortic valve repair, although bioprosthetic AVR, the Ross procedure and valve repair similarly aim to avoid the need for anticoagulation.[32,35,44]

Besides possible differences in baseline patient characteristics, the observed difference in thromboembolism and bleeding rates may also be due in part to indications for anticoagulation arising during follow-up. Two of the included studies reported that at the end of follow-up (mean ≈10 years), 25% to 30% of patients required oral anticoagulation therapy, mostly because of atrial fibrillation.[15,20] In this light, further studies on preoperative factors associated with postoperative development of indications for anticoagulation may aid in selecting patients that stand to benefit most from bioprosthetic AVR.

Endocarditis

We found an endocarditis rate after bioprosthetic AVR (0.48%/y) comparable to mechanical AVR (0.41%/y), but higher than after the Ross procedure (autograft 0.18%/y, right ventricular outflow tract 0.14%/y, total 0.27%/y) and aortic valve repair (0.16%/y) in young adults.[1,35,45] This may be a manifestation of the increased susceptibility to infection of prosthetic material as opposed to autologous tissue, which should always be taken into account.[46]

Valve selection/future perspectives

The 2017 United States and European guidelines for the management of valvular heart disease both recommend mechanical prostheses over biological alternatives for AVR in adults younger than 50 to 60 years old. If anticoagulation is contraindicated or if the

patient prefers a biological alternative, both guidelines recommend bioprostheses, and only the United States guidelines indicate that the Ross procedure may be considered.[47,48]

Improvements in the design of bioprostheses with hypothesized hemodynamic and durability benefits, continuous improvements in the safety and outcome of reinterventions and enthusiasm for the prospect of transcatheter valve-in-valve replacement as an option for reintervention have led to an increase in the use of bioprostheses in increasingly younger patients.[14,23,31,49] However, there is little clinical evidence to support the notion that durability of modern bioprostheses is improving and the future role of transcatheter valve-in-valve replacement in these young patients remains uncertain. This along with the higher rates of thromboembolism, bleeding, reintervention, and mortality than after the Ross procedure calls into question the value of bioprostheses as a biological alternative in these young patients. However, their wide availability and ease of implantation in contrast to the technically challenging nature of the Ross procedure make bioprostheses an attractive alternative in centers with limited access to expertise on the Ross procedure and in patients who are not candidates for the Ross procedure.

In light of the limitations of all currently available valve substitutes, the currently ongoing technical advances and expanding indications in aortic valve repair are promising and may provide the option of native valve preservation in an increasing number of patients in the future.[35,50]

In any case, conveyance of patient-tailored evidence- based risks and benefits of all treatment options in a shared decision-making process is of great importance.[47,48] Innovative solutions such as patient information portals and decision aids may prove useful in this setting.[51,52]

Furthermore, with growing interest in TAVI as a primary intervention in increasingly younger and lowerrisk patients, our findings provide a valuable insight into long-term outcome of the golden standard in nonelderly adult patients (surgical AVR) as a benchmark. However, the potential role of TAVI in these patients remains to be elucidated.

Limitations

First, the inherent limitations of meta-analyses of predominantly retrospective observational studies should be taken into consideration.[53] Selection bias may have affected the observed outcomes, as unpublished data, abstracts and presentations were not included. Funnel plots could not be used to investigate publication bias, as funnel plots do not allow for meaningful interpretation in case of absolute risk outcomes.[54] Direct comparisons with alternative valve prostheses are hampered by the lack of published

comparative data. Heterogeneity may have introduced uncertainty in our outcomes, although this uncertainty is reflected in our 95% confidence/credible intervals due to the use of random-effects models. The microsimulation model requires assumptions to be made about the evolution of event occurrence rates beyond the observed follow-up period, which may have introduced uncertainty. Comparison of our microsimulation results with previously published microsimulation studies on mechanical AVR is difficult due to differences in methodology.[1]

CONCLUSIONS

Bioprosthetic AVR in young adults is associated with high overall reintervention rates, mainly because of high age-dependent structural valve deterioration. Through avoidance of thrombogenicity and the burden of anticoagulation, bioprosthetic AVR in young adults is associated with low thromboembolism and bleeding rates. However, these risks are not absent and considerably higher than previously reported for the Ross procedure, although comparative data is lacking. Late mortality is high and life expectancy is impaired compared with the general population. In conclusion, outcome after bioprosthetic AVR in young adults is suboptimal, although it succeeds in providing a biological option for patients whose preferences do not align with the outcome provided by mechanical valve replacement and who are not candidates for the Ross procedure. Patients who are facing AVR are entitled to conveyance of evidence- based estimates of the risks and benefits of all treatment options in a shared decision-making process.

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SUPPLEMENTARY MATERIAL

Supplement 1. Supplemental methods

1. Search query

Embase: 3621 results

('aorta valve replacement'/de OR 'aorta valve prosthesis'/de OR ('heart valve prosthesis'/de AND 'aorta valve'/de) OR (aort* AND (valve*) NEAR/6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)):ab,ti) AND (xenograft/de OR (xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR 'Carpentier-Edwards' OR Shiley OR hancock) NEAR/6 (graft* OR transplant* OR prosthe* OR bioprosthe* OR valve* OR aort*))):ab,ti) OR ('heart valve bioprosthesis'/de OR 'Carpentier Edwards bioprosthesis'/de OR 'Hancock valve prosthesis'/de OR 'Mosaic bioprosthesis'/de OR (('Carpentier-Edwards' OR Shiley OR hancock OR freestyle* OR mosaic OR '3f enable' OR biocor OR 'toronto spv') NEAR/6 (valve* OR bioprosthe* OR prosthe*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND ('clinical study'/de OR 'case control study'/exp OR 'clinical article'/de OR 'clinical trial'/exp OR 'intervention study'/de OR 'longitudinal study'/exp OR 'major clinical study'/de OR 'prospective study'/de OR 'retrospective study'/de OR mortality/de OR 'cardiovascular mortality'/de OR 'surgical mortality'/de OR 'treatment outcome'/exp OR survival/exp OR 'graft survival'/de OR 'quality of life'/de OR 'follow up'/de OR 'evaluation study'/de OR 'comparative effectiveness'/de OR reoperation/de OR (clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long term' OR longterm OR death OR evaluat* OR effectiv* OR reoperat*):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Conference Paper]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim OR [Conference Review]/lim)

Medline: 2350 results

(("heart valve prosthesis"/ AND "aortic valve"/) OR (aort* ADJ6 (valve*) ADJ6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)).ab,ti.) AND (heterografts/ OR (xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR "Carpentier-Edwards" OR Shiley OR hancock) ADJ6 (graft* OR transplant* OR prosthe* OR bioprosthe* OR valve* OR aort*))).ab,ti.) OR ((("Carpentier-Edwards" OR Shiley OR hancock OR freestyle* OR mosaic OR "3f enable" OR biocor OR "toronto spv") ADJ3 (valve* OR bioprosthe* OR prosthe*)).ab,ti.) NOT (exp animals/ NOT humans/) AND ("Clinical Trial".pt. OR exp "Case-Control Studies"/ OR "Intervention Studies"/ OR exp "Longitudinal

Studies"/ OR exp mortality/ OR mortality.xs. OR exp "treatment outcome"/ OR survival/ OR "graft survival"/ OR "quality of life"/ OR (clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality ADJ3 life) OR result* OR (follow* ADJ up*) OR "long term" OR longterm OR death OR evaluat* OR effectiv* OR reoperat*).ab,ti.) AND english.la. NOT (congresses OR Letters OR Notes OR Editorials).pt.

Cochrane: 113 results

((aort* AND (valve*) NEAR/6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)):ab,ti) AND ((xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR 'Carpentier-Edwards' OR Shiley OR hancock) NEAR/6 (graft* OR transplant* OR prosthe* OR bioprosthe* OR valve* OR aort*))):ab,ti) OR ((('Carpentier-Edwards' OR Shiley OR hancock OR freestyle* OR mosaic OR '3f enable' OR biocor OR 'toronto spv') NEAR/3 (valve* OR bioprosthe* OR prosthe*)):ab,ti) AND ((clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long term' OR longterm OR death OR evaluat* OR effectiv* OR reoperat*):ab,ti)

Google scholar: 200 results

"aorta|aortic valve replacement|prosthesis|transplantation" xenograft|xenotransplantation|heterograft|heterotransplantation|"Carpentier-Edwards"|hancock clinical|trial|intervention|longitudinal|prospective|retrospective|mortality|outcome|survival|follow-up

2. 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)

- New York Heart Association functional class
- Urgency of the operation
- Type of prosthesis (porcine vs. bovine pericardial, stented vs. stentless)
- Concomitant procedures

Outcome events

- Early outcome events (<30 days after surgery)
  - Early mortality (all-cause mortality within the first 30 postoperative days)
  - Re-exploration for bleeding
  - Pacemaker implantation
  - Deep sternal infection/mediastinitis
  - Endocarditis
  - Stroke
  - Transient ischemic attack
  - Myocardial infarction
  - Valve thrombosis
  - Peripheral bleeding
- Late outcome events (>30 days after surgery)
  - Late mortality
    - Cardiac death
    - Valve related death
    - Sudden, unexplained death (SUD)
  - Reintervention
  - Thromboembolism
  - Valve thrombosis
  - Bleeding
  - Endocarditis
  - Structural valve deterioration (SVD)
  - Nonstructural valve dysfunction (NSVD)
  - Pacemaker implantation

3. Microsimulation model: concept

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.

4. Microsimulation model: estimation of excess mortality

For estimation of the hazard ratios of the additional excess mortality not directly resulting from valve-related events relative to background mortality, a microsimulation model containing only background mortality and mortality due to valve-related events (excluding early mortality) was run for 10,000 iterations each at the ages of 25, 35, 45 and 55 for the age groups 20-40, 40-50 and 50-60, respectively. Subsequently, the hazard ratios were estimated by fitting the survival output of these microsimulation models to the survival observed for the same age groups in the studies by Schnittman et al. 2018 and Goldstone et al. 2017 (references 9 &10) using the least squares method and excluding early mortality.

Supplement 2. Individual study characteristics.

	Study design	Origin	Patients (N)	Inclusion period	Mean/median FUP
Anantha Narayanan 2015	Retrospective	North America	63	2004-2011	2.1
Bach 2007	Retrospective	North America	57	1992-2004	8.5
Bourguignon 2015	Retrospective	EU	383	1984-2008	8.6
McClure 2014	Prospective	North America	361	1992-2013	6.5
Chan 2011	Prospective	North America	147	1976-2010	5.8
Forcillo 2014	Retrospective	North America	144	1991-2011	10.0
Christ 2013	Retrospective	EU	188	1993-2001	8.8
Minakata 2015	Retrospective	Asia	53	1986-2001	9.5
Wang 2015	Retrospective	Asia	112	2002-2009	8.7
Vrandecic 2002	Retrospective	South America	247	1990-2001	5.9
Une 2014	-	North America	304	1982-2008	14.2
Von Oppell 2001	Prospective	South Africa	52	1994-1998	-
Ruggieri 2012	Retrospective	EU	36	1983-1994	13.7
Weber 2012	Retrospective	EU	103	2000-2009	2.8
Banbury 2001	-	North America	27	1981-1984	12.0
Nishida 2014	Retrospective	Asia	51	1981-2013	9.0
Wei 2010	-	Asia	72	1989-2002	-
Vrandecic 2000	Retrospective	South America	202	1990-1999	4.4
Niclauss 2013	Retrospective	EU	84	2000-2010	4.5

"-"=variable not reported. FUP=follow-up.

FUP completeness	Mean/median age (range)	Prosthesis			
		-Porcine	-Bovine pericardial	-Stented	-Stentless
-	51.1(18.0-60.0)	0.0%	100.0%	100.0%	0.0%
82.0%	54.5(36.0-60.0)	100.0%	0.0%	0.0%	100.0%
95.3%	51.0(16.0-60.0)	0.0%	100.0%	100.0%	0.0%
-	53.9(-65.0)	11.9%	87.8%	100.0%	0.0%
-	-(-40.0)	-	-	-	-
95.0%	51.0(18.0-60.0)	0.0%	100.0%	100.0%	0.0%
90.4%	53.1(24.0-60.0)	100.0%	0.0%	0.0%	100.0%
84.9%	52.8(21.0-64.0)	0.0%	100.0%	100.0%	0.0%
95.1%	50.3(--60.0)	100.0%	0.0%	100.0%	0.0%
98.0%	47.3(30.0-79.0)	100.0%	0.0%	0.0%	100.0%
97.0%	49.2(17.0-59.0)	100.0%	0.0%	100.0%	0.0%
-	44.0(-)	100.0%	0.0%	0.0%	100.0%
-	43.9(24.0-59.0)	100.0%	0.0%	100.0%	0.0%
97.0%	55.0(46.0-59.0)	0.0%	100.0%	100.0%	0.0%
-	-(21.0-50.0)	0.0%	100.0%	100.0%	0.0%
-	46.9(-60.0)	0.0%	100.0%	100.0%	0.0%
96.5%	46.6(35.0-64.0)	100.0%	0.0%	100.0%	0.0%
-	48.1(-)	100.0%	0.0%	100.0%	0.0%
100%	54.7(22.0-64.0)	8.6%	91.4%	91.4%	8.6%

Supplement 3. Individual study outcome estimates.

[1]The reported p-values are those of the Cochran's Q test for heterogeneity. *zero events reported, for the purpose of the analyses it was assumed that 0.5 patient experienced that event. "-"=variable not reported. Yr=year. SUD=sudden unexplained death. SVD=structural valve degeneration. NSVD=nonstructural valve dysfunction.

	EARLY OUTCOME			LATE OUTCOME
	Early mortality (%)	**Reexploration for bleeding (%)**	**Thromboembolism (%)**	**Late mortality (%/yr)**
Anantha Narayanan 2015	0.79(0.05-12.55)*	0.79(0.05-12.55)*	1.59(0.23-11.09)	4.58(2.10-10.00)
Bach 2007	-	-	-	3.08(1.87-5.07)
Bourguignon 2015	1.31(0.55-3.12)	-	1.31(0.55-3.12)	2.58(2.09-3.18)
McClure 2014	1.94(0.93-4.04)	2.49(1.31-4.75)	-	2.37(1.87-3.02)
Chan 2011	-	-	-	-
Forcillo 2014	0.69(0.10-4.90)	9.03(5.38-15.16)	2.08(0.68-6.38)	2.85(2.11-3.85)
Christ 2013	3.19(1.45-7.01)	-	-	3.68(2.88-4.71)
Minakata 2015	3.77(0.97-14.70)	-	-	3.97(2.59-6.10)
Wang 2015	3.57(1.36-9.35)	1.79(0.45-7.05)	1.79(0.45-7.05)	1.13(0.63-2.04)
Vrandecic 2002	4.05(2.21-7.43)	-	-	1.08(0.65-1.78)
Une 2014	1.97(0.89-4.36)	-	-	1.46(1.14-1.86)
Von Oppell 2001	5.77(1.92-17.31)	-	-	1.75(0.44-6.93)
Ruggieri 2012	-	-	-	-
Weber 2012	4.85(2.06-11.41)	6.80(3.32-13.90)	-	3.53(1.92-6.49)
Banbury 2001	-	-	-	-
Nishida 2014	-	-	-	-
Wei 2010	8.33(3.87-17.93)	-	-	2.06(1.18-3.60)
Vrandecic 2000	5.45(3.07-9.67)	-	-	2.31(1.42-3.75)
Niclauss 2013	2.38(0.61-9.36)	-	-	2.10(1.06-4.17)
Pooled estimate (95%CI)	3.30(2.39-4.55)	4.08(1.96-8.51)	1.60(0.89-2.87)	2.39(1.13-2.94)
Heterogeneity[1]	I^2=41.7%(p=0.051)	I^2=71.4%(p=0.007)	I^2=0.0%(p=0.930)	I^2=75.0%(p<0.001)
Number of studies	14	5	4	15

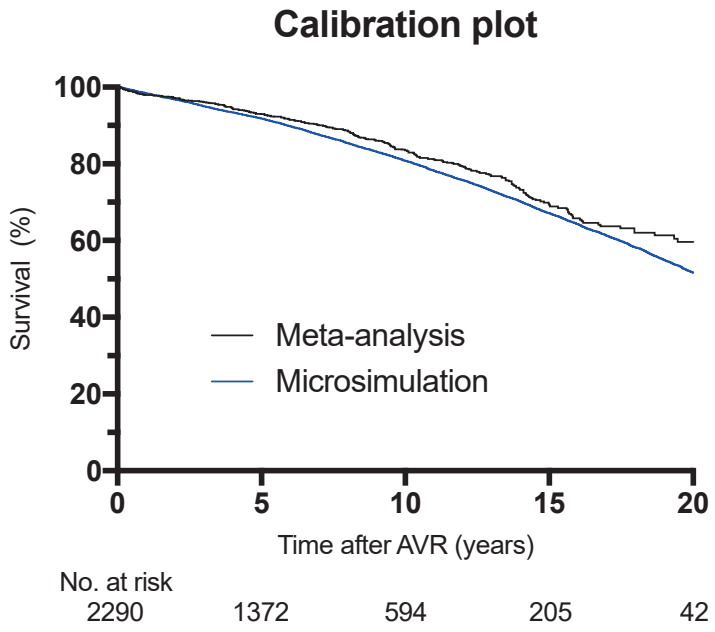
-Cardiac (%/yr)	-Valve-related (%/yr)	-SUD (%/yr)	Reintervention (%/yr)	SVD (%/yr)
-	-	-	4.58(2.10-10.00)	1.53(0.39-6.04)
0.62(0.20-1.91)	0.21(0.03-1.46)	-	1.44(0.69-3.00)	0.62(0.20-1.91)
1.21(0.89-1.65)	0.70(0.46-1.05)	0.52(0.32-0.83)	2.67(2.17-3.28)	2.36(1.90-2.94)
0.58(0.36-0.95)	-	-	0.84(0.56-1.26)	-
-	-	-	6.80(5.31-8.72)	-
1.46(0.95-2.23)	0.42(0.19-0.93)	0.14(0.03-0.55)	2.57(1.87-3.53)	2.01(1.40-2.89)
-	-	-	2.53(1.88-3.42)	2.11(1.52-2.93)
1.19(0.54-2.64)	0.60(0.19-1.84)	0.10(0.01-1.59)*	2.38(1.36-4.17)	2.38(1.36-4.17)
0.82(0.41-1.64)	0.21(0.05-0.82)	0.05(0.00-0.82)*	0.93(0.48-1.78)	0.62(0.28-1.37)
0.29(0.11-0.76)	0.04(0.00-0.57)*	0.04(0.00-0.57)*	0.22(0.07-0.67)	0.14(0.04-0.57)
-	-	-	2.32(1.91-2.81)	1.97(1.60-2.43)
1.75(0.44-6.93)	1.75(0.44-6.93)	0.88(0.12-6.17)	1.75(0.44-6.93)	2.63(0.86-8.04)
-	-	-	3.85(2.48-5.99)	4.06(2.64-6.23)
2.12(0.96-4.68)	2.12(0.96-4.68)	1.77(0.74-4.21)	0.18(0.01-2.82)*	-
-	-	-	-	-
-	-	-	-	2.18(1.18-4.03)
1.20(0.57-2.51)	0.51(0.17-1.59)	0.09(0.01-1.37)*	0.51(0.17-1.59)	0.51(0.17-1.59)
0.72(0.30-1.73)	0.58(0.22-1.53)	-	1.15(0.58-2.30)	0.29(0.07-1.15)
0.26(0.04-1.86)	-	-	1.31(0.55-3.14)	1.05(0.40-2.78)
0.96(0.71-1.29)	0.60(0.37-0.98)	0.30(0.12-0.76)	1.82(1.31-2.52)	1.59(1.21-2.10)
I^2=52.4%(p=0.017)	I^2=55.5%(p=0.017)	I^2=66.0%(p=0.004)	I^2=88.9%(p<0.001)	I^2=74.4%(p<0.001)
12	10	8	17	15

Supplement 3. (continued)

	NSVD (%/yr)	Endocarditis (%/yr)	Thromboembolism (%/yr)	Valve thrombosis (%/yr)
Anantha Narayanan 2015	-	-	-	-
Bach 2007	-	-	-	-
Bourguignon 2015	-	0.52(0.32-0.83)	0.48(0.30-0.79)	0.02(0.00-0.24)*
McClure 2014	-	-	0.58(0.36-0.95)	-
Chan 2011	-	-	-	-
Forcillo 2014	-	0.49(0.23-1.02)	0.56(0.28-1.11)	0.07(0.01-0.49)
Christ 2013	-	-	-	-
Minakata 2015	-	0.10(0.01-1.59)*	0.79(0.30-2.11)	-
Wang 2015	-	-	0.52(0.21-1.23)	-
Vrandecic 2002	0.22(0.07-0.67)	0.14(0.04-0.57)	0.04(0.00-0.57)*	0.04(0.00-0.57)*
Une 2014	-	0.44(0.28-0.69)	0.37(0.23-0.60)	-
Von Oppell 2001	-	0.88(0.12-6.17)	1.75(0.44-6.93)	0.44(0.03-6.97)*
Ruggieri 2012	-	-	-	-
Weber 2012	-	1.06(0.34-3.26)	1.06(0.34-3.26)	-
Banbury 2001	-	-	-	-
Nishida 2014	-	-	-	-
Wei 2010	-	0.34(0.09-1.37)	0.69(0.26-1.82)	-
Vrandecic 2000	0.29(0.07-1.15)	0.58(0.22-1.53)	0.43(0.14-1.34)	0.07(0.00-1.15)*
Niclauss 2013	-	-	0.26(0.04-1.86)	-
Pooled estimate (95%CI)	0.24(0.10-0.58)	0.48(0.37-0.62)	0.53(0.42-0.67)	0.07(0.02-0.20)
Heterogeneity[1]	I^2=0.0%(p=0.749)	I^2=0.0%(p=0.535)	I^2=7.5%(p=0.372)	I^2=0.0%(p=0.545)
Number of studies	2	9	12	5

Bleeding (%/yr)
-
-
0.21(0.10-0.44)
0.15(0.05-0.39)
-
-
-
0.60(0.19-1.84)
0.31(0.10-0.96)
0.04(0.00-0.57)*
0.19(0.09-0.37)
0.44(0.03-6.97)*
-
0.18(0.01-2.82)*
-
-
0.34(0.09-1.37)
0.07(0.00-1.15)*
-
0.22(0.16-0.32)
I^2=0.0%(p=0.619)
10

Supplement 4. Calibration plot of the microsimulation model. Microsimulation-based actuarial survival is plotted against observed pooled Kaplan-Meier survival rates in the all ages group (age- and gender-matched).



Supplement 5. Least squares regression of modeled survival vs. observed survival for estimation of excess mortality not directly related to valve-related events.

Hazard ratio[1]	Sum of squared residuals[2]
Age at surgery 20-40 years	
3.4	296.0
3.5	274.8
3.6	**266.4**
3.7	270.2
3.8	285.5
Age at surgery 40-50 years	
2.5	212.5
2.6	155.9
2.7	**148.2**
2.8	188.9
2.9	275.2
Age at surgery 50-60 years	
1.5	634.7
1.6	284.2
1.7	**126.9**
1.8	159.7
1.9	378.5

Bold print indicates the selected model.

[1]Hazard ratio of background mortality + excess mortality relative to background mortality.

[2]Sum of squared residuals between microsimulation-based survival and survival observed in our meta-analysis of Kaplan-Meier freedom from all-cause mortality.

Supplement 6. Sensitivity analysis including only studies with a mean age ≤50 years (n=9)

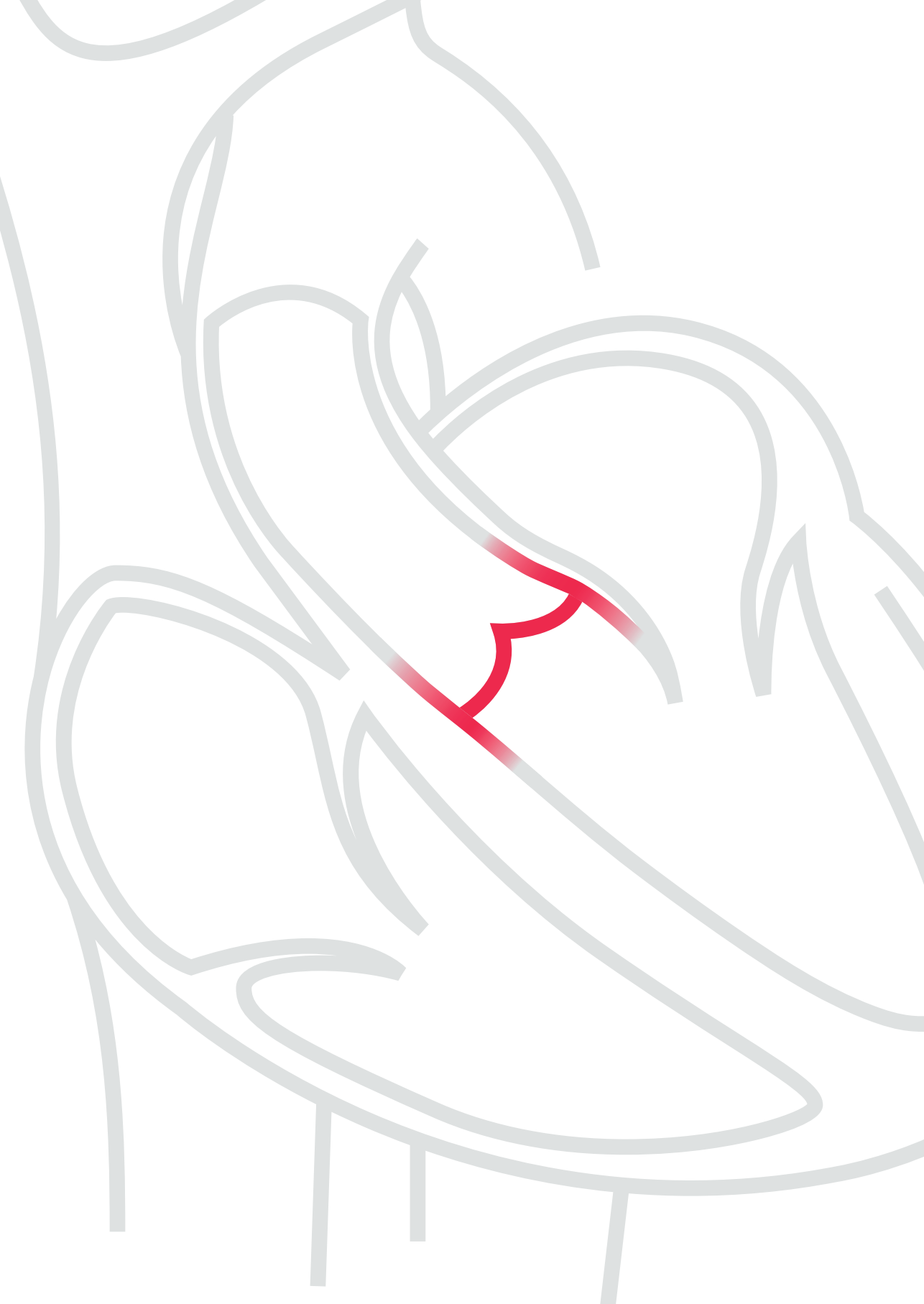
	Pooled estimate (95%CI)	Heterogeneity	Number of studies
Early outcome			
Early mortality (%)	4.59(2.94-7.16)	I^2=45.6%(p=0.118)	5
Reexploration for bleeding (%)	-	-	0
Thromboembolism (%)	-	-	0
Late outcome			
Late mortality (%/yr)	1.61(1.26-2.09)	I^2=31.6%(p=0.211)	5
-Cardiac (%/yr)	0.78(0.38-1.60)	I^2=55.1%(p=0.083)	4
-Valve-related (%/yr)	0.56(0.21-1.51)	I^2=53.0%(p=0.094)	4
-SUD (%/yr)	0.17(0.02-1.30)	I^2=50.2%(p=0.134)	3
Reintervention (%/yr)	1.69(0.87-3.28)	I^2=93.2%(p<0.001)	7
SVD (%/yr)	1.28(0.69-2.37)	I^2=84.1%(p<0.001)	7
NSVD (%/yr)	0.24(0.10-0.58)	I^2=0.0%(p=0.749)	2
Endocarditis (%/yr)	0.43(0.29-0.62)	I^2=0.0%(p=0.497)	5
Thromboembolism (%/yr)	0.50(0.25-1.00)	I^2=51.8%(p=0.081)	5
Valve thrombosis (%/yr)	0.10(0.02-0.52)	I^2=0.0%(p=0.433)	3
Bleeding (%/yr)	0.19(0.11-0.34)	I^2=0.0%(p=0.572)	5

Supplement 7. Univariable random effects meta-regression of natural log-transformed outcome measures.

	Reexploration for bleeding		Late mortality	
	β (95%CI)	p-value	β (95%CI)	p-value
Study design (prospective/RCT)	-0.72(-2.20 - 0.76)	0.339	-0.14(-0.77 - 0.50)	0.671
Median year of surgery	-0.25(-0.64 - 0.14)	0.205	0.01(-0.04 - 0.06)	0.718
Mean follow-up (/year increase)	0.06(-0.24 - 0.36)	0.702	-0.03(-0.10 - 0.04)	0.337
Mean age (/year increase)	0.09(-0.39 - 0.57)	0.710	**0.09(0.03 - 0.15)**	**0.006**
Male	1.60(-0.69 - 3.90)	0.171	0.06(-0.84 - 0.95)	0.903
Urgent	-9.85(-22.95 - 3.25)	0.140	0.71(-5.29 - 6.71)	0.816
Preop. NYHA class				
I/II	*		0.16(-1.51 - 1.83)	0.850
III/IV	*		-0.66(-1.99 - 0.68)	0.335
Hemodynamics				
Aortic stenosis	*		0.04(-2.04 - 2.11)	0.974
Aortic regurgitation	*		-2.29(-6.76 - 2.17)	0.314
Combined	*		2.19(-0.81 - 5.20)	0.152
Atrial fibrillation	*		3.31(-4.49 - 11.11)	0.406
Bicuspid AV	*		*	
Etiology				
Congenital	*		**2.00(0.85 - 3.16)**	**0.001**
Degenerative/calcification	*		0.50(-0.91 - 1.91)	0.487
Rheumatic	*		-0.66(-1.55 - 0.23)	0.144
Endocarditis	*		-2.22(-9.14 - 4.71)	0.530
Other/unknown	*		**-3.84(-5.81 - -1.86)**	**<0.001**
Previous cardiac intervention	*		-0.21(-4.09 - 3.66)	0.914
AV intervention	*		0.16(-6.07 - 6.40)	0.959
AVR	*		3.91(-23.78 - 31.59)	0.782
Prosthesis				
Porcine	*		**-0.43(-0.85 - 0.00)**	**0.050**
Bovine pericardial	*		**0.43(0.00 - 0.86)**	**0.048**
Stented	*		0.02(-0.48 - 0.52)	0.945
Stentless	*		-0.02(-0.52 - 0.48)	0.949
Concomitant procedures				
CABG	*		0.78(-2.32 - 3.89)	0.621
Ascending aortic surgery	*		1.11(-5.08 - 7.30)	0.725
Annular enlargement procedure	*		**-3.96(-6.08 - -1.84)**	**<0.001**
Other valve repair or replacement	*		-0.59(-4.38 - 3.20)	0.759
Other	*		1.57(-2.07 - 5.21)	0.397

*Could not be assessed due to insufficient sample size. CI=confidence interval. RCT=randomized controlled trial. Preop.=preoperative. NYHA=New York Heart Association. AV=aortic valve. AVR=aortic valve replacement. CABG=coronary artery bypass grafting.

	Reintervention		Structural valve deterioration	
	β (95%CI)	p-value	β (95%CI)	p-value
	0.27(-0.70 - 1.25)	0.582	0.55(-0.95 - 2.05)	0.475
	-0.04(-0.10 - 0.01)	0.136	**-0.06(-0.12 - -0.01)**	**0.030**
	0.05(-0.05 - 0.16)	0.329	**0.14(0.04 - 0.24)**	**0.007**
	-0.01(-0.10 - 0.07)	0.742	-0.03(-0.12 - 0.06)	0.472
	0.56(-0.99 - 2.10)	0.480	-0.37(-1.68 - 0.94)	0.580
	1.28(-5.67 - 8.23)	0.719	-4.47(-11.50 - 2.57)	0.214
	0.73(-1.90 - 3.36)	0.587	2.67(-0.36 - 5.70)	0.084
	-1.47(-3.72 - 0.77)	0.199	**-3.15(-5.61 - -0.68)**	**0.012**
	0.94(-0.82 - 2.70)	0.297	0.99(-1.22 - 3.20)	0.380
	-2.54(-6.76 - 1.69)	0.239	-2.54(-7.78 - 2.71)	0.343
	0.87(-3.18 - 4.92)	0.674	0.20(-5.31 - 5.71)	0.944
	-5.56(-16.24 - 5.12)	0.307	3.41(-14.99 - 21.81)	0.716
	*		*	
	1.41(-0.17 - 2.99)	0.080	0.78(-1.46 - 3.02)	0.495
	1.24(-1.01 - 3.50)	0.280	**2.51(0.15 - 4.88)**	**0.037**
	-1.68(-3.01 - -0.35)	**0.014**	-1.27(-2.92 - 0.37)	0.129
	0.29(-9.77 - 10.36)	0.955	3.36(-5.63 - 12.36)	0.463
	-8.41(-13.54 - -3.29)	**0.001**	**-8.93(-15.52 - -2.33)**	**0.008**
	-6.08(-15.78 - 3.61)	0.219	-1.05(-8.05 - 5.96)	0.770
	-9.92(-21.08 - 1.24)	0.081	0.93(-5.25 - 7.11)	0.767
	7.16(-16.52 - 30.84)	0.553	0.81(-6.44 - 8.06)	0.827
	-0.33(-0.95 - 0.29)	0.295	-0.47(-1.08 - 0.14)	0.134
	0.34(-0.28 - 0.96)	0.289	0.47(-0.14 - 1.09)	0.130
	0.33(-0.38 - 1.03)	0.366	0.39(-0.32 - 1.10)	0.283
	-0.32(-1.03 - 0.38)	0.371	-0.38(-1.09 - 0.33)	0.289
	-2.02(-6.04 - 2.01)	0.325	-2.27(-6.00 - 1.47)	0.235
	0.27(-3.67 - 4.20)	0.894	-0.55(-5.37 - 4.27)	0.823
	-0.09(-1.49 - 1.31)	0.900	0.45(-2.35 - 3.25)	0.753
	-1.58(-6.53 - 3.37)	0.531	-0.58(-6.09 - 4.93)	0.837
	1.89(-3.46 - 7.25)	0.489	0.64(-6.26 - 7.55)	0.855



7

Clinical and quality of life outcomes after aortic valve replacement and aortic root surgery in adult patients <65 years old

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ABSTRACT

Selecting the optimal surgical treatment strategy in patients below the age of 65 years (i.e., non-elderly patients) with aortic valve or aortic root disease remains challenging. The objective of the current study is to summarize contemporary research on clinical and quality of life outcomes after aortic valve replacement (AVR) and aortic root surgery in non-elderly patients. Recent systematic reviews on clinical outcome after biological and mechanical AVR, the Ross procedure and aortic root surgery show that event occurrence is considerable after any type of AVR or aortic root surgery and—with the exception of the Ross procedure— survival is suboptimal. Although thromboembolism and bleeding events are more common after mechanical AVR and root surgery, these events are also considerably present after biological AVR, the Ross procedure and valve-sparing aortic root surgery (VSRR). Similarly, reoperation is more common after biological AVR, the Ross procedure and VSRR, but also occurs frequently after mechanical AVR and root replacement. Published evidence in AVR patients points to the direction of better health-related quality of life (HRQoL) outcomes with a biological solutions, while the HRQoL after aortic root surgery is limited and contradictory. This review illustrates that treatment for non-elderly aortic valve and aortic root disease patients needs to be tailored to the individual patient, considering both clinical and HRQoL outcomes as crucial factors to reach a treatment decision that best reflects the patient's values and goals in life.

INTRODUCTION

Due to continued improvements in surgical technique and perioperative management, morbidity and mortality after aortic valve and aortic root surgery has decreased.[1,2] The available tools in the tool-box of the cardiac surgeon have expanded. Besides the more common surgical procedures (i.e., valve replacement with mechanical or tissue valve prosthesis, with or without replacement of the aortic root), techniques that may be considered include the Ross procedure [3], valve-sparing root replacement and external aortic support [Personalized External Aortic Root Support [4], Florida sleeve [5]]. Under-usage of the more demanding Ross procedure is likely.[6] However, not all procedures are equally applicable and careful patient selection is required. The choice for the optimal treatment strategy in patients aged 18-65 years (i.e., non-elderly patients) with aortic valve or aortic root disease is especially challenging. It requires careful weighing of the risks associated with the various treatment modalities, life expectancy and preferences of these young, mostly active patients. The objective of the current study is to present an overview of clinical outcomes and quality of life after aortic valve replacement (AVR) and aortic root surgery in non-elderly patients.

AVR

To provide an overview of contemporary clinical outcomes after AVR, three recently published systematic reviews with meta-analysis and microsimulation analysis will be discussed.

Mechanical aortic valve replacement (MAVR)

"Mechanical Aortic Valve Replacement in Non-Elderly Adults: Meta-Analysis and Microsimulation" by Korteland et al. [7] is a systematic review and meta-analysis published in 2017 including studies published between 01/1995- 12/2015 reporting clinical outcome after contemporary MAVR in patients with a mean age ≥18 and ≤55 years. Twenty-nine papers were included, encompassing 5,728 patients, 32,515 patient-years, and a pooled mean follow-up of 5.7 years. A bileaflet mechanical valve was implanted in 99.9% of pooled patients.

Bioprosthetic aortic valve replacement (BAVR)

"Bioprosthetic Aortic Valve Replacement in Nonelderly Adults: A Systematic Review, Meta-Analysis and Microsimulation" by Etnel et al. [8] is a systematic review and meta-analysis published in 2019 including studies published between 01/2001-09/2016 reporting clinical outcome after contemporary BAVR in patients with a mean age between ≥18

and ≤55 years. Nineteen papers were included, encompassing 2,686 patients, 21,117 patient-years, and a pooled mean follow-up of 7.9 years. Fifty-two percent of pooled patients received a porcine biological valve, 47.9% received a bovine pericardial valve. Seventy-eight point two percent of implanted valves were stented, 21.7% were stentless.

The Ross procedure (Ross)

"The Ross Procedure: A Systematic Review, Meta-Analysis, and Microsimulation" by Etnel et al. [9] is a systematic review and meta-analysis published in 2018 including studies published between 01/2001-11/2017 reporting clinical outcome after the Ross procedure in adult and/or pediatric patients. Only the adult subgroup was considered in this review, including 35 papers, 6,892 patients, 49,435 patient-years and a pooled mean follow-up of 8.4 years. Ninety-five point three percent of pooled patients received a total root replacement (TRR), 3.8% received an inclusion cylinder and 0.8% received a subcoronary implantation. The right ventricle outflow tract conduit was an allograft in 86% and a bioprosthesis in 14%.

All three papers used a microsimulation model to extrapolate pooled outcome estimates from the meta-analyses. Details of the concept of microsimulation have been previously published.[9-11] In brief, meta-analysis-based estimates of operative and long-term mortality and surgery-related event rates are entered into the microsimulation model.

Using this data, the model estimates age-specific lifetime event risks, life expectancy, event free life expectancy and causes of mortality.

Clinical outcome

Table 1 depicts the patient and procedural characteristics of the AVR studies. The clinical outcome estimates are depicted in Table 2.

Early morbidity and mortality

Early stroke rate in MAVR was comparable to early thromboembolism rate in BAVR. Other early events could not be presented due to inconsistent reporting in the included studies. Early mortality risks were comparable after MAVR and BAVR. Early mortality was slightly lower after Ross compared to MAVR and BAVR. This difference is possibly due to the Ross procedure being performed by specialized surgeons.[12] Furthermore, a selection bias in Ross patients towards a lower pre-operative risk could be present due to high-risk patients not being selected for the Ross procedure.

Table 1. Baseline characteristics—aortic valve replacement

Variable	Mechanical AVR		Bioprosthetic AVR		Ross	
	Pooled estimate	Range	Pooled estimate	Range	Pooled estimate	Range
Total patient number	5,728	20-865	2,686	36-383	6,892	21-1,779
Surgical period	1977-2014		1976-2013		1986-2016	
Total follow-up (patient-years)	32,515		21,117		49,435	
Mean follow-up (years)	5.7	1-12	7.9	2.1-14.2	8.4	1.4-15.9
Mean age (years)	48	33-55	51	44-55	42	23-50
Male (%)	72	50-91	53	0.2-85	73	51-87
Aortic valve haemodynamics (%)						
Stenosis	43	0-100	41	20-77	41	11-73
Regurgitation	40	0-70	40	25-52	33	9-62
Mixed disease	16	0-30	19	12-49	26	0-55
Etiology (%)						
Degenerative	22	0-78	36	7-85	8	1-44
Endocarditis	10	0-100	13	0-11	19	3-100
Rheumatic	36	0-78	30	2-89	14	2-30
Congenital	17	0-57	10	0-62	52	38-84
Prosthetic valve dysfunction	4	0-22	-	-	-	-
Other/unknown	12	0-66	10	0-30	6	5-18
NYHA class (%)						
I/II	-	-	56	25-80	62	30-100
III/IV	-	-	44	21-81	38	0-70
Bicuspid aortic valve (%)	25	1-100	15	14-19	63	34-94
Prior cardiac operation (%)	8.4	0-26	8	0-13	13	8-72
Emergency/urgent surgery (%)	3	0-35	6	0-21	4	1-50
Concomitant surgery (%)						
Ascending aorta	9	0-33	8	0-18	16	0-60
CABG	7	0-18	12	0-27	5	0-26
Other valve	3	0-25	12	0-27	5	0-23

AVR, aortic valve replacement; Ross, the Ross procedure; Range, range of the means of included studies; NYHA, New York Heart Association; CABG, coronary artery bypass grafting.

Late morbidity

The valve-related reintervention rate was highest after BAVR and slightly lower after the Ross procedure. Valve-related reintervention rate after MAVR was significantly lower compared to BAVR and Ross, however, still considerable. The reinterventions after MAVR were mostly caused by non-structural valve dysfunction (NSVD), valve thrombosis or prosthetic valve endocarditis. As expected, structural valve deterioration (SVD) was absent in the MAVR population. In the BAVR population, SVD event rate was 1.59%/y

(95% CI, 1.21-2.10%/y). NSVD was comparable between MAVR and BAVR. SVD and NSVD rates could not be presented for the Ross population due to insufficient reporting.

Thromboembolism rates were significantly higher after MAVR compared to BAVR and Ross. Major bleeding event rates were higher in MAVR compared to BAVR and Ross, due

Table 2. Outcome estimates—aortic valve replacement

Variable	Mechanical AVR		Bioprosthetic AVR		Ross	
	Pooled estimate	Range	Pooled estimate	Range	Pooled estimate	Range
Early <30 days (%)						
Mortality	3.15	2.37-4.21	3.3	2.39-4.55	2.01	1.44-2.82
Re-exploration for bleeding	5.15	2.57-11.81	4.08	1.96-8.51		
Peripheral bleeding	0.41	0.15-1.09				
Thromboembolism			1.6	0.89-2.87		
Stroke	1.55	0.98-2.46				
Transient ischemic attack	0.81	0.38-1.72				
Valve thrombosis	0.3	0.09-1.05				
Myocardial infarction	0.87	0.40-1.87				
Endocarditis	0.43	0.16-1.13				
DSI/mediastinitis	2.48	1.56-3.94				
Pacemaker implantation	3.53	2.47-5.05				
Late >30 days (%/y)						
Overall mortality	1.55	1.25-1.92	2.39	1.13-2.94	0.59	0.46-0.76
Cardiac	0.95	0.71-1.27	0.96	0.71-1.29	0.24	0.17-0.33
Valve-related	0.6	0.44-0.81	0.6	0.37-0.98	0.21	0.14-0.32
SUUD	0.37	0.26-0.54	0.3	0.12-0.76	0.16	0.10-0.25
Valve-related reoperation	0.51	0.37-0.71	1.82	1.31-2.52	1.2	1.01-1.42
Ross autograft					0.83	0.68-1.01
Ross RVOT					0.47	0.37-0.59
Hemorrhage	0.85	0.65-1.12	0.22	0.16-0.32	0.1	0.01-0.67
Thromboembolism	0.9	0.68-1.21	0.53	0.42-0.67	0.17	0.11-0.27
Valve thrombosis	0.14	0.08-0.25	0.07	0.02-0.20	0.03	0.01-0.09
SVD	0.00	0.00-0.00	1.59	1.21-2.10		
NSVD	0.39	0.21-0.76	0.24	0.10-0.58		
Endocarditis	0.41	0.29-0.57	0.48	0.37-0.62		
Ross autograft					0.18	0.09-0.39
Ross RVOT					0.14	0.09-0.21
Pacemaker implantation					0.25	0.05-1.17

AVR, aortic valve replacement; Ross, the Ross procedure; CI, confidence interval; DSI, deep sternal wound infection; RVOT, right ventricular outflow tract.

to the use of oral anticoagulant therapy after MAVR. Although lower compared to MAVR, anticoagulant therapy related events were considerable in BAVR and Ross and should be taken into consideration in prosthetic valve selection. Event risks accumulate during the patients' lifetime and are considerable, especially in young patients. This accumulation of risks ("lifetime event risks") can be calculated using microsimulation. The lifetime event risks for a 45-yearold patient receiving either a MAVR, BAVR or a Ross procedure are presented in Figure 1. It is important to note that these estimates should not be compared between the populations due to the differences in patient characteristics. Visualization of lifetime risks using microsimulation provides more comprehensive insight into the risks for an individual patient and can aid in decision-making.

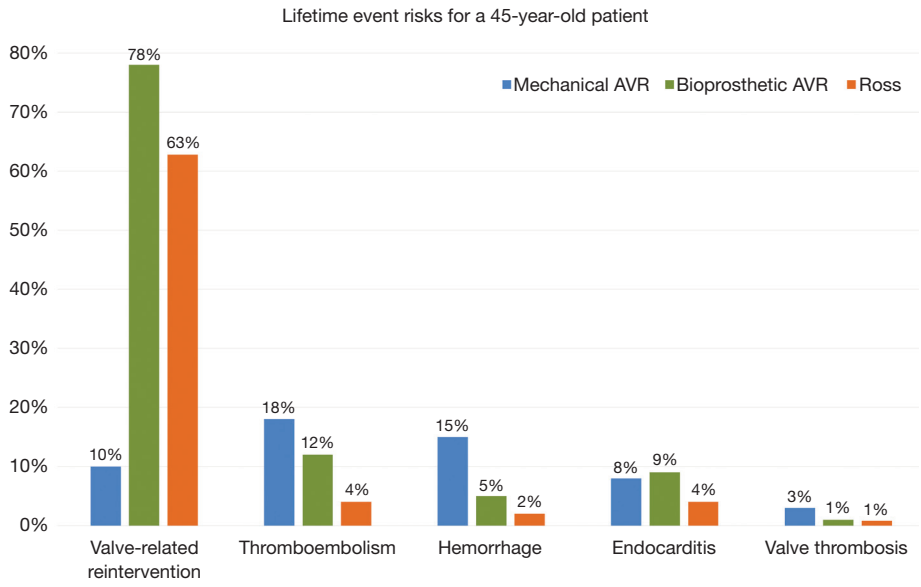

Figure 1. Microsimulation estimated lifetime event risks for a 45-year-old mechanical AVR, biological AVR or Ross patient. For Ross valve-related reintervention both autograft and RVOT reinterventions are included: isolated autograft reintervention 43.46%, isolated RVOT reintervention 14.09%, concomitant autograft + RVOT reintervention 5.23%. AVR, aortic valve replacement; RVOT, right ventricular outflow tract.

Late mortality

Late overall mortality rates were highest after BAVR, followed by MAVR. Late overall mortality after the Ross procedure was significantly lower compared to mechanical and bioprosthetic AVR. Late valve-related mortality rates were comparable between mechanical and bioprosthetic AVR and significantly lower after the Ross procedure. Whether the observed difference is due to patient selection or due to the Ross procedure providing the patient with a living neo-aortic valve with excellent hemodynamics, is a topic of debate.

The higher overall mortality in BAVR patients might be due to a worse preoperative profile, including older age, larger proportion of female patients and degenerative etiology. BAVR patients also undergo concomitant CABG and valve procedures more often, suggesting more advanced cardiac disease. In addition, BAVR patients might have a lower life expectancy due to various reasons and therefore receive a BAVR, causing a selection bias.

The higher overall mortality in BAVR patients is not likely to be attributable to the differences in valve-related mortality causes, as is shown by the comparable late valve-related mortality. This is important when considering prosthetic valve selection.

Ross patients have lower postoperative endocarditis, thromboembolism and bleeding rates, possibly explaining the lower late mortality rate. The difference in overall and valve-related mortality in Ross patients is small, suggesting that there is little excess mortality. This might be due to their preoperative profile (i.e., younger patients, lower NYHA class, congenital etiology), specialized surgeons and excellent hemodynamics following the Ross procedure.[12,13] In addition, patients receiving the Ross procedure might experience better postoperative surveillance due to the complexity of the surgery and the specialization of institutions in which they are operated. Another factor that might contribute is that congenital patients and patients with a higher socio-economic status or education level might be more involved in their disease and treatment decision-making, do more research, and therefore choose the Ross procedure more often. This type of patient might also be more involved in their postoperative care and thus receive better care and in addition might generally live a healthier lifestyle.[14,15] This underlines the need for more patient involvement and empowerment to improve clinical outcome and quality of life.

The meta-analysis based microsimulation estimates of life expectancy for patients undergoing MAVR, BAVR and Ross are presented in Figure 2 alongside the respective general population life expectancies. It is important to note that the differences between the interventional population estimates cannot be compared as they were derived from different study populations.

AORTIC ROOT SURGERY

Two recent systematic reviews with meta-analysis give an overview of current available evidence for outcomes after mechanical TRR and valve-sparing root replacement.

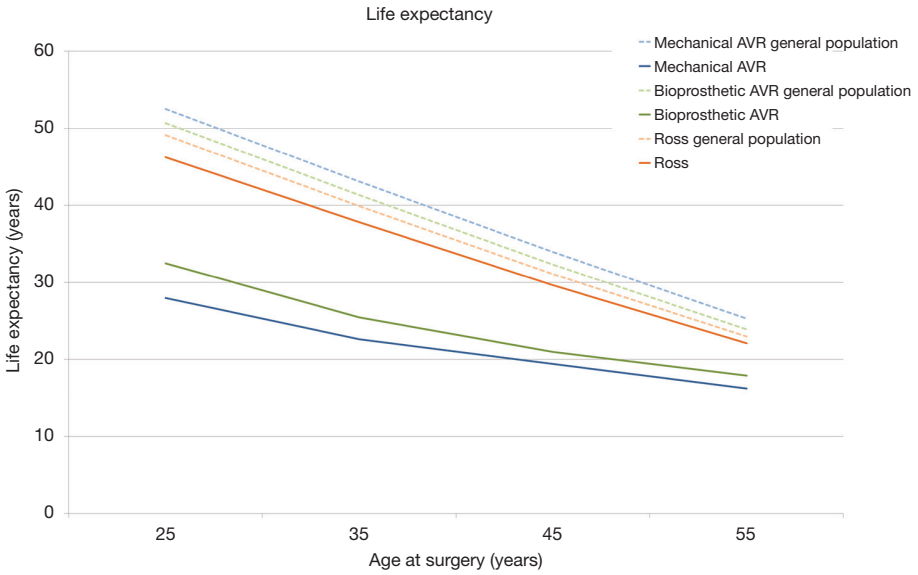

Figure 2. Microsimulation estimated life expectancy following mechanical AVR, biological AVR and Ross surgery (solid lines) and age- and sex-matched general population (dashed lines). AVR, aortic valve replacement.

Total root replacement (TRR)

Mookhoek et al. published a meta-analysis of the reported outcomes after mechanical Bentall operations.[16] They included 46 studies and a total of 7,629 patients, operated between 1968-2012. Mean clinical follow-up was 6.4 years (range, 3.0-10.4 years), resulting in 49,175 patient-years. The pooled average age was 49.8 years.

Valve sparing root replacement (VSRR)

Arabkhani et al. published a meta-analysis of reported outcomes after valve-sparing aortic root replacement in 2015.[17] Their search resulted in 31 reports over a 14-year period [2000-2014], including 4,777 patients, operated between 1988-2012. Mean clinical follow-up was 4.4 years (range, 1.5-13.2 years) and 21,716 patients-years. The pooled average age was 51.0 years.

Clinical outcome

The pooled pre- and perioperative characteristics of both studies are depicted in Table 3. Table 4 depicts the pooled early and late clinical outcomes.

Early mortality

Early morbidity was not reported in the systematic reviews. Pooled early mortality was higher after TRR compared to VSRR. This difference can be explained by the higher

Table 3. Baseline characteristics—aortic root surgery

Variable	TRR		VSRR	
	Pooled estimate	Range	Pooled estimate	Range
Total patient number	7,629	40-675	4,777	32-430
Surgical period		1968-2012		1988-2012
Total follow-up (patient-years)	49,175		21,716	
Mean follow-up (years)	6.4	3-10.4	4.4	1.5-13.2
Mean age (years)	50	29-65	51	29-63
Male (%)	76	55-91	71	57-85
Aortic valve haemodynamics (%)				
Stenosis				
Regurgitation			46*	6-100
Mixed disease				
Etiology (%)				
Type A dissection	15	0-39	11	0-33
Endocarditis	2	0-15		
Connective tissue disease	23	0-100	24	0-100
Bicuspid aortic valve	25	4-100	14	0-33
Prior cardiac operation (%)	16	1-7	4	2-12
Mechanical valve (%)	93	43-100		
Concomitant surgery (%)				
CABG	12	0-31	9	0-19
Valve surgery	6	0-12	5	0-12
(Hemi)arch	12	0-39	22	0-68

*severe AR is reported. TRR, total root replacement; VSRR, valve-sparing root replacement; Range, range of the means of included studies; CABG, coronary artery bypass grafting.

prevalence of emergency surgery, aortic dissections and previous cardiac surgery in the TRR population.

Late morbidity

Reoperation rates were higher after VSRR compared to TRR. Bleeding rates were higher after TRR, due to the mandatory use of life-long anticoagulation therapy in TRR.

Late mortality

The pooled late mortality rate was lower after VSRR compared to TRR. This difference can be explained by the preoperative differences between the populations and the lower overall event occurrence in the VSRR population. However, it should be stressed that a direct comparison between these two populations cannot be made using these data.

Table 4. Outcome estimates—aortic root surgery

Variable	TRR		VSRR	
	Pooled estimate	95% CI	Pooled estimate	95% CI
Early <30 days (%)				
Mortality	5.6	-	2.2	-
Late >30 days (%/y)				
Overall mortality	2.02	1.77-2.31	1.53	1.19-1.96
Valve-related	0.46	0.36-0.59		
Valve-related reoperation	0.3	0.22-0.41	1.32	1.0-1.74
Root-related reoperation	0.46	0.36-0.59		
Hemorrhage	0.64	0.47-0.87	0.23	0.13-0.42
Thromboembolism	0.77	0.60-1.00	0.41	0.22-0.77
Endocarditis	0.39	0.33-0.46	0.23	0.11-0.51
MAVRE	2.66	2.17-3.24	1.66	1.24-2.23

TRR, total root replacement; VSRR, valve-sparing root replacement; CI, confidence interval; %/y, percentage per patient-year; MAVRE, major adverse valve-related event.

HEALTH RELATED QUALITY OF LIFE OUTCOMES

There is a growing body of observational evidence on quality of life after AVR. The landmark paper by Aicher et al. studied quality of life and anxiety and depression after mechanical valve implantation, the Ross procedure and aortic valve repair. It found that quality of life, including valve-related aspects such as valve sound, frequency of doctor visits and fear of potential complications, is influenced by the type of operation. Patients who received mechanical prostheses had worse general health, physical functioning and mental health and more cardiac-related anxiety.[18] These observations have been confirmed by several other studies, that all point into the direction of a better QoL with a biological solution.[19,20]

Contemporary evidence on QoL outcomes after aortic root surgery was reviewed by de Heer et al. and showed that limited and only observational data with contradicting results are available.[21] Although a study by Olsson et al. in 1999 showed significantly worse health-related QoL outcomes for patients after thoracic aortic surgery compared to the general population, an updated study in 2013 showed comparable QoL.[22,23] This may be the result of advances in cardiac surgery and improved cardiovascular care in more recent years and is in agreement with other recent studies that report QoL in thoracic aortic surgery patients to be comparable to the general population.[24-26] There is some evidence on differences in QoL between aortic root surgery strategies: observational evidence suggests that QoL after surgery is significantly worse in most of the domains of the SF-36 in patients after TRR versus VSRR surgery. TRR patients reported to be signifi-

cantly more disturbed by valve sound, more afraid that their valve will fail and assigned a lower score to their overall condition.[27] There is no evidence that there is a difference between mechanical versus biological TRR surgery.[28]

Given these observations, the notion arises that it is important to consider QoL as a crucial factor in treatment selection for both AVR and aortic root surgery, in order to reach an evidence-based and patient-centered treatment decision that best reflects the patient's values and goals in life. The concept of shared decision-making allows physicians and patients to reach such decisions, and is gaining interest throughout the world and even in the European and US guidelines for the management of valvular heart disease.[29,30] There is growing evidence that tools to support shared decision-making in prosthetic heart valve selection are indeed effective in reducing anxiety and depression and improving mental health and knowledge in patients who are facing heart valve replacement.[31]

FUTURE PERSPECTIVES

Patient tailored treatment

The continued decline in mortality after aortic valve and aortic root surgery over the years calls for a shift in focus in clinical decision-making towards quality of life. As demonstrated by the evidence outlined above, all currently available options for aortic valve and root surgery remain imperfect. The outcome profiles of the various treatment options are in stark contrast to one another, each with different implications for many aspects of patients' lives, both physical and psychosocial.

As treatment decisions have such an important impact on patients' lives, choosing the optimal treatment tailored for each patient with regard for individual values, preferences and life planning is of utmost importance. Because preferences and treatment goals vary between individual patients and also between patients and their physicians, involvement of patients in the decision-making process is essential. Although both physicians and patients have been found to prefer shared roles in decision-making, physicians still experience substantial difficulty in adequately informing and involving their patients.[32-34] Thus, there is an urgent need for innovative solutions to aid in more effectively informing and involving patients. In this light, online patient information portals and decision aids present promising opportunities.[31,35] Methods for elucidating patients' values, preferences and treatment goals and how these can effectively be incorporated in decision-making should be explored.

The evolution of clinical outcome over the years should also translate to a shift in research focus from classical outcome measures such as survival and event occurrence towards patient-centered outcomes that better reflect what is valuable and meaningful to patients. It remains to be elucidated which outcomes patients value most after aortic valve and aortic root surgery. In any case, high quality evidence on clinical outcome remains indispensable. The AVIATOR initiative of the Heart Valve Society (HVS) is a longitudinal multicenter international registry that focuses on patients with aortic valve insufficiency and/or a dilated ascending aorta. The wish is to embrace the complete disease trajectory, starting from the diagnoses, including operation and long-time follow-up. Since 2013 the AVIATOR Adult Surgical Registry is enrolling patients and comprises already 5,000 cases.[36] Furthermore, the HVS started a new initiative to evaluate prosthetic AVR: the LEOPARD registry. These multicenter registries should provide a solid evidence base, by applying uniform definitions, to evaluate long-term patient outcomes for the different treatment strategies for aortic valve root disease in non-elderly patients. The addition of quality of life outcomes to the AVIATOR and LEOPARD registries could be of great added value.

Novel treatment strategies

Unfortunately, "one valve for life" is not yet on the horizon. Research into tissue engineered valves has made great progress, however in vivo use in humans is not yet available.[37,38] Meanwhile, other novel treatment strategies are available that are possibly underutilized.

Advances in aortic valve repair might provide improved outcomes. Furthermore, minimally invasive techniques are developing. In the prevention of further aortic root dilatation in Marfan patients, a new stabilization technique was introduced: Personalized External Aortic Root Support (PEARS). The individual's aortic root is replicated by a 3-dimensional printed model to produce an individualized polymer mesh sleeve, which is wrapped around the aorta. Over a 12-year period [2004-2016] more than 60 patients were treated with PEARS in six centers.[4]

With the promise of more durable bioprostheses, the possibility of transcatheter valve-in-valve procedures might become available for younger patients. However, both the prolonged durability of bioprostheses and transcatheter valve-in-valve outcomes are not sufficiently researched in non-elderly patients.

If anticoagulation therapy is unavoidable, reducing associated events is of great importance. New mechanical prostheses are being developed that require lower INR levels.[39] Optimized anticoagulation therapy through self-management can achieve comparable

survival between Ross patients and MAVR patients.[40] Two studies included in the BAVR systematic review reported that at the end of follow-up 25-30% of the BAVR patients required oral anticoagulants, mostly due to atrial fibrillation.[41,42] In an effort to reduce anticoagulation-related events, characteristics that put BAVR patients at risk for atrial fibrillation should be explored. Furthermore, research into the use of NOAC's for atrial fibrillation shows this might be a safe treatment strategy in BAVR.[43]

CONCLUSIONS

This review provides an overview of current evidence on aortic valve and aortic root replacement in non-elderly adults. The differences in clinical outcome between treatment options are not a black-and-white issue and this underlines the need for individual patient tailored treatment and shared decision-making. Involved and empowered patients can make informed decisions and consequently experience improved clinical outcome and quality of life.

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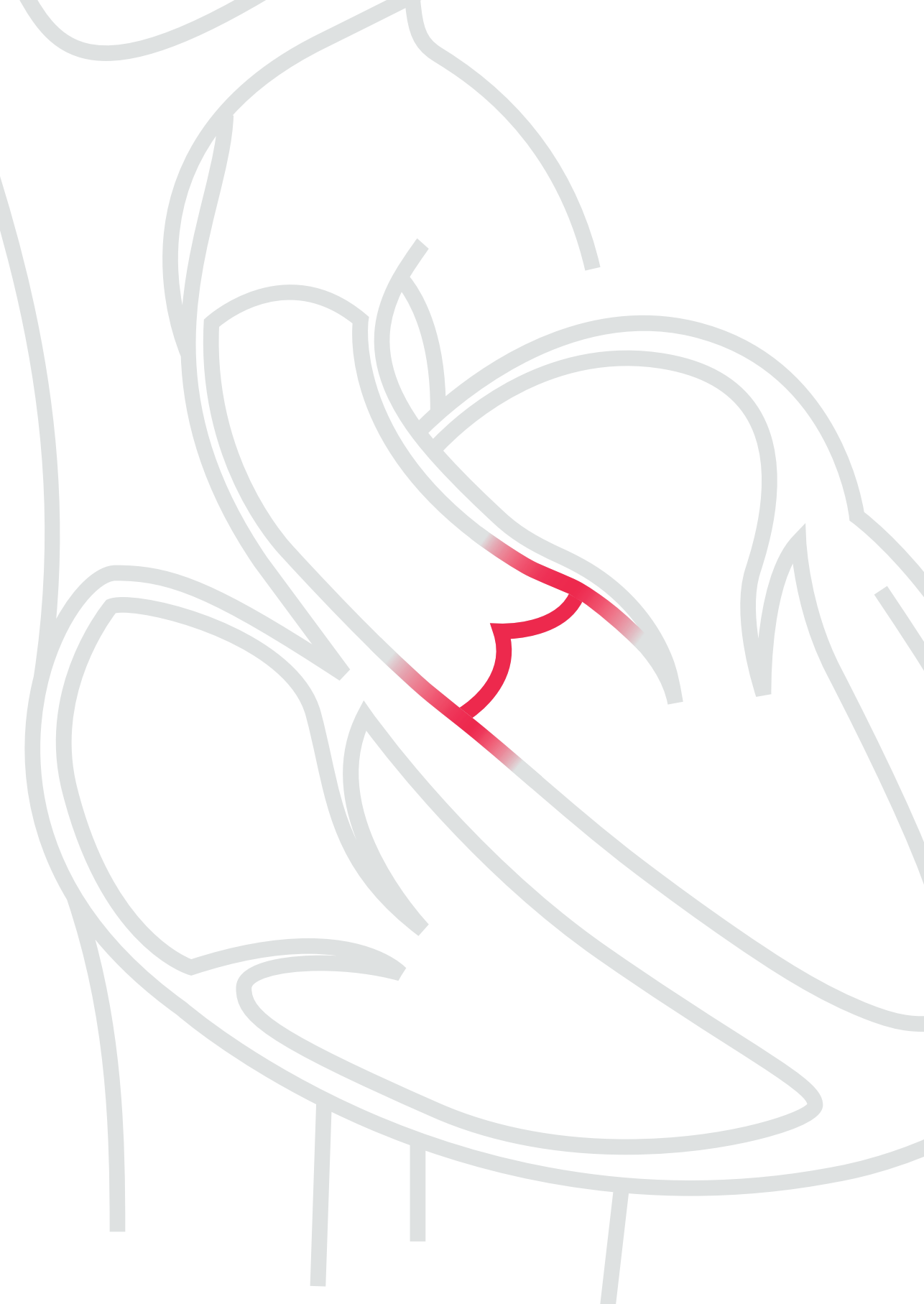

8

Decellularized versus standard pulmonary allografts in the Ross procedure: propensity-matched analysis

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ABSTRACT

Background

It is hypothesized that decellularization of allografts used for right ventricular outflow tract reconstruction may result in decreased valve deterioration. This study compared the durability of fresh decellularized pulmonary allografts with standard cryopreserved pulmonary allografts in patients undergoing the Ross procedure.

Methods

The Ross procedure was performed in 144 patients with decellularized allografts (DA) from 2005 to 2014 and in 619 with standard cryopreserved allografts (SCA) from 1990 to 2014. Propensity score matching was used to compare early and midterm clinical outcome and echocardiographic allograft function over time between the two groups.

Results

We matched 94 DA patients (79.3% male; median age, 34.0 years; mean follow-up, 2.4 ± 1.9 years) to 94 SCA patients (78.3% male; median age, 35.0 years; mean follow-up, 9.4 ± 4.2 years). There were no significant differences in baseline characteristics after matching. The matched DA vs SCA groups, respectively, were comparable in actuarial 5-year freedom from allograft dysfunction (85.6% [95% confidence interval {CI}, 53.9% to 96.2%] vs 93.3% [95% CI, 85.7% to 96.9%], $p = 0.892$), freedom from allograft reintervention (98.8% [95% CI, 91.7% to 99.8%] vs 95.5% [95% CI, 88.5% to 98.3%], $p = 0.383$), survival (95.3% [95% CI, 87.8% to 98.2%] vs 97.7% [95% CI, 91.3% to 99.4%], $p = 0.323$), and event-free survival (83.5% [95% CI, 70.6% to 91.1%] vs 84.5% [95% CI, 75.2% to 90.5%], $p = 0.515$). Longitudinal echocardiographic analyses showed a similarly modest increase in allograft gradient and regurgitation grades over time in both groups, although direct statistical comparison was not possible.

Conclusions

Up to 5 years of follow-up, DA and SCA used for right ventricular outflow tract reconstruction in the Ross procedure are associated with comparably excellent clinical and hemodynamic outcome. Longer follow-up and dedicated echocardiographic studies will shed light on the long-term performance of DAs.

INTRODUCTION

Replacement of the aortic valve with a pulmonary autograft (the Ross procedure) was introduced in the late 1960s [1] and is considered the preferred option for aortic valve replacement in children and young adults by many experts owing to the favorable hemodynamic characteristics, low risk of endocarditis, low thrombogenicity, avoidance of anticoagulation therapy, and its growth potential.[2, 3] However, this procedure requires reconstruction of the right ventricular outflow tract (RVOT) from which the pulmonary autograft was harvested, which is most commonly accomplished with pulmonary allografts.[4]

Standard cryopreserved allografts are susceptible to valve degeneration, which results in an increased risk of reoperation.[3] There is increasing experimental and clinical evidence that suggests the limited durability of these valves may be partly caused by the elicited host immune response.[5-8] In response, decellularization techniques have been developed that reduce the graft cellularity, leaving an intact extracellular matrix scaffold.[9] These decellularized allografts have been introduced into clinical use for RVOT reconstruction, and although early results have been promising, midterm comparisons of decellularized allografts (DAs) with standard cryopreserved allografts (SCAs) are scarce, often small in size, and seldom focused on the Ross procedure.[10-13] Consequently, the effect of decellularization on late RVOT allograft function remains unclear, especially when applied in the setting of the Ross procedure.

We therefore conducted a propensity-matched comparison of midterm clinical outcomes and echocardiographic allograft function over time after RVOT reconstruction with fresh DAs vs SCAs in the Ross procedure.

METHODS

Between May 2005 and July 2014, 144 patients underwent the Ross procedure with the use of fresh DAs for RVOT reconstruction at Santa Casa de Curitiba, Pontifícia Universidade Católica do Paraná.[14] In addition, 619 patients underwent the Ross procedure with the use of SCA for RVOT reconstruction at the University of L€ubeck between February 1990 and August 2014.[15] All allografts were of pulmonary origin, and no aortic allografts were used. Demographic, clinical, and echocardiographic data on all patients in the DA and the SCA groups were prospectively collected. This study was approved by The Institutional Review Board of the participating centers, and informed consent was waived.

Table 1. Operative details

Variable[a]	Unmatched			Matched		
	DA (n = 144)	SCA (n = 619)	*p* Value	DA (n= 94)	SCA (n = 94)	*p* Value
Operative technique			<0.001			<0.001
Root replacement	121 (84.0%)	15 (2.4%)		78 (83.0%)	2 (2.1%)	
Subcoronary implantation	0 (0.0%)	571 (92.2%)		0 (0.0%)	91 (96.8%)	
Inclusion cylinder	23 (16.0%)	33 (5.3%)		16 (17.0%)	1 (1.1%)	
Allograft diameter, mm	24 (14-30)	26 (22-32)	<0.001	24 (18-30)	26 (24-30)	<0.001
RVOT adjustment[b]	70 (48.6%)	232 (37.5%)	0.014	40 (42.6%)	39 (41.5%)	1.000
Fenestration	57 (39.6%)	226 (36.5%)	0.492	36 (38.3%)	32 (34.0%)	0.636
Donor age, y	42 (5-59)	49 (0-69)	<0.001	42 (18-59)	51 (21-63)	<0.001
Male donor	104 (72.2%)	387 (62.5%)	0.641	67 (71.3%)	60 (63.8%)	1.000

[a] Continuous data are expressed as median (range) and categorical data as count (%). [b] RVOT myocardial resection and/or patch augmentation.
DA = decellularized allograft; RVOT = right ventricular outflow tract; SCA = standard cryopreserved allograft.

Surgical technique and decellularization

The surgical techniques have been previously described.[13, 15] In summary, all operations were performed by a single surgeon in each center (F.D.A.C. and H.H.S.) through a median sternotomy with standard cardiopulmonary bypass and mild to moderate systemic hypothermia with the use of cold blood or crystalloid cardioplegia for myocardial protection. Operative details are listed in Table 1. Implantation of the pulmonary allografts was performed in a similar fashion for DA and SCA patients (Supplement 1).

All pulmonary allografts in the DA group were decellularized with a proprietary 0.1% solution of sodium dodecylsulfate and kept in cold (4°C) phosphate-buffered saline solution for up to 90 days before implantation. Further details on the acquisition, processing, and decellularization process have been previously described.[6, 13]

Clinical and echocardiographic follow-up

Postoperative clinical and two-dimensional echocardiographic assessment was scheduled at discharge and at 6 months, 1 year, and yearly thereafter for all patients. SCA patients had an additional examination at 3 months after the operation. Maximum velocities across the RVOT allograft were obtained by continuous Doppler measurement, and pressure gradients were calculated by the modified Bernoulli equation. The degree of conduit regurgitation was estimated by the maximum length and area of the regurgitant jet at the level of the outflow tract [16] and graded as absent, trivial, mild (grade 1), moderate (grade 2), or severe (grade 3/4). Follow-up in the unmatched cohort was 98.5% complete overall, consisting of 91.8% in the DA group and 98.8% in the SCA group.

Data collection

All data were prospectively collected. Outcome events were defined according to the reporting guidelines.[17] Allografts that developed grade 3 or higher regurgitation or a peak Doppler gradient of 36 mm Hg or more, or both, were considered dysfunctional .[18] The composite end point of "any event" included death from any cause, endocarditis, thromboembolism, major bleeding, reintervention, development of allograft dysfunction, and permanent pacemaker implantation.

Propensity score construction and analyses

As there were significant differences between the DA and SCA patients in most baseline characteristics (Table 2), we performed both propensity score adjustment and propensity score matching.[19, 20] The propensity scores were constructed using a nonparsimonious multivariable logistic regression model with the treatment variable (DA vs SCA) as the dependent variable. Because of their statistical and/or clinical significance, all baseline characteristics listed in Table 2 were included as covariates in the propensity model.[19, 21, 22]

For propensity score-adjusted analyses, the propensity score and the treatment allocation variable (DA vs SCA) were both entered into a logistic regression model for 30- day mortality and Cox proportional hazards models for late death, allograft reintervention, allograft dysfunction, and the occurrence of any event.

In addition, propensity score matching was conducted at a 1:1 ratio with the use of the nearest neighbor matching method because there was evidence of inadequate propensity adjustment in the propensity score-adjusted analyses (the propensity score was statistically significant in the adjusted Cox regression model for late death and allograft dysfunction).[22, 23] A propensity score difference of 0.25 was used as a maximum caliper width for matching 2 patients.

Statistical analysis

Analyses of clinical data

Analyses of clinical data were performed in IBM SPSS Statistics 21.0.0.1 software (IBM Corp, Armonk, NY). Continuous data are presented as mean ± SD or median (range), and comparison in the unmatched cohort was done using the unpaired t test unless the data were not normally distributed (Kolmogorov-Smirnov test); in these instances, the Mann-Whitney *U* test was used for comparison. Categorical data are presented as proportions, and comparison in the unmatched cohort was done using the χ^2 test or the

Table 2. Baseline characteristics

Variable[a]	Unmatched			Matched		
	DA (n = 144)	SCA (n = 619)	*p* Value	DA (n= 94)	SCA (n = 94)	*p* Value
Implantation period	2005-2014	1990-2014		2005-2014	1995-2014	
Age at operation, y	30.11 (3.03-60.44)	45.57 (13.80-70.52)	<0.001	33.97 (3.04-60.44)	34.98 (13.81-58.75)	0.607
Body mass index, kg/m2	24.22 (13.19-38.27)	25.18 (16.14-40.48)	0.007	24.5 (14.36-38.27)	24.79 (17.99-40.48)	0.494
Male sex	110 (76.4%)	471 (76.1%)	1.000	74 (78.7%)	75 (79.8%)	1.000
Blood group						
O	78 (54.2%)	212 (34.2%)	<0.001	48 (51.1%)	45 (47.9%)	0.798
A	46 (31.9%)	258 (41.7%)	0.026	32 (34.0%)	36 (38.3%)	0.607
B	10 (6.9%)	77 (12.4%)	0.056	8 (8.5%)	5 (5.3%)	0.623
AB	10 (6.9%)	37 (6.0%)	0.825	6 (6.4%)	7 (7.4%)	0.958
Missing	0 (0.0%)	35 (5.7%)		0 (0.0%)	1 (1.1%)	
Etiology						
Congenital	96 (66.7%)	366 (59.1%)	0.116	68 (72.3%)	72 (76.6%)	0.618
Rheumatic	26 (18.1%)	6 (1.0%)	<0.001	13 (13.8%)	3 (3.2%)	0.322
Degenerative/calcified	9 (6.3%)	28 (4.5%)	0.783	6 (6.4%)	3 (3.2%)	0.743
Prosthetic valve dysfunction	6 (4.2%)	2 (0.3%)	0.309	1 (1.1%)	2 (2.1%)	0.469
Endocarditis	7 (4.9%)	152 (24.6%)	<0.001	6 (6.4%)	2 (2.1%)	0.809
Missing	0 (0.0%)	65 (10.5%)		0 (0.0%)	12 (12.8%)	
Hemodynamics						
Stenosis	48 (33.3%)	104 (16.8%)	<0.001	25 (26.6%)	21 (22.3%)	0.618
Regurgitation	49 (34.0%)	159 (25.7%)	0.048	30 (31.9%)	33 (35.1%)	0.755
Combined	47 (32.6%)	355 (57.4%)	<0.001	39 (41.5%)	40 (42.6%)	1.000
Missing	0 (0.0%)	1 (0.2%)		0 (0.0%)	0 (0.0%)	
Aortic valve morphology						
Tricuspid	39 (27.1%)	140 (22.6%)	0.275	20 (21.3%)	17 (18.1%)	0.884
Bicuspid	91 (63.2%)	450 (72.7%)	0.025	68 (72.3%)	70 (74.5%)	0.677
Unicuspid	14 (9.7%)	15 (2.4%)	<0.001	6 (6.4%)	4 (4.3%)	0.754
Missing	0 (0.0%)	12 (1.9%)		0 (0.0%)	3 (3.2%)	
Angina	2 (1.4%)	158 (25.5%)	<0.001	2 (2.1%)	4 (4.3%)	0.625
Missing	0 (0.0%)	1 (0.2%)		0 (0.0%)	0 (0.0%)	
NYHA Classification			<0.001			0.790
I/II	76 (52.8%)	504 (81.4%)		59 (62.8%)	63 (67.0%)	
III/IV	45 (31.3%)	114 (18.4%)		22 (23.4%)	31 (33.0%)	
Missing	23 (16.0%)	1 (0.2%)		13 (13.8%)	0 (0.0%)	

Table 2. Baseline characteristics (continued)

Variable[a]	Unmatched			Matched		
	DA (n = 144)	SCA (n = 619)	*p* Value	DA (n= 94)	SCA (n = 94)	*p* Value
Comorbidities						
Concomitant congenital disease	8 (5.6%)	6 (1.0%)	0.001	4 (4.3%)	4 (4.3%)	1.000
Cerebrovascular disease	3 (2.1%)	29 (4.7%)	0.246	1 (1.1%)	1 (1.1%)	1.000
Diabetes mellitus	1 (0.7%)	29 (4.7%)	0.029	1 (1.1%)	1 (1.1%)	1.000
Hypertension	31 (21.5%)	203 (32.8%)	0.009	23 (24.5%)	24 (25.5%)	1.000
Renal disease	0 (0.0%)	35 (5.7%)	0.001	0 (0.0%)	0 (0.0%)	NA
Coronary artery disease	3 (2.1%)	36 (5.8%)	0.090	2 (2.1%)	2 (2.1%)	1.000
Peripheral artery disease	1 (0.7%)	3 (0.5%)	0.568	1 (1.1%)	0 (0.0%)	NA
Chronic pulmonary disease	2 (1.4%)	12 (1.9%)	1.000	2 (2.1%)	3 (3.2%)	1.000
Previous cardiac operation	29 (20.1%)	31 (5.0%)	<0.001	10 (10.6%)	15 (16.0%)	0.405
Urgent (<24 h)	1 (0.7%)	4 (0.6%)	1.000	0 (0.0%)	0 (0.0%)	NA

[a] Continuous data are expressed as median (range) and categorical data as count (%).
DA = decellularized allograft; NA = not assessable due to the small number of cases; NYHA = New York Heart Association; SCA = standard cryopreserved allograft.

Fisher exact test where appropriate. Comparison in the matched cohort was done using paired-sample *t* test, McNemar test, or Wilcoxon signed rank test, where appropriate.

Actuarial freedom from events was estimated according to the Kaplan-Meier method, and the Tarone-Ware test was used for comparisons. Logistic regression and Cox proportional hazards models were used for propensity-adjusted analyses, as described above. All tests were two-sided, and statistical significance was inferred at a *p* value of less than 0.05.

Analyses of echocardiographic data

Echocardiographic data were analyzed in R 2.13.0 software (R Foundation for Statistical Computing, Vienna, Austria). Mixed-effects models were used to assess changes in echocardiographic measurements over time while accounting for the correlation between repeated follow-up measurements in each patient. Linear mixed models were used for the continuous outcomes, and mixed-effects continuation ratio models were used for the ordinal outcomes. To allow for more flexibility in the specification of the patient-specific longitudinal trajectories, we used natural cubic splines with three internal knots placed at the corresponding percentiles of the follow-up times. Residual plots were used to validate the model's assumption, and transformations of the outcome variables were performed when appropriate. Missing echocardiogram measurements were assumed to be missing at random.[24, 25]

RESULTS

Clinical outcome in the unmatched cohort

Baseline characteristics of the unmatched DA (n = 144; mean follow-up, 2.4 ± 1.9 years) and SCA (n = 619; mean follow-up, 9.9 ± 4.9 years) patients are listed in Table 2. Outcome events in the unmatched cohort are listed in Table 3. Overall, 15-year actuarial freedom from allograft reintervention and all Ross-related reinterventions was 94.8% (95% confidence interval [CI], 91.4% to 96.9%) and 90.0% (95% CI, 85.9% to 92.9%), respectively. Details of outcome in the unmatched DA and SCA groups have been previously published.[14, 15]

Hazards of allograft dysfunction and reintervention were comparable between DA and SCA before and after propensity adjustment (Table 4). After propensity adjustment, the hazard of late death was significantly higher in the DA group than in the SCA group. However, the propensity score variable was statistically significant in the regression model, which suggests inadequate adjustment for baseline differences.

The hazard of any event was significantly higher in the DA group before propensity adjustment, but this difference was not significant after propensity adjustment.

Exploration of the propensity score distribution of the two treatment groups revealed extreme skewness of the propensity score of the SCA patients (Appendix 2).

Clinical outcome in the matched cohort

Baseline characteristics of the matched cohort are listed in Table 2 and those of the patients who could not be matched are listed in Supplement 4. The propensity score was used to match 94 DA patients (mean follow-up, 2.4±1.9 years) to 94 SCA patients (mean followup, 9.4 ± 4.2 years). After propensity matching, there were no significant differences in baseline characteristics between the two groups. There was adequate covariate balance across the two groups (Appendix 2 and 3). Outcome events in the matched cohort are listed in Table 3. In the propensity-matched DA and SCA cohorts, respectively, early mortality (1.1% vs 0.0%, $p = 1.00$) and 5-year actuarial freedom from allograft dysfunction (85.6% [95% CI, 53.9% to 96.2%] vs 93.3% [95% CI, 85.7% to 96%.9], $p = 0.892$), freedom from allograft reintervention (98.8% [95% CI, 91.7% to 99.8%] vs 95.5% [95% CI, 88.5% to 98.3%], $p = 0.383$), survival (95.3% [95% CI, 87.8% to 98.2%] vs 97.7% [95% CI, 91.3% to 99.4%], $p = 0.323$), and event-free survival (83.5% [95% CI, 70.6% to 91.1%] vs 84.5% [95% CI, 75.2% to 90.5]%, $p = 0.515$) were comparable (Fig 1).

In the first 5 years of follow-up of the matched cohort, all cases of allograft dysfunction concerned moderate-tosevere stenosis. There was no severe regurgitation in this period.

Table 3. Outcome events

Variable	Unmatched		Matched	
	DA (n = 144)	SCA (n = 619)	DA (n = 94)	SCA (n = 94)
Follow-up				
Mean ± SD, years	2.4 ± 1.9	9.9 ± 4.9	2.4 ± 1.9	9.4 ± 4.2
Total, patient-years	339	6,150	225	887
Patients with events, No.	18	169	12	27
Early death, No. (%)	2 (1.39)	2 (0.32)	1 (1.06)	0 (-)
Late death, No. (%/y)	3 (0.88)	54 (0.88)	3 (1.33)	4 (0.45)
Bleeding, No. (%/y)	1 (0.29)	8 (0.13)	1 (0.44)	0 (-)
Thromboembolism, No. (%/y)	2 (0.59)	31 (0.50)	2 (0.89)	4 (0.45)
Reintervention, No. (%/y)	3 (0.88)	51 (0.83)	3 (1.33)	11 (1.24)
Autograft only	2 (0.59)	21 (0.34)	2 (0.89)	4 (0.45)
Allograft only	1 (0.29)	21 (0.34)	1 (0.44)	9 (1.01)
Both	0 (-)	9 (0.15)	1 (0.44)	9 (1.01)
Allograft dysfunction, No. (%/y)	8 (2.36)	68 (1.11)	4 (1.78)	16 (1.80)
Regurgitation grade ≥3	0 (0.00)	19 (0.31)	0 (0.00)	3 (0.34)
Stenosis, V_{max} ≥3.0 m/s	8 (2.36)	56 (0.91)	4 (1.78)	15 (1.69)
Endocarditis, No. (%/y)	2 (0.59)	23 (0.37)	2 (0.89)	6 (0.68)
Permanent pacemaker implantation, No. (%/y)	2 (0.59)	5 (0.08)	1 (0.44)	0 (-)

[a] Data expressed as No. (%/y) is the count (linearized occurrence rate/y). Event counts represent the number of events, not the number of patients.

DA = decellularized allograft; No. = number; SCA = standard cryopreserved allograft; RVOT = right ventricular outflow tract; V_{max} = aortic valve area.

Table 4. Regression in unmatched cohort[a]

Variable	DA Compared With SCA			
	Unadjusted		Propensity Adjusted	
	OR/HR[b] (95% CI)	*p* Value	OR/HR[b] (95% CI)	*p* Value
Early death	4.35 (0.61-31.11)	0.144	5.07 (0.35-72.67)	0.232
Late death	2.02 (0.57-7.16)	0.276	4.99 (1.18-21.02)[c]	0.029
Allograft reintervention	0.70 (0.09-5.51)	0.735	0.60 (0.06-6.22)	0.665
Allograft dysfunction	2.20 (0.998-4.87)	0.051	1.17 (0.44-3.07)[c]	0.754
Any event	1.70 (1.01-2.86)	0.045	1.58 (0.83-3.00)	0.165

[a] SCA is the reference group. [b] Data expressed as OR (95% CI) for early mortality and HR (95% CI) for the other outcomes. [c] The propensity score variable was statistically significant in the regression model, which suggests inadequate propensity adjustment.

CI = confidence interval; DA = decellularized allografts; HR = hazard ratio; OR = odds ratio; SCA = standard cryopreserved allografts.

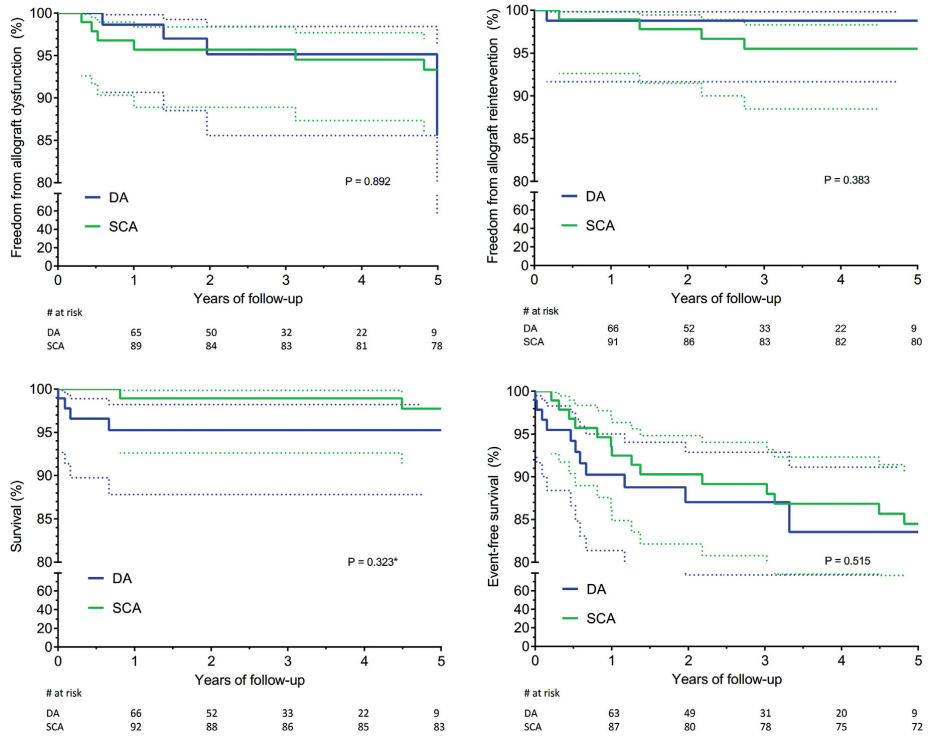

Figure 1. Kaplan-Meier plots of freedom from allograft dysfunction, freedom from allograft reintervention, survival, and event-free survival. The dotted lines indicate the 95% confidence interval. (DA = decellularized allografts; SCA = standard cryopreserved allografts.)

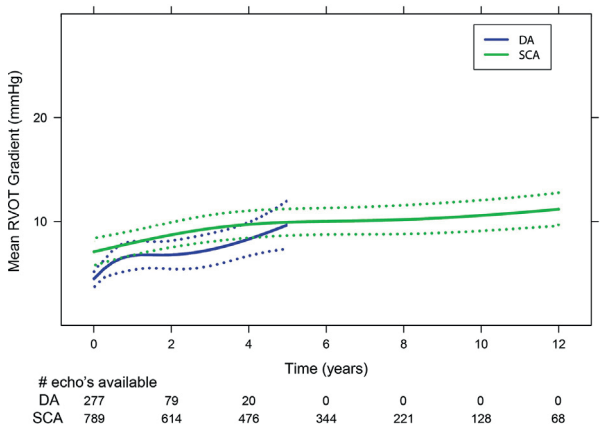

Figure 2. Mixed-effects model of mean allograft gradient over time. The dotted lines indicate the 95% confidence interval. (DA = decellular-ized allografts; RVOT = right ventricular outflow tract; SCA = standard cryopreserved allografts.)

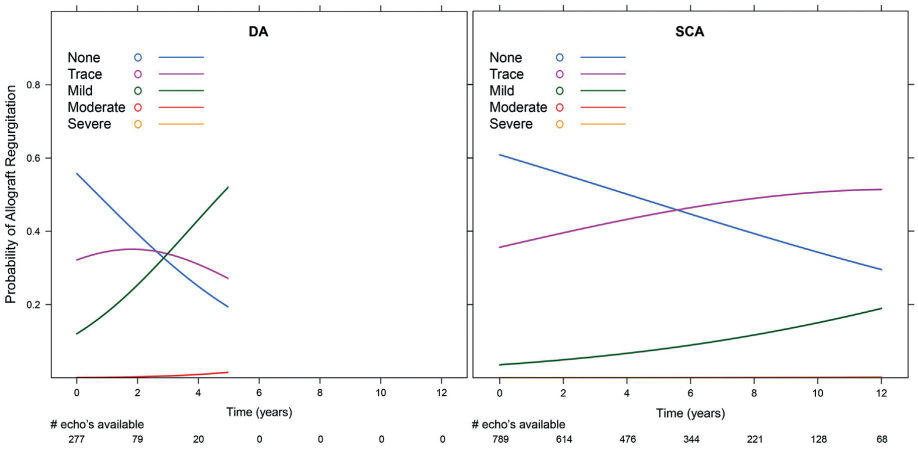

Figure 3. Mixed-effects model of allograft regurgitation over time. (DA = decellularized allografts; SCA = standard cryopreserved allografts.)

Echocardiographic outcomes in the matched cohort

For the 188 matched patients (94 pairs), 1,066 echocardiograms were available (mean, 5.7 per patient). During the first 5 years of follow-up, the mean allograft gradient increased from 4.5 to 9.6 mm Hg in the DA group and from 7.1 to 9.9 mm Hg in the SCA group (Fig 2). During this period, there was also a marked increase in allograft regurgitation grades over time, although there was no progression to moderate or severe stenosis (Fig 3).

DISCUSSION

Our study shows that fresh DAs and SCAs both perform well up to 5 years postoperatively. After propensity adjustment as well as propensity matching, actuarial freedom from allograft dysfunction, freedom from allograft reintervention, survival, and event-free survival were comparable between the two groups. Longitudinal echocardiographic analyses showed a similarly modest increase in allograft gradient and regurgitation grades over time in both groups.

Allograft dysfunction

One of the most important limitations of the Ross procedure is that single-valve disease is treated with doublevalve replacement because it requires reconstruction of the RVOT from which the pulmonary autograft was harvested. This is usually accomplished with pulmonary valve allografts. Besides the risk of autograft failure, structural valve deterioration of the RVOT allografts, although less life-threatening, does pose an additional risk of reintervention, especially in younger patients.[3]

Structural allograft deterioration is a complex multifactorial process that is not yet well defined. In general, there are two components of allograft deterioration. Firstly, there is a component of early progressive stenosis, characterized by gradients that rise predominantly within the first 2 to 5 years postoperatively. Secondly, there appears to be a slow, linear progression of regurgitation grades, only rarely reaching grade 3 or greater within the first postoperative decade.[4, 26-28]

Immunologic factors appear to play an important role in the mechanism of allograft degeneration. Research has shown that implantation of valve allografts elicits an immune response that has been reported to lead to early, progressive allograft stenosis due to inflammatorymediated adventitial fibrosis and neointimal proliferation.[5] Furthermore, although not consistently, ABO blood group and human leukocyte antigen donor mismatch have been found to be predictive of structural RVOT allograft failure.[8, 29, 30]

Decellularization aims to reduce this immune response by removing donor cells from the allograft by osmotic or chemical cell lysis while preserving the extracellular matrix, thus providing the benefit of acellularity in grafts with biomechanical properties similar to untreated allografts. Furthermore, the decellularized extracellular matrix is also believed to serve as a scaffold for repopulation by autologous cells with the potential of providing a valve capable of remodeling and regeneration. Prior histologic analyses of allografts explanted from patients in our DA group revealed evidence of partial reendothelialization and progressive repopulation of the tunica media with autogenous cells.[13] Various decellularization techniques have proven to be safe and successful in substantially reducing graft cellularity and subsequently reducing the host immune response, and early clinical results have been promising.[6, 7, 9-13]

In present study, the DAs and SCAs both showed excellent performance at 5 years of follow-up, with 100% freedom from severe allograft regurgitation in both matched groups and freedom from moderate allograft stenosis of 86% and 93% ($p = 0.892$) in the DA and SCA groups, respectively. Longitudinal analysis of serial echocardiographic measurements revealed a similarly modest increase in allograft gradient and regurgitation grades over time in both groups. Unfortunately, these echo data represent opportunistic clinical echocardiographic reports from 2 different centers that have not been validated in a core research laboratory setting, which precludes direct statistical comparison. In this light, studies that allow more comprehensive and direct echocardiographic comparison, such as high-quality single-center studies and dedicated prospective echocardiographic studies, are warranted.

Moreover, because the two study groups were recruited from 2 centers in different countries and were operated on by 2 different surgeons, interinstitutional practice variation and differences in background population risks, national health care practices, and surgical technique should also be taken into account.[31] Also, because the DAs were fresh and the SCAs were cryopreserved, the effects of cryopreservation on allograft function should also be taken into account.

All of the above factors should be taken into consideration in the interpretation of the results of our study, which to our knowledge is the first to provide such a comprehensive comparison of DAs vs SCAs in the RVOT position. Bearing the above in mind, this study found no substantial evidence of the hypothesized benefit of decellularization on hemodynamic allograft function at up to 5 years of follow-up. Longer follow-up of the DAs may shed light on the effect of decellularization on long-term allograft function and how these effects translate to clinical implications such as reintervention and other valve-related events. Furthermore, future studies should explore other areas of potential improvement of allograft function and the effect of decellularization, such as ABO blood group and human leukocyte antigen matching, use of antiinflammatory medication, and details of the decellularization procedure.

Further insight into the mechanism of the effects of decellularization may also provide potential for improving its effectiveness. For instance, decellularization may prove beneficial to allograft function from an immunologic standpoint but may also be associated with detrimental effects such as reduction of beneficial inflammation and impairment of structural integrity resulting from the decellularization process.

Furthermore, the availability of adequately sized (fresh) DAs should also be taken into account when considering their potential for widespread use, although availability and costs can be expected to improve substantially if a clear benefit is demonstrated.

Reintervention

The additional risk of reintervention imposed by the requirement of allograft RVOT reconstruction in the Ross procedure is substantial. Depending on the operative technique, patient-related factors, and institutional indications for reintervention, RVOT allograft reinterventions represent approximately 30% to 50% of the total Ross-related reintervention risk in the first 15 postoperative years.[2, 14, 32, 33] This is echoed by our overall results in the unmatched cohort, with a 15-year actuarial freedom from allograft reintervention of 95% compared with 90% for all reinterventions.

The 5-year actuarial freedom from allograft reintervention was comparable between the DA and SCA groups (99% vs 96%, respectively), as a result of the low incidence of reintervention in both groups in the first 5 years. This is, however, to be expected because allograft reinterventions have been previously described to occur mostly beyond the 5-year or even 10-year mark.[14, 27] Hence, longer follow-up of the decellularized grafts is required to reveal any differences in reintervention rates. Long-term follow-up may also elucidate how the effect of decellularization on allografts translates to reintervention rates, because there are other important indications for reintervention besides structural valve deterioration, such as endocarditis, upon which the effect of decellularization remains unclear.

Strengths and limitations

In the absence of a randomized trial, this study used propensity score matching to produce comparable study groups, which provides the unique opportunity for a direct comparison between DA and SCA for RVOT reconstruction in a large cohort of patients undergoing the Ross procedure. Moreover, the large number of available echocardiograms and the powerful longitudinal data analysis techniques allowed us to analyze hemodynamic allograft function over time in addition to clinical outcome. Furthermore, all patients were operated on by a single dedicated surgeon in each of the 2 dedicated centers, which greatly increases consistency and comparability.

This study has several limitations. As a consequence of the novelty of allograft decellularization, the follow-up duration of the DA group was insufficient to gain insight into long-term allograft function. There may still be other factors of influence on outcome that were not included in the propensity score. As mentioned, because the two study groups were recruited from 2 centers in different countries, international and interinstitutional practice variation precluded direct statistical echocardiographic comparison and may have affected the results. Not all DA patients could be matched owing to the extreme skewness of the propensity score in the SCA group.

CONCLUSIONS

Up to 5 years of follow-up, fresh DAs and SCAs used for RVOT reconstruction in the Ross procedure are associated with comparably excellent clinical and hemodynamic outcome. Longer follow-up is required to shed light on the long-term performance of the DAs.

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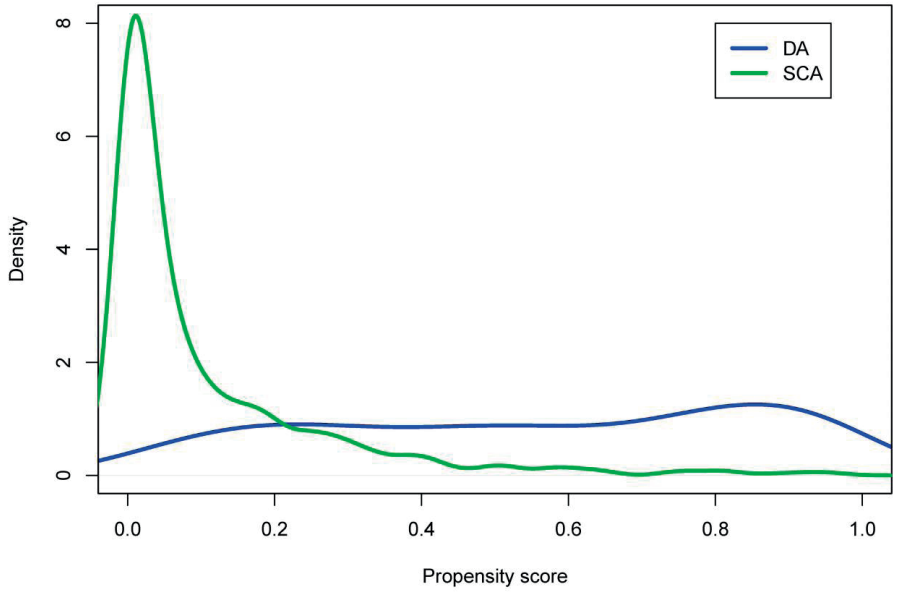
SUPPLEMENTARY MATERIAL

Supplement 1. Technique for implantation of the pulmonary allografts.

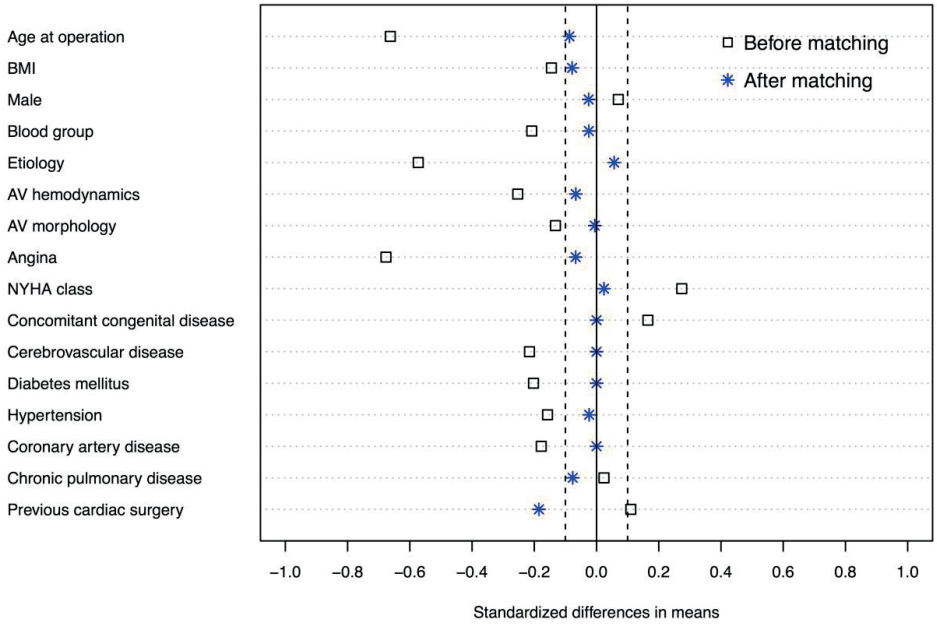
In both the DA and SCA groups, the pulmonary allografts were implanted with running Prolene 4-0 or 5-0 sutures both proximally and distally, with wide resection of residual allograft myocardium, leaving only a 2-3 mm myocardial rim for proximal anastomosis. If this did not allow for tension-free anastomosis, the proximal end of the allograft was extended with pericardium, which was performed in 70 (48.6%) DA and 232 (37.5%) SCA patients to achieve a tension-free anastomosis in all cases. Distal sutures were spaced close together to avoid constriction by the suture line. Long allografts (up to the bifurcation) were used whenever possible.

Supplement 2. Kernel density plots of propensity score distribution in each treatment group.



DA=decellularized allografts, SCA=standard cryopreserved allografts.

Supplement 3. Standardized differences in baseline covariate means between patients receiving fresh decellularized pulmonary allografts versus standard cryopreserved pulmonary allografts for right ventricular outflow tract reconstruction in the Ross procedure, before and after propensity score matching (Love plot).



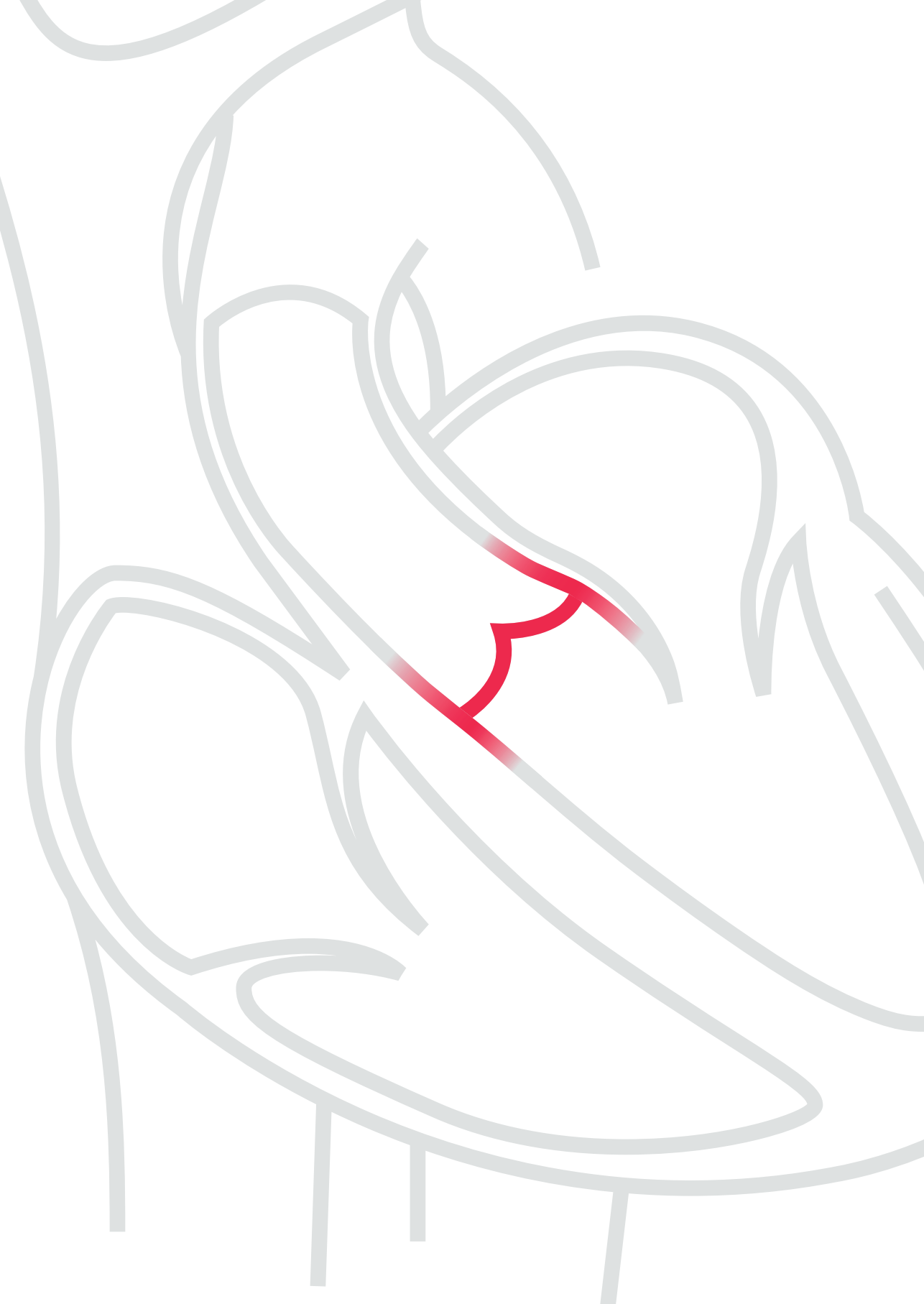
BMI=body mass index, AV=aortic valve, NYHA=New York Heart Association.

Supplement 4. Baseline characteristics of the patients that could not be matched, as well as the matched and unmatched cohorts.

	Unmatched (total cohort)			
	DA (n=144)		SCA (n=619)	
Age at Operation	30.11	(3.03-60.44)	45.57	(13.80-70.52)
BMI	24.22	(13.19-38.27)	25.18	(16.14-40.48)
Male	110	(76.4%)	471	(76.1%)
Blood Group				
0	78	(54.2%)	212	(34.2%)
A	46	(31.9%)	258	(41.7%)
B	10	(6.9%)	77	(12.4%)
AB	10	(6.9%)	37	(6.0%)
Missing	0	(0.0%)	35	(5.7%)
Etiology				
Congenital	96	(66.7%)	366	(59.1%)
Rheumatic	26	(18.1%)	6	(1.0%)
Degenerative/Calcified	9	(6.3%)	28	(4.5%)
Prosthetic valve dysfunction	6	(4.2%)	2	(0.3%)
Endocarditis	7	(4.9%)	152	(24.6%)
Missing	0	(0.0%)	65	(10.5%)
Hemodynamics				
Stenosis	48	(33.3%)	104	(16.8%)
Regurgitation	49	(34.0%)	159	(25.7%)
Combined	47	(32.6%)	355	(57.4%)
Missing	0	(0.0%)	1	(0.2%)
AV Cusps				
Tricuspid	39	(27.1%)	140	(22.6%)
Bicuspid	91	(63.2%)	450	(72.7%)
Unicuspid	14	(9.7%)	15	(2.4%)
Missing	0	(0.0%)	12	(1.9%)
Angina	2	(1.4%)	158	(25.5%)
Missing	0	(0.0%)	1	(0.2%)
NYHA				
I/II	76	(52.8%)	504	(81.4%)
III/IV	45	(31.3%)	114	(18.4%)
Missing	23	(16.0%)	1	(0.2%)
Comorbidities				
Concomitant Congenital Disease	8	(5.6%)	6	(1.0%)
Cerebrovascular Disease	3	(2.1%)	29	(4.7%)
DM	1	(0.7%)	29	(4.7%)
Hypertension	31	(21.5%)	203	(32.8%)
Renal Disease	0	(0.0%)	35	(5.7%)
Coronary Artery Disease	3	(2.1%)	36	(5.8%)
Peripheral Artery Disease	1	(0.7%)	3	(0.5%)
Chronic Pulmonary Disease	2	(1.4%)	12	(1.9%)
Previous Cardiac Surgery	29	(20.1%)	31	(5.0%)
Urgent (<24h)	1	(0.7%)	4	(0.6%)

Data expressed as "median (range)" or "count (percentage)". DA=decellularized allografts, SCA=standard cryopreserved allografts, BMI=body mass index, AV=aortic valve, NYHA=New York Heart Association.

Matched?							
Yes				No			
DA		SCA		DA		SCA	
(n=94)		(n=94)		(n=50)		(n=525)	
33.97	(3.04-60.44)	34.98	(13.81-58.75)	25.23	(3.03-57.07)	46.55	(15.20-70.52)
24.50	(14.36-38.27)	24.79	(17.99-40.48)	23.68	(13.19-36.16)	25.53	(16.14-37.86)
74	(78.7%)	75	(79.8%)	36	(72.0%)	396	(75.4%)
48	(51.1%)	45	(47.9%)	30	(60.0%)	167	(31.8%)
32	(34.0%)	36	(38.3%)	14	(28.0%)	222	(42.3%)
8	(8.5%)	5	(5.3%)	2	(4.0%)	72	(13.7%)
6	(6.4%)	7	(7.4%)	4	(8.0%)	30	(5.7%)
0	(0.0%)	1	(1.1%)	0	(0.0%)	34	(6.5%)
68	(72.3%)	72	(76.6%)	28	(56.0%)	294	(56.0%)
13	(13.8%)	3	(3.2%)	13	(26.0%)	3	(0.6%)
6	(6.4%)	3	(3.2%)	3	(6.0%)	25	(4.8%)
1	(1.1%)	2	(2.1%)	5	(10.0%)	0	(0.0%)
6	(6.4%)	2	(2.1%)	1	(2.0%)	150	(28.6%)
0	(0.0%)	12	(12.8%)	0	(0.0%)	53	(10.1%)
25	(26.6%)	21	(22.3%)	23	(46.0%)	83	(15.8%)
30	(31.9%)	33	(35.1%)	19	(38.0%)	126	(24.0%)
39	(41.5%)	40	(42.6%)	16	(32.0%)	315	(60.0%)
0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
20	(21.3%)	17	(18.1%)	19	(38.0%)	123	(23.4%)
68	(72.3%)	70	(74.5%)	23	(46.0%)	380	(72.4%)
6	(6.4%)	4	(4.3%)	8	(16.0%)	11	(2.1%)
0	(0.0%)	3	(3.2%)	0	(0.0%)	9	(1.7%)
2	(2.1%)	4	(4.3%)	0	(0.0%)	154	(29.3%)
0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
59	(62.8%)	63	(67.0%)	17	(34.0%)	441	(84.0%)
22	(23.4%)	31	(33.0%)	23	(46.0%)	83	(15.8%)
13	(13.8%)	0	(0.0%)	0	(0.0%)	1	(0.2%)
4	(4.3%)	4	(4.3%)	4	(8.0%)	2	(0.4%)
1	(1.1%)	1	(1.1%)	2	(4.0%)	28	(5.3%)
1	(1.1%)	1	(1.1%)	0	(0.0%)	28	(5.3%)
23	(24.5%)	24	(25.5%)	8	(16.0%)	179	(34.1%)
0	(0.0%)	0	(0.0%)	0	(0.0%)	35	(6.7%)
2	(2.1%)	2	(2.1%)	1	(2.0%)	34	(6.5%)
1	(1.1%)	0	(0.0%)	0	(0.0%)	3	(0.6%)
2	(2.1%)	3	(3.2%)	0	(0.0%)	9	(1.7%)
10	(10.6%)	15	(16.0%)	19	(38.0%)	16	(3.0%)
0	(0.0%)	0	(0.0%)	1	(2.0%)	4	(0.8%)



9

Patient and physician view on patient information and decision-making in congenital aortic and pulmonary valve surgery

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ABSTRACT

Background

To assess the current state of patient information and decision-making in congenital aortic and pulmonary valve disease, we conducted a survey among patients, parents and physicians.

Methods

A questionnaire was sent by ground mail to 157 adults and 32 parents of children who previously underwent surgery for congenital aortic or pulmonary valve disease at 0-40 years of age between January 2005 and February 2014 at the Erasmus University Medical Center and to all paediatric and adult congenital cardiologists and congenital cardiac surgeons in the Netherlands (n=88).

Results

73 patients/parents (39% response rate, 62 adult patients, 11 parents of paediatric patients) and 35 physicians (40% response rate) responded. Median patient age at the time of surgery was 25.7 years. Basic disease-specific knowledge was adequate in 42% of patients/parents and numeracy was sufficient in 47%. Patients/parents reported that they rely heavily on their physicians for information and often experience difficulty in finding reliable information elsewhere. They lack information on psychosocial aspects of disease (29% of respondents) and risks and benefits of treatment options (26%). They feel less involved in decisionmaking than they would prefer to be (p=0.014). Decisional conflict at the time of surgery was experienced by 31% of patients/parents. If they had to do it again, 72% of patients/ parents would want the same treatment. Quality of life is often impaired due to various valve-related anxieties and lifestyle changes. Physicians reported that they are unable to fully inform and sufficiently involve patients, due to limited patient/parent knowledge and understanding (56%) and limited time during consultations (32%). Patients/parents (98%) and physicians (97%) agree that they should have shared roles in decision-making.

Conclusions

The substantial shortcomings in our current practice of patient information and decision-making underline the need for innovative solutions, such as careful implementation of patient information tools and shared decision-making in the care path.

INTRODUCTION

Due to major advances in the management of congenital heart disease over the past decades, approximately 90% of patients with congenital heart disease currently reach adulthood.[1-3] This increasingly allows patients to live full, active and longer lives. However, congenital heart disease often has consequences that impact many facets of life, both clinical and personal.[1 4] Furthermore, it often requires important decisions to be made about treatment, both in choosing between treatment or a conservative approach and choosing between different treatment options such as the choice for a mechanical or a bioprosthetic valve replacement. These decisions may have important implications for the patients' further lives with regard to, for instance, longevity, pregnancy, career planning and daily life, especially in younger patients with more dynamic lifestyles.[4] Congenital aortic and pulmonary valve diseases, in particular, usually allow for a relatively long and active life, but often with important consequences for lifestyle and life planning and requiring multiple crucial decisions about treatment to be made along the way.[2 3 5]

To allow patients to better understand, cope with and adhere to the lifestyle changes imposed by their heart defect and to allow treatment to be tailored to their personal values and preferences, it is essential to inform patients and their relatives and involve them in the decision process.[6-19] However, patients may not always be sufficiently informed and involved in their own care, which has been previously shown to lead to substantial impairments in quality of life, anxiety, depression, poor treatment adherence, poor health behaviour, suboptimal treatment decisions and poorer clinical outcome, and also poorer healthcare utilisation and higher healthcare costs.[6-19]

To investigate the current state of patient information and decision-making in congenital aortic and pulmonary valve surgery in the Netherlands, we conducted a cross-sectional survey among adult patients, parents of paediatric patients and physicians involved in the care for these patients.

METHODS

Patient survey

This study was approved by the institutional review board (MEC-2015-099) and written informed consent was obtained from all participants.

Participants

Between January 2005 and February 2014, 198 consecutive patients aged between 0 and 40 years underwent valve repair or replacement for congenital aortic and/ or pulmonary valve disease at the Erasmus University Medical Center. On 1 March 2015, patients ≥18 years old and parents of patients <18 years old at the time of the survey who were alive and residing in the Netherlands (total n=189, 157 adult patients and 32 parents) were approached by ground mail and asked to complete and return a printed questionnaire.

Questionnaire

An example of the patient questionnaire is listed in Supplement 1.

Basic knowledge on postoperative outcome was assessed by asking respondents what the largest risk is after mechanical valve replacement (only aortic valve surgery patients), biological valve replacement (aortic and pulmonary valve surgery) and valve repair (only aortic valve surgery patients) using multiple choice questions for each. Possible answers were (1) thromboembolism and bleeding, (2) reoperation and (3) I don't know. Knowledge was also assessed by asking respondents which procedure they/their child had undergone using a multiple choice question and comparing their answers with their medical records. Possible answers in this question were (1) mechanical valve replacement, (2) biological valve replacement and (3) valve repair.

Numeracy (ie, the understanding of numerical information, such as quantitative probabilities) was assessed using the validated Numeracy Scale[20] and respondents were asked to indicate which form of risk visualisation (bar chart, pie chart or icon array) they preferred for presentation of risk information.

Experiences and views with regard to patient information and (shared) decision-making were assessed using multiple choice questions, 5-point Likert scales, open questions and the validated Control Preferences Scale.[21]

Uncertainty about treatment decision-making was assessed using the Decisional Conflict Scale.[22]

Postoperative valve-specific quality of life was assessed with a validated valve-specific questionnaire.[5]

Physician survey

Participants

All board registered paediatric cardiologists, adult congenital cardiologists and congenital cardiac surgeons in the Netherlands (n=88) were approached by email via the Dutch Associations for Pediatrics, Cardiology and Thoracic Surgery and asked to complete an electronic questionnaire.

Questionnaire

An example of the physician questionnaire is listed in Supplement 2. Physician age, specialty and years of experience were recorded. Experiences and views with regard to patient information and (shared) decision-making were assessed using multiple choice questions, 5-point Likert scales, open questions and the Control Preferences Scale.[21]

Analyses

Analyses of clinical data were performed in Microsoft Office Excel 2011 (Microsoft, Redmond, Washington, USA) and in the R statistical software (V.3.3.3, R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). Continuous data are presented as mean±SD or median (range) and categorical data (including Likert scales) are presented as proportions and/or counts. Paired comparisons of Likert scale responses were done using Wilcoxon signed-rank test. All tests were two-tailed and statistical significance was inferred at a $p<0.05$.

RESULTS

Patients

A total of 73 patients/parents responded and gave informed consent and were subsequently included in the study (39% response rate). Patient and respondent characteristics are shown in table 1.

Knowledge, numeracy and risk visualisation preference

Considering all knowledge questions collectively, 42% of respondents answered all questions correctly. Specifically, 51% of respondents answered all questions on postoperative risks correctly and 89% of respondents knew which procedure they/their child had undergone.

Table 1. Patient/respondent characteristics

	Total (n=73)	Adult patients (n=62)	Parents of paediatric patients (n=11)
Age at survey (years)	36.3 (18.5-56.7)	34.7 (18.5-47.6)	46.2 (32.7-56.7)*
Patient age at surgery (years)	25.7 (0.1-40.0)	28.1 (12.2-40.0)	8.6 (0.1-15.2)†
Time from surgery to survey (years)	6.6 (1.1-10.1)	7.3 (1.1-10.1)	4.6 (1.1-9.3)
Surgery			
Aortic valve surgery	59% (43)	58% (36)	64% (7)†
Pulmonary valve surgery	41% (30)	42% (26)	36% (4)†
Education level			
None/elementary	8% (6)	8% (5)	9% (1)
Lower secondary or vocational	5% (4)	5% (3)	9% (1)
Higher secondary	58% (42)	61% (38)	36% (4)
Higher professional	18% (13)	18% (11)	18% (2)
University	11% (8)	8% (5)	27% (3)

Data presented as median (range) or percentage (count). Data on parents of paediatric patients concerns the parents, unless indicated otherwise.
*Concerns age of parents, children were 12.9 years (range: 7.7-24.5) of age at the time of survey.
†Concerns children.

Forty-seven per cent of respondents answered all three numeracy questions correctly, 27% answered two out of three correctly, 16% 1 out of 3, and 10% 0 out of 3. Patients/parents indicated a strong preference for pie charts (61%) over bar graphs (29%) and icon arrays (10%) for visualisation of risk information.

Patient information

Patient/parent experiences and opinions with regard to patient information are presented in figure 1. Additionally, patients/parents report cardiologists (89%) and cardiac surgeons (26%) as their main sources of information, whereas patient information leaflets (8%) and the internet (5%) were less frequently reported as important information sources. The advantages and drawbacks of treatment options were discussed with the cardiologist in 93% of cases and with the cardiac surgeon in 42% of cases. This consultation took place >1 week prior to surgery in most cases (89%), but sometimes also between 1 day and 1 week prior to surgery (3%) or <1 day prior to surgery (8%).

The most important topics patients/parents reported to lack information on (open question) were implications for personal life, life planning, prognosis and psychosocial aspects (29% of respondents), risks, benefits and drawbacks of treatment (options) (26%) and practical information on (early) postoperative care (17%).

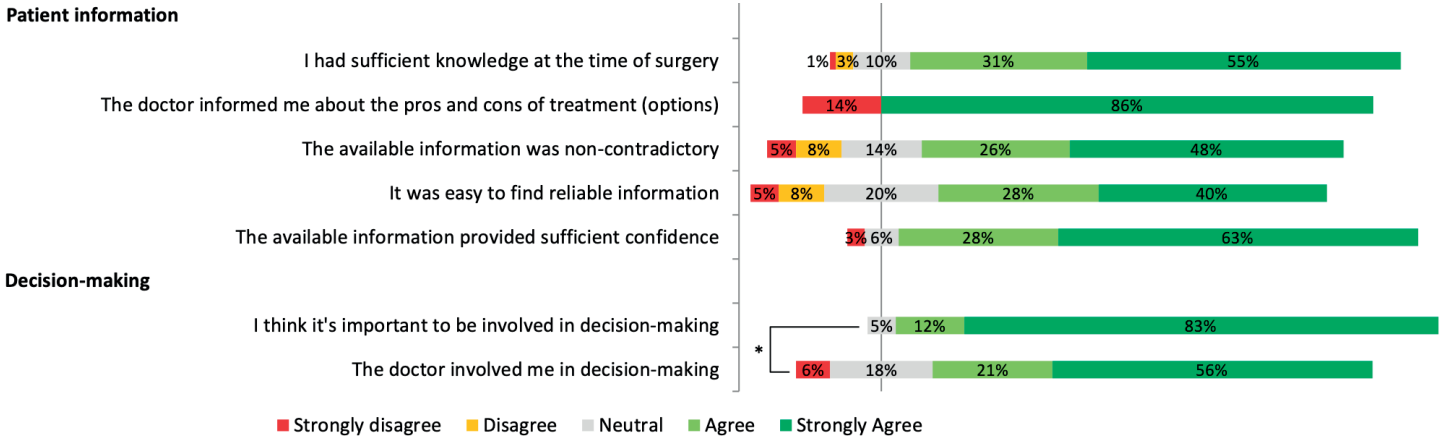

Figure 1. Patient/parent (n=73) experiences and opinions with regard to patient information and decision-making. The graphs are centred on the response category 'Neutral' (vertical grey line in the centre of the graph). *Wilcoxon signed-rank p=0.014.

Decision-making

Patient/parent experiences and views with regard to decision-making are presented in figure 1. Respondents felt less involved in decision-making than they would prefer to be (figure 1, Wilcoxon signed-rank p=0.014). The vast majority of patients/parents (98%) agree that they should have shared roles in decision-making (figure 2).

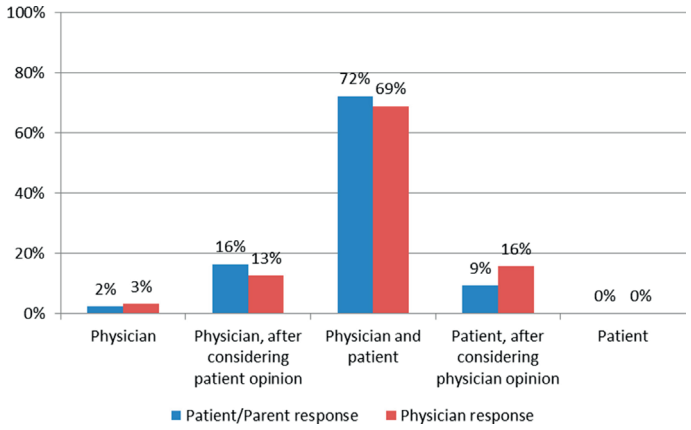

Figure 2. Control Preferences Scale: Who should make the final decisions about treatment? (73 patients/parents and 35 physicians responded). The sum of the middle three response categories represents the respondents that think that patients/parents and physicians should have shared roles in decision-making (98%).

Furthermore, at the time of surgery, 31% of patients/ parents experienced decisional conflict (Decisional Conflict Scale score >25) and 13% experienced severe decisional conflict (score >37.5). Decisional conflict was highest in the subscales uncertainty about the best choice (35%, severe: 30%), clear about personal values for benefits and drawbacks (30%, severe: 23%) and feeling informed (23%, severe: 16%), followed by feeling supported (21%, severe: 16%) and decision effectiveness (16%, severe: 12%).

At the time of survey, 80% of patients/parents were satisfied with their replaced or repaired heart valve (10% neutral, 10% not satisfied) and 72% of patients/ parents would want the same treatment if they had to do it all over again (18% neutral, 10% different treatment).

Valve-specific quality of life

Patients/parents experience impairments to quality of life due to various valve-related anxieties and lifestyle changes (figure 3), most frequently related to fear of reintervention (38% 'frequently' or 'always'), anticoagulation use (34%), fear of thrombosis (31%) or bleeding (26%), valve sound (22%), fear of valve failure (22%) or the regular doctor visits and blood tests (9%).

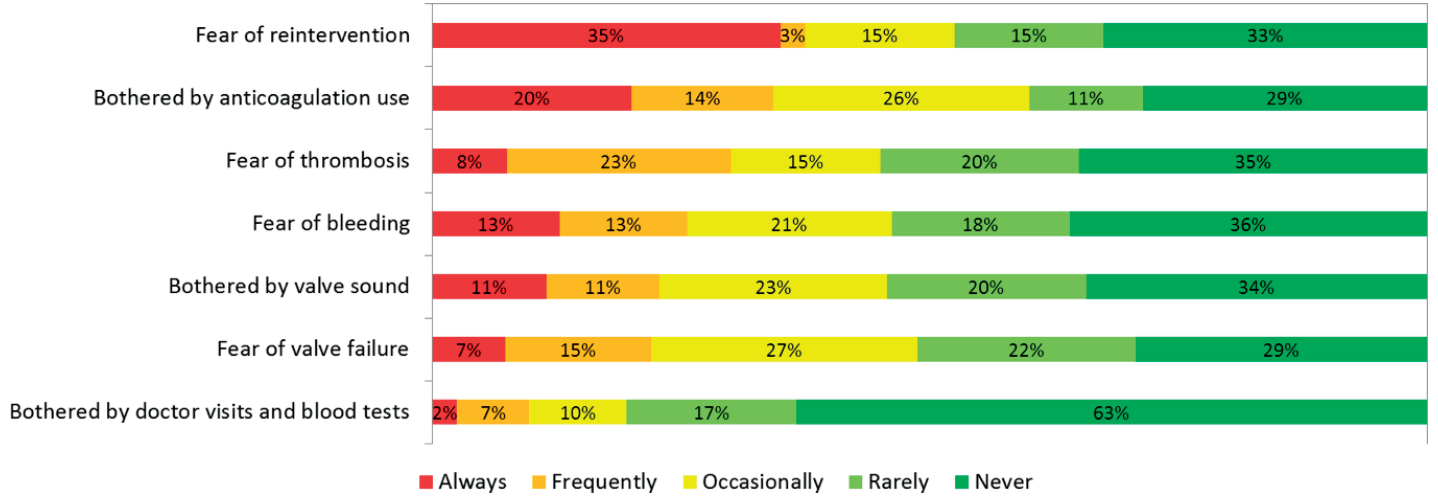

Figure 3. Factors that patients/parents (n=73) report as impairments of their quality of life. Always=more impairment=unfavourable.

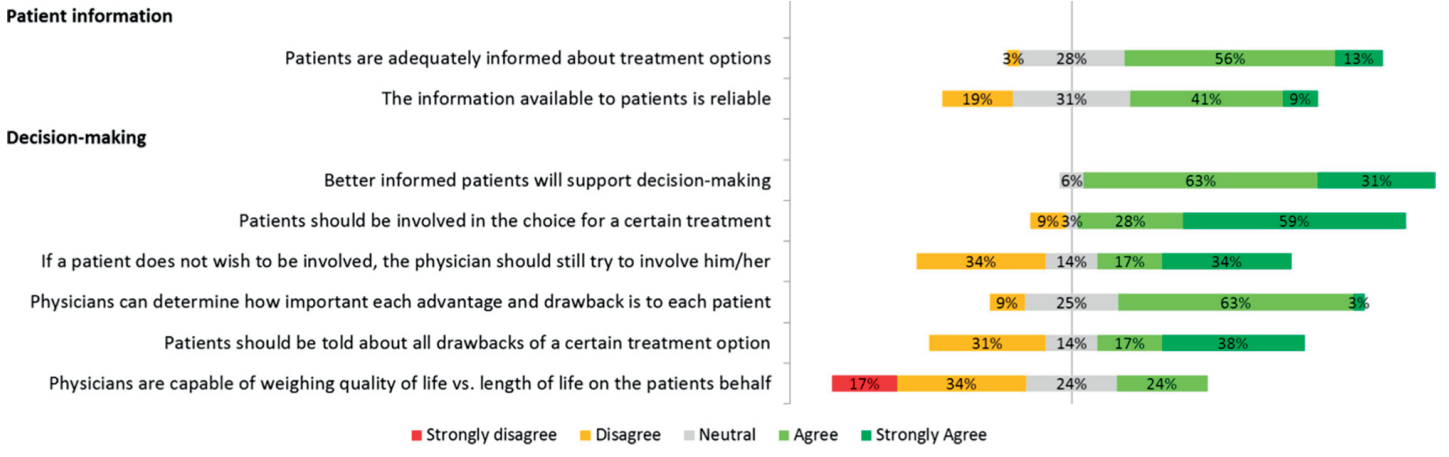

Figure 4. Physician (n=35) experiences and opinions with regard to patient information and decision-making. The graphs are centred on the response category 'Neutral' (vertical grey line in the centre of the graph).

Physicians

A total of 35 physicians responded (40% response rate), 14 paediatric cardiologists, 14 adult congenital cardiologists and 7 congenital cardiac surgeons. Median physician age was 44 years (range 33-64) and median experience in their respective fields was 9 years (range 0.3-32).

Patient information

Physician experiences and opinions with regard to patient information are presented in figure 4. Additionally, physicians report cardiologists (94%) and cardiac surgeons (19%) as the main sources of information for patients/parents and the internet (3%) less so. Physicians report that do not always fully inform patients/ parents of all the implications of their treatment (figure 5).

Decision-making

Physician experiences and opinions with regard to decision- making are presented in figure 4. The vast majority of physicians (97%) agree that they should have shared roles in decision-making (figure 2). Additionally, physicians report the most important barriers in involving patients/parents in decision-making (open question) to be limited patient/parent knowledge and understanding (56% of respondents), limited time during consultations (32%) and anxiety and uncertainty among patients/parents (24%).

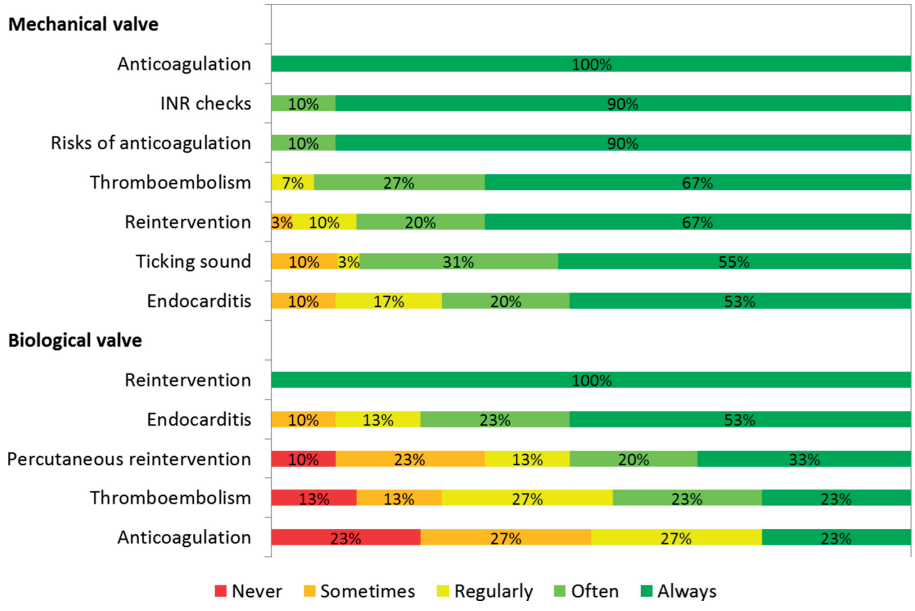

Figure 5. Physicians (n=35): How often do you inform your patients about the various advantages and drawbacks of treatment? INR, international normalised ratio.

DISCUSSION

This study shows that in contemporary Dutch practice of congenital aortic and pulmonary valve surgery, patient/parent knowledge of basic information on their (child's) condition is limited and their numeracy is poor. Patients/parents are not satisfactorily informed and rely heavily on their physicians for information. They feel less involved in decision-making than they would prefer to be and often experience substantial decisional conflict and valve-related anxiety. Physicians in turn are unable to inform patients/parents completely in the limited time they have, given the patients'/parents' limited knowledge and understanding. Subsequently, although both physicians and patients/parents agree that they should have shared roles in decision-making, physicians experience challenges in involving patients/ parents in their own care.

In congenital cardiac care, treatment often has a profound impact on lifestyle, life planning, quality of life and longevity, especially in younger patients with more dynamic lifestyles. Our results show that patients and their parents are often insufficiently informed of the consequences of the treatments they undergo. Our findings of limited knowledge among patients and parents are in line with prior research in (parents of) patients with congenital heart disease.[16-18 23-28] Limited knowledge and limited availability of information have been previously described to be associated with anxiety, depression and impaired quality of life, which underlines the importance of adequately informing our patients and their parents.[29 30]

But why are patients/parents currently not satisfactorily informed? Our results show that they rely heavily on physicians to provide them the information they require and often experience difficulty in finding reliable information elsewhere. However, we found that the knowledge gap between patients and physicians along with the limited time reported to be available during consultations presents a challenge to physicians in meeting their patients' information needs. Subsequently, physicians are not able to discuss all relevant information with all patients.

Furthermore, prior studies have shown that, of the information that is discussed during the consultation, only a small fraction is retained by patients/ parents, only about 20%-60% as described in the literature.[29 31 32] Our results show that, other than their physicians, there are few sources of reliable information available to patients, and the information that is available is often poorly comprehensible, contradictory and not tailored to their information needs and their specific disease state. Furthermore, current information, including information provided by caregivers, was reported to focus mainly on medical aspects of the disease and patients lack information on practical, psychosocial and

lifestyle topics. Also, our findings of limited numeracy among patients/parents shows that the content and the format of patient information should be carefully considered.

Limited patient/parent knowledge also has an impact on treatment decisions and treatment outcome. As treatment decisions have such an important impact on patients' personal lives, treatment outcome and goals should always be placed in the perspective of each individual patient's lives and values. Optimal outcome for each patient can only be achieved if treatment is in alignment with patient preferences.[5 19 33-35]

As evidenced by our results, physicians are often confident that they are capable of reliably determining patient values themselves and sometimes even think they are capable of making value trade-offs on the patients' behalf. However, prior research in other disease states has shown that there is often a substantial mismatch between patient values and physicians' estimation thereof.[36-38]

Consequently, patients often undergo treatments with consequences that they are inadequately informed about and that do not match personal values and preferences. Our results show that this may be associated with substantial potentially avoidable impairments in quality of life. Thus, elucidating patient values and taking these values into account in treatment decision-making is crucial. Fortunately, the patients themselves are seasoned experts on their own values and an integral part of every healthcare setting. Involvement of patients in their own care is therefore essential.

However, our findings indicate that there are several barriers for patient involvement in clinical practice. Our study shows that physicians often experience difficulty in involving patients, most often due to a gap in knowledge and understanding between physicians and patients. This is confirmed by our findings of limited knowledge and numeracy among patients and parents. Thus, patients' active participation in their own care first requires ample knowledge of medical and psychosocial aspects of their disease. However, this knowledge is currently limited in these patients and physicians are currently not always capable of sufficiently providing them this knowledge.

Our findings represent a major area for improvement in our current practice of congenital cardiac care and provides the potential to substantially improve outcome in these patients.[16-18 23-28] Better informed and more activated patients have been found to be associated with improved quality of life, treatment adherence, health behaviour and clinical outcome and also with more efficient healthcare utilisation and lower healthcare costs.[6-19] Furthermore, improved information and knowledge may provide patients

the confidence and reassurance of knowing what to expect and when and how to act, thereby reducing anxiety.

This underlines the urgent need for innovative solutions in more effectively informing our patients and their parents. A platform easily accessible to users at all times, such as an online information portal, presents promising opportunities. This would ideally allow for a dynamic environment in which information can be tailored to patients' information needs and their specific disease state. To ensure quality, reliability and acceptance among patients/parents and physicians alike, patient information should be evidence-based and endorsed, supported and actively used by physicians. Furthermore, the content of patient information should not only be focused on medical topics should be tailored to the information needs expressed by patients/parents, which are often broader than expected, as evidenced by our results. Special attention should be paid to the specific needs of different user groups, for instance, patients' parents, teenage patients, adult patients and relatives. The information should also be formatted to be comprehensible and attractive to users of a wide variety in education level, health literacy and numeracy. In light of our findings of limited numeracy among patients and parents, further research should also focus on how the comprehensibility of patient information can be improved and should explore the effectiveness of supporting tools such as illustrations, animations, risk visualisations and virtual reality. Furthermore, it remains unclear how improved patient knowledge affects anxiety and uncertainty. Further investigation may provide insight into how we may best inform patients/parents to also provide them the reassurance they often need, thereby reducing anxiety. Last, how improved patient information and knowledge relates to patient activation, involvement and concordance of treatment decisions with patient values remains to be elucidated.

Limitations

As this was a Dutch study in which patients/parents were recruited from a single centre, possible international differences in medical practice, culture and language as well as interinstitutional practice variation should be taken into consideration, although our findings are in line with prior studies in other centres and countries.[16-18 23-28] Our disease-specific knowledge questionnaire was only aimed at capturing the most basic knowledge of disease, and the level of more in-depth disease-specific knowledge among these subjects remains to be elucidated. Regarding questions about patient/parent personal experiences with decision-making, the time between surgery and survey may have given rise to recall bias. Results may differ for disease states other than aortic and pulmonary valve surgery, which should be taken into account when interpreting our results. The limited sample size did not allow for analysis of the effects of gender, age

and prosthesis type. Lastly, as this was a survey, response bias may have had an influence on our results.

CONCLUSIONS

Patients, parents and physicians alike experience important shortcomings in patient information and decision- making in congenital aortic and pulmonary valve surgery. Patient knowledge is severely limited due to the limited availability, reliability and comprehensibility of patient information. Furthermore, the provided information often does not meet the patients' information needs. This may be associated with our findings of suboptimal patient activation and involvement and substantial decisional conflict and valve-related anxiety. This underlines the need for innovative solutions, such as careful implementation of patient information tools and shared decision-making in the care path.

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SUPPLEMENTARY MATERIAL

Supplement 1. Example of patient questionnaire.

This example concerns a questionnaire for an adult patient (as opposed to a parent/caregiver of a pediatric patient) who had undergone aortic valve surgery (as opposed to pulmonary valve surgery).

1. Patient information and knowledge

1.1. Did you know that there are different treatment options?

O Yes
O No

1.2. Which treatment did you undergo? (If you underwent multiple treatments, this question concerns the most recent treatment)

O Valve replacement with a mechanical valve
O Valve replacement with a biological valve
O Valve repair
O Other, namely……
O I don't know

1.3. Which treatment provides the most durable result (i.e. the lowest risk of reoperation)?

O Valve replacement with a mechanical valve
O Valve replacement with a biological valve
O Valve repair
O I don't know

1.4. What is the largest risk after valve repair?

O Reoperation
O Bleeding and thrombosis (blood clots)
O I don't know

1.5. What is the largest risk after valve replacement with a mechanical valve?

O Reoperation
O Bleeding and thrombosis (blood clots)
O I don't know

1.6. What is the largest risk after valve replacement with a biological valve?

O Reoperation
O Bleeding and thrombosis (blood clots)
O I don't know

1.7. Did your physician inform you about the various treatment options?

O Yes
O No

1.8. Did your physician inform you about the advantages and drawbacks of the various treatment options?

O Yes
O No

1.9. Do you feel like you had sufficient knowledge about the advantages and drawbacks of the various treatment options at the time of surgery?

Strongly disagree 1 2 3 4 5 Strongly agree

1.10. What was your <u>most important</u> source of information about your condition and the treatment options?

O The internet
O Patient information leaflets
O The cardiologist
O The heart surgeon
O Friends/relatives
O Other, namely……

1.11. And what were <u>other</u> important sources of information about your condition and the treatment options?

……...……
……
……...

1.12. The information about my condition and the treatment options that i obtained from different care providers and/or other sources of information did not always correspond.

Strongly disagree 1 2 3 4 5 Strongly agree

Explanation……
……
……...

1.13. It was easy to find reliable information.

Strongly disagree 1 2 3 4 5 Strongly agree

What was the source of this information?
……

1.14. The available information provided me sufficient certainty about the choice for a certain treatment.

Strongly disagree 1 2 3 4 5 Strongly agree
O I did not need to make a decision

1.15. Did you lack any information about your condition and the treatment options? If so, can you indicate what you would like to have received more information about?

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1.16.Do you have ideas for the improvement of patient information?

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2. Decision-making

2.1. Was there a choice between different treatment options for you?

O Yes
O No

Explanation……
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……...

2.2. With whom did you have the consultation regarding treatment options? (Multiple answers possible)

O With the cardiologist
O With the heart surgeon
O Other, namely……
O I did not have such a consultation

2.3. How long prior to surgery was this consultation? (If you had multiple consultations regarding treatment options, this question concerns the first consultation)

O Less than one day prior to surgery
O More than one day, but less than 1 week prior to surgery
O More than one week prior to surgery
O I did not have such a consultation

2.4. The final decision for a treatment should be made by:

O The physician
O The physician, after considering the patient's opinion
O The patient and physician together
O The patient, after considering the physician's opinion
O The patient

2.5. Did you have enough time to make a well-thought-out decision?

O Yes
O No
O I don't know
O Not applicable

2.6. Besides your care providers, was anyone else involved in the decision for a certain treatment? (multiple answers possible)

O Yes, family
O Yes, a good friend
O Yes, ……
O No
O Not applicable

2.7. The doctor involved me in the decision for a certain treatment.

Strongly disagree 1 2 3 4 5 Strongly agree
O I don't know
O Not applicable

2.8. I think it is important to be involved in the decision for a certain treatment.

Strongly disagree 1 2 3 4 5 Strongly agree
O I don't know
O Not applicable

2.9. Do you feel like you had a choice in the decision for a certain treatment?

O Yes
O No
O I don't know
O Not applicable

Explanation……
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……..

2.10. What could have gone better when the decision for a certain treatment was being made?

……
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……
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……

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
2.11.	**This decision was difficult for me to make**	☐	☐	☐	☐	☐
2.12.	**I was clear about the best choice for me**	☐	☐	☐	☐	☐
2.13.	**I was not sure what to choose**	☐	☐	☐	☐	☐
2.14.	**I knew which treatment options were available to me**	☐	☐	☐	☐	☐
2.15.	**I knew the benefits of each treatment option**	☐	☐	☐	☐	☐
2.16.	**I knew the risks and side effects of each treatment option**	☐	☐	☐	☐	☐
2.17.	**I would like to have had more advice and information about the treatment options**	☐	☐	☐	☐	☐
2.18.	**I was clear about which benefits mattered most to me**	☐	☐	☐	☐	☐

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
2.19.	**I was clear about which risks and side effects mattered most to me**	☐	☐	☐	☐	☐
2.20.	**It was difficult to decide whether the benefits or the risks and side effects were more important to me**	☐	☐	☐	☐	☐
2.21.	**I felt pressured by others while making this decision**	☐	☐	☐	☐	☐
2.22.	**I had enough support from others while making a decision**	☐	☐	☐	☐	☐
2.23.	**I feel I have made an informed choice**	☐	☐	☐	☐	☐
2.24.	**My decision shows what is important to me**	☐	☐	☐	☐	☐
2.25.	**I expect to stick with my decision**	☐	☐	☐	☐	☐
2.26.	**I am satisfied with my decision**	☐	☐	☐	☐	☐

2.27. I am afraid of bleeding.

Never 1 2 3 4 5 Always

O Not applicable

2.28. I am afraid of thrombosis (blood clots).

Never 1 2 3 4 5 Always

O Not applicable

2.29. I have problems with taking medication.

Never 1 2 3 4 5 Always

O Not applicable

2.30. I am afraid of possibly needing another valve operation in the future.

Never 1 2 3 4 5 Always

O Not applicable

2.31. I am afraid that my valve may fail.

Never 1 2 3 4 5 Always

O Not applicable

2.32. Taking anticoagulation for the rest of my life bothers me.

Never 1 2 3 4 5 Always

O Not applicable

2.33. Is there a valve sound that bothers me?

Never 1 2 3 4 5 Always

O Not applicable

2.34. Following my valve surgery, the frequency of doctor visits and blood tests bothers me.

Never 1 2 3 4 5 Always

O Not applicable

2.35. I am satisfied with my new/repaired aortic valve.

Never 1 2 3 4 5 Always

O Not applicable

2.36. If i had to do it over again, would I make the same decision?

Never 1 2 3 4 5 Always

O Not applicable

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.

2.37. A person taking drug B has a 1 in 1,000 chance of having an allergic reaction. What percentage of people taking drug B will have an allergic reaction?

…… %

2.38. Imagine that a coin was flipped 1,000 times. Out of 1,000 flips, how many times do you expect the coin to come up heads?

…… times out of 1000.

2.39. Imagine the risk of reoperation after heart valve replacement is 5 percent (%). This is represented in the figures below. Please rank the figures based on how clear they are to you. 1 = most clear, 4 = least clear. Please fill in Figure A, B, C or D corresponding to each number. Each letter can only be used once.

Most clear 1. Figure ……

2. Figure ……

3. Figure ……

Least clear 4. Figure ……

Figure A:

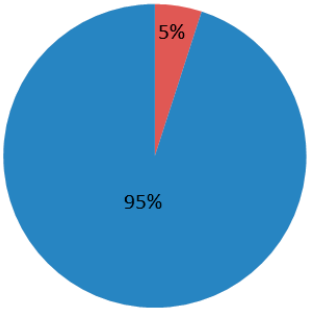


Figure B:

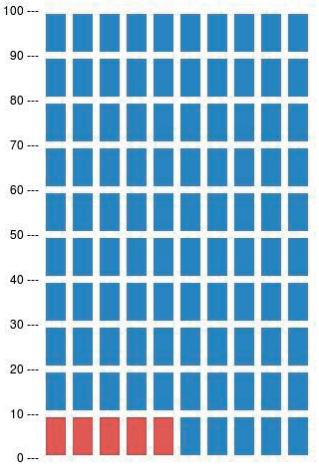


Figure C:

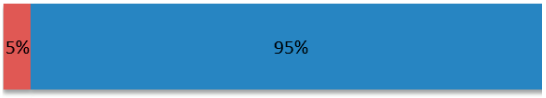
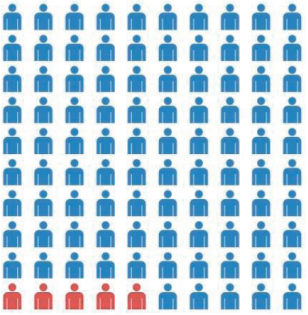


Figure D:



Explanation……

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Supplement 2. Physician questionnaire.

1. What do you think is the most important source of information about treatment options for your patients?

O The internet
O The cardiologist
O The cardiac surgeon
O Patient information leaflets
O Other,namely……...

2. In my opinion, patients are sufficiently informed about treatment options.

Strongly disagree 1 2 3 4 5 Strongly agree
Explanation……

3. The information about treatment options that is available to patients is reliable.

Strongly disagree 1 2 3 4 5 Strongly agree
Explanation……

4. In my opinion, better informed patients will … decision-making:

Hinder 1 2 3 4 5 Support
Explanation……

5. Should patients be involved in the choice for a certain treatment?

Never Sometimes Regularly Often Always
O I don't know

Explanation……

6. If a patient does not wish to be involved in the choice for a certain treatment, should the physician still try to involve the patient in the decision?

Never Sometimes Regularly Often Always
O I don't know

Explanation……

7. The final decision for a treatment should be made by:

O The physician
O The physician, after considering the patient's opinion
O The patient and physician together
O The patient, after considering the physician's opinion
O The patient

Explanation……

8. In decision-making the advantages and drawbacks of the different treatment options are considered. Do you think that physicians are capable of determining how important each advantage and drawback is to each patient?

Never Sometimes Regularly Often Always
I don't know

Explanation……

9. Should patients be informed about *all* drawbacks of a certain treatment option (even if the risk is low)?

Never Sometimes Regularly Often Always
I don't know

Explanation……

10. How often do you inform your patients about the following factors concerning valve replacement with a *mechanical valve*?

Lifelong anticoagulation
Never Sometimes Regularly Often Always

Regular INR checks
Never Sometimes Regularly Often Always

Risks of anticoagulation
Never Sometimes Regularly Often Always

Thrombogenicity of the valve/thromboembolism
Never Sometimes Regularly Often Always

Ticking valve sound
Never Sometimes Regularly Often Always

Risk of reintervention lower than with other treatment options, but certainly not zero
Never Sometimes Regularly Often Always

Risk of endocarditis
Never Sometimes Regularly Often Always

Explanation……

11. How often do you inform your patients about the following factors concerning valve replacement with a *bioprosthesis, allograft, the Ross procedure or valve repair*?

Risk of reintervention

Never Sometimes Regularly Often Always

Risk of endocarditis

Never Sometimes Regularly Often Always

Risk of thromboembolism

Never Sometimes Regularly Often Always

Anticoagulation may still be(come) necessary

Never Sometimes Regularly Often Always

Percutaneous or transapical valve replacement as a possible option for reintervention

Never Sometimes Regularly Often Always

Explanation……

12. If the decision concerns quality of life versus life expectancy after a certain treatment, do you think that physicians are capable of weighing these on the patients behalf?

Never Sometimes Regularly Often Always

I don't know

Explanation..

13. In your experience, what are barriers/obstacles in involving patients in decision-making?

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14. In your opnion, what are the most important shortcomings in patient information on congenital aortic and pulmonary valve disease? And what would you like to improve?

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15. Which essential components should a newly developed patient information portal contain to support you in patient information, decision-making and patient communication?

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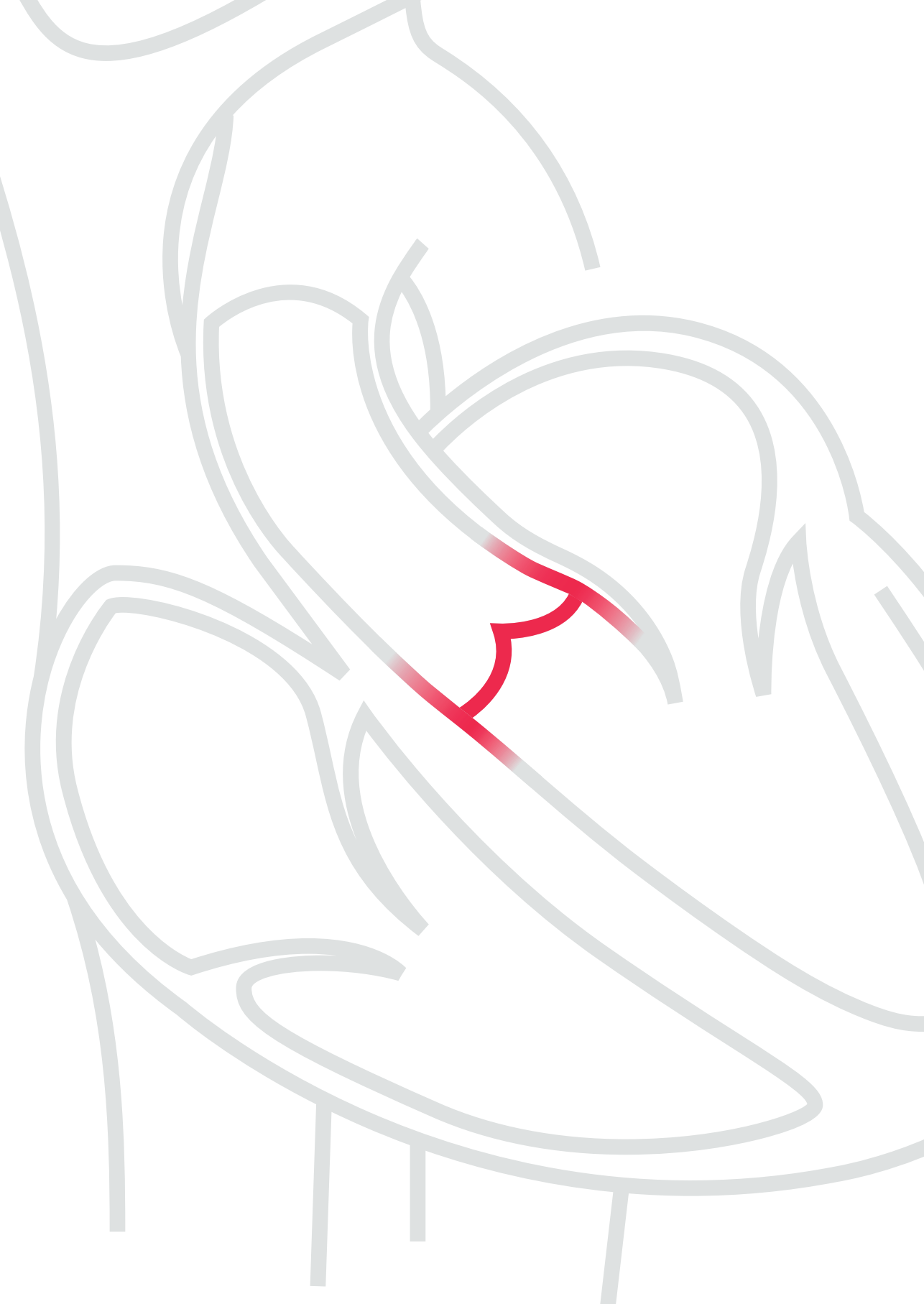

10

Do risk visualizations improve the understanding of numerical risks? A randomized, investigator-blinded general population survey

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ABSTRACT

Background

Risk visualizations are often employed to support risk communication. However, their effectiveness in communication of single absolute risks remains unclear. We investigated the effectiveness of risk visualizations in conveying verbatim knowledge of single absolute risks among the general population.

Methods

Randomly sampled members of the general Dutch population completed four basic risk conversions from percentages to natural frequencies and vice versa. By random investigator-blinded allocation, these conversions were supported by either icon arrays, pie charts, bar graphs or no visualization. Verbatim risk knowledge was scored as the number of conversions completed correctly.

Results

393 subjects were included. Overall, 60% of respondents answered all four questions correctly. Risk format (percentages vs. natural frequencies, p=0.677) and risk magnitude (p=0.532) were not associated with verbatim risk knowledge score. Younger age (p=0.001) and higher education level ($p < 0.001$) were independently associated with higher scores. The use of risk visualizations was not associated with higher scores (OR=1.08; 95% confidence interval: 0.69-1.69; p=0.745). All three forms of risk visualization were equally ineffective. These findings held when stratifying by risk format, risk magnitude and user preference for a certain form of risk visualization. There were no significant interactions with age or education level.

Conclusions

Risk visualizations did not improve conveyance of verbatim knowledge of single absolute risks, irrespective of age, education level, risk magnitude, risk format and form of risk visualization. Risk visualizations may therefore be less suitable for settings in which detailed conveyance of single absolute risks is the main objective, although their effect on user experience and perception of risk communication and subsequent patient activation and participation remains to be elucidated.

INTRODUCTION

With the growing importance of patient empowerment and shared decision-making in healthcare, effective patient communication is increasingly important. Better informed and more activated patients are associated with improved quality of life, treatment adherence, health behavior and clinical outcome, but also with more efficient healthcare utilization and lower healthcare costs.[1-13] Therefore, informing patients and their relatives in an adequate and understandable manner is essential in optimizing treatment outcome.

One of the most important challenges in informing patients is effective communication of risk and benefit information about their current disease state and the various treatment options. Risk visualizations, such as icon arrays, bar charts and pie charts, are often employed to aid in this risk communication. They have been previously found to be effective in improving perception, understanding and interpretation of quantitative information over textual and numeric formats.[14,15]

Previous studies have focused largely on risk comparisons, trade-offs and gist knowledge (e.g. the understanding of the general risk message). However, many healthcare settings require informing patients about single absolute probabilities of risks and prognosis, often aside from treatment comparisons and decisions. For example, patients that have been diagnosed with a disease in whom treatment is not (yet) indicated or patients that have already undergone a certain treatment will face various health risks imposed by their disease and/or treatment during the course of their lives, health risks that they will need to take into account and that may require lifestyle changes, preventive measures or medical management. In this setting, an adequate and accurate understanding of the magnitude of the risk (verbatim knowledge), is essential in gaining insight into outcome and prognosis, motivating positive health behaviors and improving treatment adherence.[16] Evidence on the effect of risk visualizations on verbatim knowledge in the communication of single absolute risks is scarce.

This study therefore aims to investigate the effectiveness of various risk visualizations in improving verbatim knowledge in the communication of single absolute risks in a randomized, investigator-blinded general population survey.

METHODS

This study was approved by the institutional review board and written informed consent was waived (MEC-2016-424).

Participants

Subjects were recruited at random from 11 public locations across the Netherlands (Supplement 1) between June 2016 and August 2016. Surveyors (JMdG, EA, MEJ, AM, NAN) were posted in pairs at public locations across these cities and approached every person they encountered for participation in the survey. Potential participants were verbally approached to participate in the survey, which was introduced as a medical research project aimed at improving patient communication with a short background about the challenges in risk communication. All subjects 18 years of age or older were considered for inclusion. Subjects were excluded if they were color blind and/or were not literate in Dutch. There were no quotas for age or gender.

Questionnaire

All participants completed a printed Dutch questionnaire. As there are no validated methods for assessing verbatim risk knowledge, we formulated our own questionnaire based on the Numeracy Scale.[17] The Numeracy Scale tests subjects' ability to convert numerical risks from one format to another (e.g. natural frequencies, percentages, etc.). Because adequate verbatim knowledge of the presented risk is a prerequisite for such conversions, for the purposes of this study we operationalized verbatim risk knowledge as risk conversion tasks such as those in the Numeracy Scale. An adaptation of the Numeracy Scale consisting of four questions on risk conversions from percentages to natural frequencies (2 questions) and vice versa (2 questions) was used to assess verbatim knowledge of the presented numerical risk probabilities (Supplement 2). Furthermore, within each of these two pairs of questions, one question concerned a large risk (> 30%) and one concerned a small risk (< 5%). As such, each of the four questions represented one of the four possible combinations of direction of conversion and risk magnitude. The order of the questions was alternated at random between individual copies of the questionnaire.

There were four versions of the questionnaire. In each version, the four aforementioned questions were supported by either icon arrays, pie charts, bar charts or no visualization (Supplement 3). Each of these visualizations were designed to show part-to-whole relationship by presenting both affected and unaffected individuals, including the full denominator where possible and a legend that indicated which colors represented affected and unaffected individuals.

All subjects were also asked to indicate whether they preferred pie charts, icon arrays or bar charts for risk visualization, before any exposure to the visualization they were randomized to.

Gender, age and highest achieved education level were recorded as demographics.

Randomization and survey

The various versions of the questionnaires were printed at a 1:1 ratio. Random sequence was generated by shuffling by an investigator (JRGE) independent from the surveyors (JMdG, EA, MEJ, AM, NAN). Allocation concealment and blinding of surveyors was achieved by use of a universal cover page on all versions of the questionnaires. Questionnaires were handed out in sequence, after which surveyors withheld from further assistance with completion of the questionnaire.

Analysis

Respondents' verbatim knowledge of the presented numerical risks was scored ordinally from 0-4 corresponding with the number of risk conversion questions they answered correctly out of a total of four questions. To investigate the influence of risk magnitude and direction of conversion, questions on low vs. high risks (2 questions each) and for each direction of conversion (2 questions each) were also scored separately from 0-2, also corresponding with the number of these questions answered correctly. Respondents that did not complete all four verbatim knowledge questions were excluded from analysis. Analysis of these verbatim risk knowledge scores was conducted using ordinal regression and, for paired intra-subject comparisons, the Wilcoxon signed-rank test.

All analyses of the association between visualization preference and effectiveness were corrected for the relative difference in effectiveness between the three different forms of risk visualization.

Respondent demographics were compared to those of the general Dutch population for the year the survey was conducted in (2016) using the Chi-squared test, in which age distribution was analyzed categorically in 10-year age groups.

Statistical analyses were conducted in Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA) and IBM SPSS Statistics (version 22.0.0.0, IBM Corp., Armonk, NY, USA).

Sample size

Required sample size was calculated based on a previously conducted general population survey on numeracy.[18] In this previous survey, among subjects that did not receive

support of risk visualizations (control group), 40.5% answered all 4 questions correctly, 16.7% 3 correct, 19.0% 2 correct, 11.9% 1 correct and 11.9% 0 correct. Assuming the same score distribution in the control group of present study, we calculated that at least 90 subjects per study arm would be required to detect a 10% ordinal difference in verbatim risk knowledge scores between groups (meaning that at least 10% of the subjects in the intervention group would score *on average* one point higher or lower on verbatim risk knowledge than the subjects in the control group) with 80% power at a 0.05 significance level using ordinal regression. Thus, across the four study arms (no visualization, pie charts, icon arrays and bar charts) at a 1:1 sampling ratio, this totaled a required minimum of 360 subjects. These sample size calculations were conducted assuming data-analysis using ordinal regression and based on methodology described in the literature for sample size calculations for ordinal data.[19]

RESULTS

Of the 400 subjects who agreed to participate in the survey, a total of 393 subjects completed all four verbatim risk knowledge questions and were subsequently included in the study (Table 1). The other seven were excluded because they did not complete all four verbatim risk knowledge questions.

Table 1. Respondent demographics.

	Total	No visual	Pie chart	Bar chart	Icon array
Number of participants	393	100	98	98	97
Median age, years (range)	26 (18-88)	26 (18-74)	27 (18-84)	27 (18-88)	25 (18-81)
Male	194 (49%)	52 (52.0%)	50 (51.0%)	50 (51.0%)	42 (43.3%)
Education level					
None	4 (1.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	2 (2.1%)
Elementary	3 (0.8%)	0 (0.0%)	2 (2.1%)	1 (1.0%)	0 (0.0%)
Lower secondary or vocational	55 (14.1%)	9 (9.0%)	18 (18.8 %)	11 (11.3%)	17 (17.5%)
Higher secondary	171 (43.8%)	47 (47.0%)	37 (38.5 %)	42 (43.3%)	45 (46.4%)
University (bachelor) or higher professional	101 (25.9%)	29 (29.0%)	27 (28.1%)	25 (25.8%)	20 (20.6%)
University (master) or PhD	56 (14.4%)	14 (14.0%)	12 (12.5%)	17 (17.5%)	13 (13.4%)
Missing	3 (0.8%)	0 (0.0%)	2 (2.0%)	1 (1.0%)	0 (0.0%)

Gender distribution of this cohort was comparable to the general Dutch population ($p=0.934$), whereas age was lower ($p < 0.001$) and education level was higher ($p < 0.001$).

Respondent verbatim risk knowledge score distribution is shown in Fig. 1. Younger age and higher education level were independently associated with higher scores, whereas gender was not (Table 2). Respondent performance was comparable between conversions from percentages to natural frequencies vs. natural frequencies to percentages (Wilcoxon signed-rank p=0.677) and between questions on small risk magnitude vs. large risk magnitude (Wilcoxon signed-rank p=0.532).

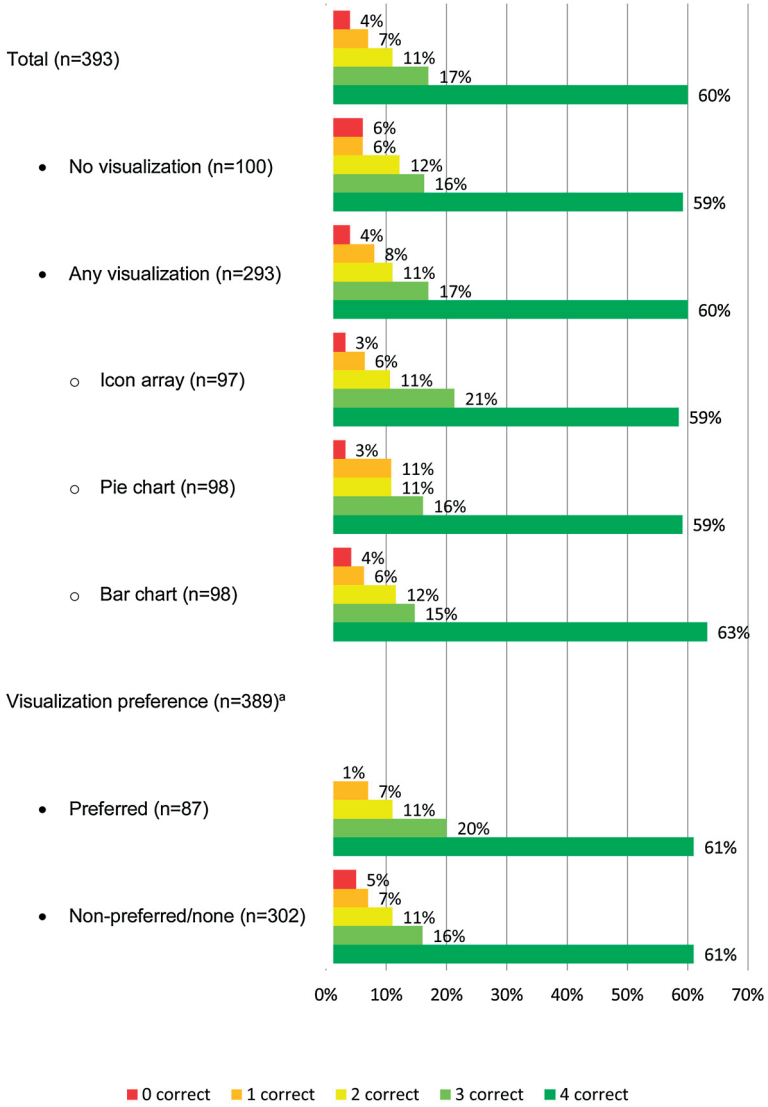

Figure 1. Respondent verbatim risk knowledge score distribution in relation to the use of risk visualizations and visualization preference. [a]Four respondents did not indicate a visualization preference.

Table 2. Association between demographics and verbatim risk knowledge scores.

	Univariable[a]		Multivariable[b]	
	OR (95%CI)	**p-value**	**OR (95%CI)**	**p-value**
Younger age (/10 years)	1.17 (1.05-1.30)	0.006	1.20 (1.07-1.34)	0.001
Higher education level	1.82 (1.46-2.27)	<0.001	1.85 (1.48-2.30)	<0.001
Male vs. female gender	1.25 (0.84-1.85)	0.278	1.31 (0.87-1.98)	0.190

[a] Model containing only the respective covariate.
[b] Model containing all three covariates. OR = odds ratio; CI = confidence interval.

Respondent verbatim risk knowledge score distribution in relation to the use of risk visualizations and visualization preference are presented in Fig. 1 and Table 3. The use of risk visualizations was not associated with higher scores, neither when icon arrays, pie charts and bar charts were considered separately nor when considered collectively. The effectiveness of all three different forms of risk visualization was comparable. These findings held when considering small and large risk magnitude and each conversion direction separately (Supplement 4 & 5) and there were no significant interactions between these effects and age or education level.

Respondents (n = 389; 4 respondents did not report a preference) reported a strong preference for pie charts (72%; n=281) over icon arrays (14%; n=54) and bar charts (14%; n=54). Of these 389 respondents, 87 (22%) were randomized to the visualization they indicated a preference for.

Respondents that were randomized to the visualization that they preferred did not achieve higher verbatim risk knowledge scores than those that were not (Fig. 1 & Table 3). Again, this finding held when considering small and large risk magnitude and each conversion direction separately (Supplement 4 & 5) and there were no significant interactions between this effect and age or education level.

To assess the impact of the difference in baseline score distribution between the current study and the previous study our sample size calculations were based on, we estimated which minimum effect size could have been detected with 80% power at a 0.05 significance level with the actual sample size under the observed score distribution. This analysis was done using the same methodology described above for our sample size calculation.[19] At the score distribution observed in the control group (Fig. 1, "No visualization") we had sufficient sample size (n=393 taking into account the observed actual sampling ratio and higher than the projected n=360) to detect an ordinal difference of at least 11% (vs. the assumed 10% difference) between groups with 80% power at a 0.05 significance level.

Table 3. Association between use of visualization and verbatim risk knowledge scores.

	Unadjusted		Adjusted[a]	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Any visualization vs. no visualization	1.08 (0.69-1.69)	0.745	1.16 (0.73-1.85)	0.518
Icon array vs. no visualization	1.06 (0.61-1.84)	0.833	1.17 (0.66-2.07)	0.589
Pie chart vs. no visualization	1.00 (0.57-1.74	0.993	1.15 (0.64-2.05)	0.638
Bar chart vs. no visualization	1.18 (0.67-2.07)	0.561	1.19 (0.67-2.12)	0.562
Icon array vs. pie chart	1.07 (0.61-1.87)	0.821	1.03 (0.58-1.83)	0.917
Bar chart vs. pie chart	1.19 (0.67-2.09)	0.556	1.04 (0.57-1.88)	0.897
Bar chart vs. icon array	1.12 (0.64-1.97)	0.699	1.02 (0.57-1.83)	0.948
Preferred vs. non-preferred/none	1.18 (0.63-2.22)	0.611	1.32 (0.69-2.52)	0.404

[a] Adjusted for age and education level. OR = odds ratio; CI = confidence interval.

DISCUSSION

This randomized, investigator-blinded survey among a sample of the general Dutch population found that risk visualizations do not improve verbatim knowledge of absolute numerical risks, irrespective of risk magnitude and risk format (i.e. natural frequency vs. percentage). Furthermore, icon arrays, pie charts and bar charts are equally ineffective and user preference for a certain form of risk visualization does not alter its effectiveness. Younger age and higher education level are associated with a better understanding of numerical risks, but have no interaction with the effectiveness of risk visualizations.

Risk visualizations are increasingly employed to aid in risk communication. They have been previously found to be effective in improving perception, understanding and interpretation of quantitative information over textual and numeric formats.[14,15] However, in a sufficiently powered, randomized, investigator-blinded setting, we found no effect of risk visualizations in improving verbatim knowledge of numerical risks. To our knowledge, our study is the first to focus on the conveyance of verbatim knowledge of single absolute numerical risks, as opposed to gist knowledge (understanding of the general risk message) and/or comparisons/trade-offs of multiple risks as in prior studies. This may explain in part the differences between our findings and those previously described, as many other factors play a role in gist comprehension, risk comparisons and trade-offs, for instance anecdotal reasoning, framing effects, denominator neglect, risk magnitude and the magnitude of risk differences.[20,21] The previously described effects of visualizations on gist knowledge may be due to effects on these factors rather than effects on the verbatim knowledge that underlies gist knowledge, as risk visualizations have been described to reduce the bias of these other factors in understanding the gist.[20,22] However, besides gist knowledge, verbatim knowledge has been shown to be

of substantial importance in risk communication independently of gist knowledge.[16,23] Verbatim knowledge is a precursor to gist knowledge, thus accurate gist knowledge, risk comparisons and trade-offs require a fundamental understanding and adequate and accurate perception of the probabilistic information they are based on.[24] Our findings show that this fundamental understanding is considerably impaired in the general population and we found no evidence that it is improved by the use of risk visualizations. This may be due to the fact that part of the challenge in communicating risk lies in inherent difficulties in understanding probabilistic information. Moreover, it has been previously described that visual displays may lead users to focus more on the pattern of the data or gross-level information and less on the precise values.[23,25,26] This may further explain why, in our study, risk visualizations appear to be less effective in the communication of single absolute risks. Thus, risk visualizations may be less suitable for use in settings that require a more detailed interpretation of the risk, such as communication of absolute risks, than for settings in which gist knowledge or a basic understanding of a broad larger-smaller relationship is the objective, as in risk comparisons and trade-offs for instance. Further research into how verbatim communication of absolute risks can be improved is warranted, as accurate patient understanding of numerical risk data, also outside the context of risk comparisons and trade-offs, has been previously found to be of essential importance in healthcare by improving patient autonomy and information-seeking and motivating positive health behaviors.[16]

Furthermore, graph literacy should also be taken into account. Graph literacy concerns the ability to extract data and meaning from visual displays, and has been shown to differ strongly between individuals and to be predictive of the potential benefit of risk visualizations.[27,28] Numeracy should also be taken into account, as it has been previously shown to influence the effectiveness of risk visualizations in conveying both verbatim and gist knowledge of probabilities. [23] The age of our sample was lower than in the general population and the education level was higher, both factors that may be associated with higher numeracy levels.[29] Future studies with a specific focus on low-numeracy individuals in a similar setting as the present study may reveal whether risk visualizations are more effective among low-numeracy individuals in the verbatim conveyance of single absolute risks. However, although we did not formally assess graph literacy and numeracy in our study, we found no interactions between the effectiveness of risk visualizations and age and education level. Further exploration of potential demographic factors associated with graph literacy and numeracy may allow for a more effective selective and individual-tailored application of risk visualizations.

Prior studies have also found differences in effectiveness between different forms of risk visualization, such as icon arrays, pie charts and bar charts.[23,24,30,31] In these studies, no

one form of risk visualization appears to be consistently more effective than the other, but rather the effectiveness of each type of visualization appears to depend heavily on the type of data being presented (natural frequencies vs. percentages, small vs. large risk magnitude) and the goal of the communication (e.g. gist vs. verbatim knowledge, comparisons vs. absolute risks).[23] However, the studies that describe these differences focus largely on risk perception, risk comparisons/relative risks and gist knowledge.

In the setting of single absolute risks, on the other hand, we found no difference in effectiveness between icon arrays, pie charts and bar charts in conveying verbatim risk knowledge, also after taking risk magnitude and textual format (natural frequencies vs. percentages) into account. This lack of an effect of risk visualizations in this setting may lie in part in the basic concept of graphical representation of risk probabilities rather than the specific graphical format.

Although we did not find evidence of the effectiveness of risk visualizations with regard to improving verbatim understanding in this setting, their value may lie more in their potential to make risk communication more appealing to users and to aid in drawing users' attention to the data, which may improve patient activation and participation. Further research on how this may affect risk communication in a broader perspective and patient empowerment is therefore warranted.

Future perspective

Further studies on the complex relationship between verbatim knowledge of risk and prognosis of the disease and treatment, gist knowledge and ultimately health behavior, treatment decisions, treatment adherence and quality of life may help identify in which healthcare settings patients could benefit most from risk visualizations. This may inform more effective and selective application of risk visualizations.

Also, replication of this study in different countries and languages may yield insight into potential cultural, societal and language-related factors that may be of influence on the effectiveness of risk visualizations.

Moreover, studies on this topic to date have focused largely on written risk communication. They also seldom study risk visualizations in real-world healthcare settings, but rather often employ methods of presenting hypothetical scenarios to general population samples to which the subject matter is not relevant, as in our study. However, the role and potential effectiveness of risk visualizations in verbal risk communication and in real-world healthcare settings among subjects with a more vested interest in understanding the risk information remain to be elucidated.

Strengths and limitations

To our knowledge, our study is the first randomized general population sample evaluation of the effectiveness of risk visualizations in verbatim communication of single absolute risks. Our adequately powered, randomized and investigator-blinded study design allows for accurate and reliable direct inference with a low risk of bias. Furthermore, the general population sampling and broad inclusion greatly enhance generalizability.

However, there are some limitations that should be taken into account. There were still some demographic differences between our study population and the general Dutch population that could not be completely accounted for, however we do not believe that this affected our results as we found no interactions between demographics and the measured effects. As this was a uni-national study, cultural, societal and language-related factors could not be taken into account. The baseline score distribution in current study was different than the baseline score distribution of the prior study we based our sample size calculations on, possibly due in part to a slightly lower age and higher education level in the current study. However, our sample size was considerably higher than projected (n=393 vs n=360) and our power analysis shows that, therefore, the difference in baseline score distribution did not substantially impact the power of our study.

CONCLUSIONS

In the communication of single absolute risks, the use of risk visualizations in addition to textual and numeric formats did not improve conveyance of verbatim risk knowledge, irrespective of age, education level, risk magnitude and risk format (natural frequency vs. percentage). Icon arrays, pie charts and bar charts were equally ineffective. Risk visualizations may therefore be less suitable for settings in which detailed conveyance of single absolute risks is the main objective, although their effect on user experience and perception of risk communication and subsequent patient activation and participation remains to be elucidated.

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SUPPLEMENTARY MATERIAL

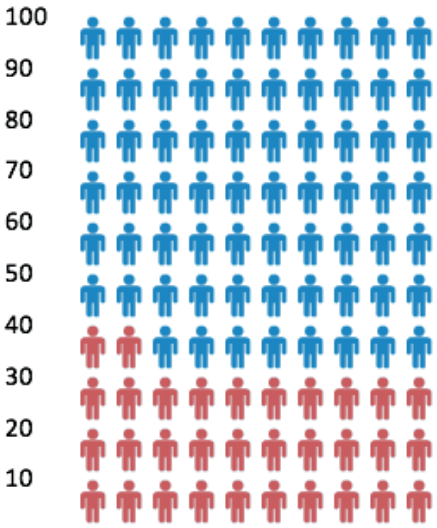
Supplement 1. Surveying locations.

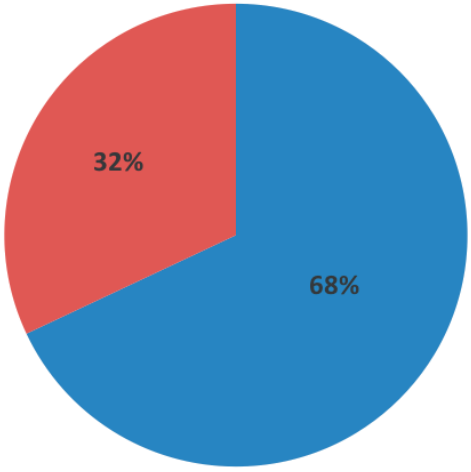
- Amsterdam, North Holland
- Breda, Brabant
- Zwolle, Overijssel
- Utrecht, Utrecht
- Rijswijk, South Holland
- Den Haag, South Holland
- Rotterdam, South Holland
- Leiden, South Holland
- Zoetermeer, South Holland
- Dordrecht, South Holland
- Barendrecht, South Holland

Supplement 2. Verbatim risk knowledge questions.

1. A patient that uses drug A has a 1% chance of having an allergic reaction.
   If 1000 patients take drug A, how many people would you expect to have an allergic reaction?
   _____ patient(s) out of 1,000
2. A patient that uses drug B has a 30 in 1,000 chance of having an allergic reaction.
   What percent of patients that take drug B have an allergic reaction?
   _____ %
3. A patient that undergoes operation C has a 32% chance of experiencing pain after surgery.
   If 1000 patients undergo operation C, how many people would you expect to experience pain after surgery?
   _____ patient(s) out of 1,000
4. A patient that undergoes operation D has a 450 in 1,000 chance of experiencing pain after surgery.
   What percent of patients that undergo operation D experience pain after surgery?
   _____ %

Supplement 3. Examples of an icon array, pie chart and bar chart.





Supplement 4. Association between use of visualization and verbatim risk knowledge scores by risk magnitude.

	Small risk magnitude (<5%)			
	Unadjusted		Adjusted[a]	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Any visualization vs. no visualization	0.91 (0.55-1.48)	0.692	1.00 (0.60-1.67)	0.996
Icon array vs. no visualization	0.89 (0.49-1.63)	0.714	1.07 (0.57-2.00)	0.842
Pie chart vs. no visualization	0.92 (0.50-1.68)	0.784	1.11 (0.58-2.13)	0.743
Bar chart vs. no visualization	0.91 (0.50-1.66)	0.752	1.15 (0.61-2.16)	0.666
Icon array vs. pie chart	0.98 (0.54-1.77)	0.934	0.94 (0.50-1.76)	0.853
Bar chart vs. pie chart	0.99 (0.54-1.80)	0.962	0.80 (0.42-1.51)	0.493
Bar chart vs. icon array	1.01 (0.56-1.83)	0.975	0.84 (0.45-1.56)	0.583
Preferred vs. non-preferred/none	1.01 (0.51-1.98)	0.983	1.14 (0.56-2.29)	0.719

[a]Adjusted for age and education level. OR = odds ratio; CI = confidence interval.

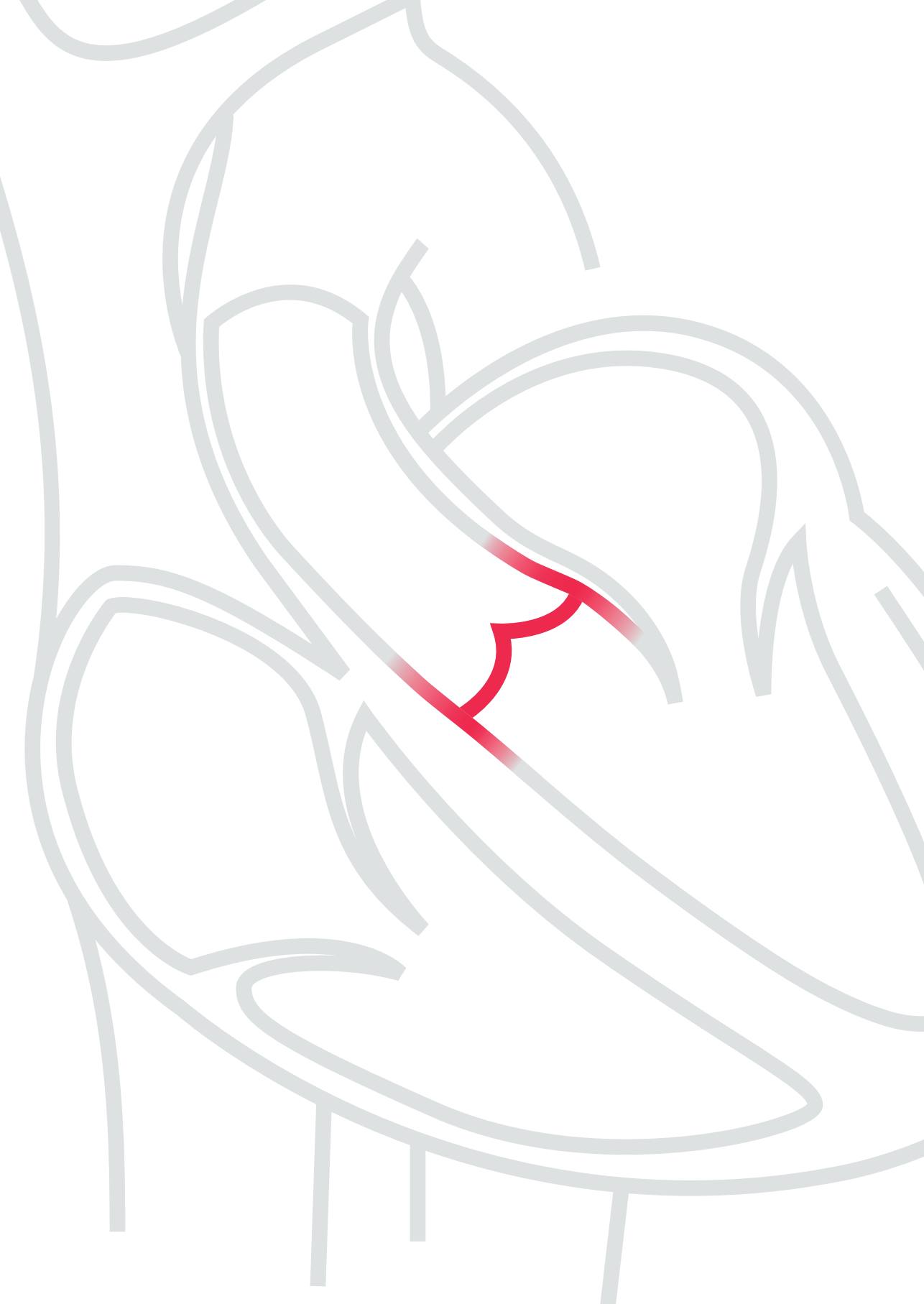
Supplement 5. Association between use of visualization and verbatim risk knowledge scores by direction of conversion.

	% → Natural frequency			
	Unadjusted		Adjusted[a]	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Any visualization vs. no visualization	1.04 (0.65-1.68)	0.863	1.13 (0.69-1.86)	0.622
Icon array vs. no visualization	1.10 (0.61-1.99)	0.754	1.22 (0.66-2.26)	0.523
Pie chart vs. no visualization	0.80 (0.45-1.43)	0.455	0.90 (0.50-1.64)	0.735
Bar chart vs. no visualization	1.32 (0.72-2.43)	0.368	1.31 (0.69-2.46)	0.409
Icon array vs. pie chart	1.37 (0.76-2.46)	0.299	1.33 (0.72-2.46)	0.358
Bar chart vs. pie chart	1.64 (0.90-3.00)	0.107	1.42 (0.75-2.70)	0.277
Bar chart vs. icon array	1.20 (0.64-2.24)	0.565	1.04 (0.54-2.00)	0.914
Preferred vs. non-preferred/none	1.21 (0.62-2.36)	0.585	1.31 (0.65-2.63)	0.449

[a]Adjusted for age and education level. OR = odds ratio; CI = confidence interval.

Large risk magnitude (>30%)			
Unadjusted		Adjusted[a]	
OR (95%CI)	p-value	OR (95%CI)	p-value
1.23 (0.76-2.01)	0.400	1.38 (0.83-2.29)	0.209
1.28 (0.69-2.37)	0.432	1.40 (0.74-2.63)	0.303
0.98 (0.54-1.78)	0.954	1.13 (0.61-2.09)	0.704
1.53 (0.81-2.87)	0.188	1.71 (0.88-3.32)	0.113
1.30 (0.70-2.43)	0.402	1.26 (0.66-2.39)	0.480
1.56 (0.82-2.94)	0.172	1.45 (0.74-2.84)	0.274
1.20 (0.62-2.30)	0.592	1.14 (0.58-2.27)	0.702
1.50 (0.74-3.08)	0.263	1.77 (0.84-3.71)	0.130

Natural frequency → %			
Unadjusted		Adjusted[a]	
OR (95%CI)	p-value	OR (95%CI)	p-value
1.17 (0.71-1.91)	0.543	1.30 (0.78-2.16)	0.320
1.19 (0.65-2.19)	0.578	1.32 (0.70-2.50)	0.394
1.23 (0.66-2.28)	0.522	1.49 (0.76-2.91)	0.241
1.09 (0.60-1.99)	0.783	1.16 (0.62-2.19)	0.644
0.96 (0.51-1.81)	0.898	0.89 (0.46-1.72)	0.728
0.88 (0.47-1.65)	0.693	0.76 (0.39-1.48)	0.426
0.91 (0.49-1.69)	0.774	0.86 (0.46-1.63)	0.643
1.72 (0.82-3.57)	0.149	2.03 (0.94-4.36)	0.071



11

Development of an online, evidence-based patient information portal for congenital heart disease: a pilot study

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Background

In response to an increased need for patient information on congenital heart disease in the Netherlands, we initiated a nationwide initiative to develop an online, evidence-based patient information portal, starting with a pilot project aimed at the subgroup of patients with congenital aortic and pulmonary valve disease.

Methods and results

We developed an information portal that aims to (1) improve patient knowledge and involvement and to subsequently reduce anxiety and decisional conflict and improve mental quality of life and (2) to support physicians in informing and communicating with their patients. The information portal was developed according to the systematic International Patient Decision Aid Standards development process employing Delphi techniques by a multidisciplinary workgroup of pediatric and adult congenital cardiologists, a congenital cardiothoracic surgeon, a psychologist, an epidemiologist, a patient representative, and web and industrial design experts. First, patients and physicians were surveyed and interviewed to assess the current state of patient information and explore their preferences and needs to determine the focus for the development of the information portal. We found that patient knowledge and numeracy are limited, reliable information is scarce, physicians inform patients selectively and patient involvement is suboptimal, and there is a need for more reliable, tailored, and multi-faceted information. Based on the findings of these surveys and interviews, a patient-tailored information portal was designed that presents evidence-based disease- and age-specific medical and psychosocial information about diagnosis, treatment, prognosis, and impact on daily life in a manner that is comprehensible and digestible for patients and that meets the needs expressed by both patients and physicians. The effect of the website on patient outcome is currently being assessed in a multicenter stepped-wedge implementation trial.

Conclusions

The present pilot project succeeded in developing an online, evidence-based information portal that is supported by both patients and physicians. The information portal will be further developed and expanded to include all other major forms of congenital heart disease, translations into other languages, and a public information portal to serve patients' relatives and the general public at large.

INTRODUCTION

Congenital heart disease is the most common congenital birth defect with an incidence of approximately 1% of all live births.[1, 2] Due to major advances in the treatment of congenital heart disease over the past decades, approximately 90% of these patients now reach adulthood.[3] This has, however, made congenital heart disease a chronic illness with, for example, an estimated 2.4 million people currently living with a congenital heart defect in the United States of America alone and an estimated 65,000 in the Netherlands.

The consequences of congenital heart disease for the individual patient are complex, time varying, and heavily dependent on the specific defect(s), individual patient-related factors, and treatment options and decisions. These consequences may have a significant impact on many facets of the patients' lives, both clinical and personal. Therefore, informing patients and their relatives in a complete, objective, and understandable manner is essential in optimizing patient quality of life, lifestyle, health behavior, treatment adherence, and patient involvement in treatment decisions.[4-16]

In response to an increased need for patient information in congenital heart disease in the Netherlands, we therefore initiated a nationwide initiative to improve patient information, starting with a pilot project aimed at a subgroup of congenital heart disease patients with aortic or pulmonary valve disease, including Tetralogy of Fallot.[13-15, 17-21]

The objective of this pilot project was to develop an online information portal that aims to (1) improve patient knowledge and involvement and to subsequently reduce anxiety, depression, and decisional conflict and improve mental quality of life and (2) to support physicians in informing and communicating with their patients.

METHODS AND RESULTS

The present pilot study comprises a complete comprehensive development process for a target subgroup restricted to patients with congenital aortic and/or pulmonary valve disease and/or Tetralogy of Fallot as a proof of concept. The subsequent full-scale project will entail expansion to all other major forms of congenital heart disease, building on this proof of concept.

The focus of this pilot project was to develop a nationwide patient-tailored, evidence-based patient information tool to be incorporated into specialist congenital cardiac

care developed by and for patients, caregivers, and physicians, based on both patient/caregiver and physician preferences.

First, we evaluated the current state of patient information in congenital heart disease in the Netherlands to determine key focus points for development. Next, we developed the information portal in a multidisciplinary national working group (Table 1) according to the systematic International Patient Decision Aid Standards (IPDAS) development process, employing Delphi techniques.[22, 23] Finally, we designed and are currently conducting a stepped-wedge cluster randomized implementation trial. All three steps are described below.

Table 1. Working group members.

Role	Center	Appointed by
Clinical		
Patient representative[a]	-	Dutch Patient Association for Congenital Heart Disease
Pediatric cardiologist	LUMC, Leiden	Dutch Association for Pediatrics
Adult congenital cardiologist	Radboudumc, Nijmegen	Dutch Association for Cardiology
Congenital cardiac surgeon	AMC, Amsterdam	Dutch Association for Cardiothoracic Surgery
Clinical psychologist	Erasmus MC, Rotterdam	-
Methodological		
Epidemiologists	Erasmus MC, Rotterdam	Dutch Heart Foundation
Web and industrial design firm[b]	-	-

[a]Chairman of the Dutch Patient Association for Congenital Heart Disease. [b]Specialized in the development and implementation of patient information portals and decision aids.
-, not applicable; LUMC, Leiden University Medical Center; Radboudumc, Radboud University Medical Center; AMC, Academic Medical Center; Erasmus MC, Erasmus University Medical Center.

EVALUATION OF THE CURRENT STATE OF PATIENT INFORMATION

The first crucial step in the development of the portal was a thorough evaluation of the current state of patient information and information needs in congenital heart disease in the Netherlands. The results of this phase would define the key focus points for the development of the information portal and, thus, represent the primary input for the next phase of the project.

We carried out this phase by conducting comprehensive surveys and interviews among patients (N = 63), caregivers of pediatric patients (N = 10), and physicians (N = 32). A detailed report of these surveys will be published separately, but the main findings included the following:

- **Patient/caregiver knowledge is limited:** although patients/ caregivers think they are adequately informed, actual diseasespecific knowledge was objectively sufficient in only half of the respondents, which is in line with previous findings.[13, 14, 17-21]
- **Reliable information is scarce:** only 62% of patient/caregiver respondents agreed that reliable information was readily available to them. Subsequently, patients rely heavily on their physicians for information as evidenced by a mere 13% of patients citing sources other than their cardiologist or cardiac surgeon as one of their main sources of information.
- **Patient/caregiver numeracy is limited:** only 46% of respondents were able to successfully complete a 3-question basic numeracy test adapted from the Numeracy Scale.[24, 25]
- **Patient/caregiver involvement is suboptimal:** both physicians and patients/ caregivers agree that patients/caregivers are insufficiently involved. Physicians agree that most difficulty they experience in involving patients/caregivers is due to limited patient knowledge and comprehension.
- **Physicians inform patients/caregivers selectively:** as selfreported by physicians, the information they convey is mostly based on their own judgment of what is important and comprehensible to each patient/caregiver. This may not always correspond with what patients/caregivers themselves think is important.
- **Patient information preferences and needs:** in line with previous findings,[26] the most important preferences and needs with regard to patient information expressed by *patients/caregivers* were as follows:
  - o More (reliable) information on:
    - Implications for personal life (education, career, pregnancy, insurance, etc.)
    - Health behavior and lifestyle recommendations
    - Prognosis
    - Psychosocial aspects
    - Pros and cons of various treatment options
    - Recovery after surgery
  - o Disease-specific information
  - o Age-specific information
  - o Non-contradictory information.

  Whereas *physicians* expressed a strong need for:
  - o A single, trusted, evidence-based source of reliable patient information to which they can refer their patients
  - o Tools to aid communication with patients/caregivers.

DEVELOPMENT OF INFORMATION PORTAL

Based on the findings of the surveys and interviews and in response to the needs expressed by both patients and physicians therein, a first prototype of an information portal was drafted according to the IPDAS development process and employing Delphi techniques. This prototype was then internally reviewed and revised by all members of the working group in live meetings until a consensus was reached on all topics (Table 1) (alpha-testing). The resulting second prototype was then again extensively reviewed by independent adult patients ($n = 2$), caregivers of pediatric patients ($n = 2$), physicians ($n = 6$; two pediatric cardiologists, two adult congenital cardiologists and two congenital cardiac surgeons), and clinical psychologists ($n = 2$) from outside the working group, sampled from clinical practice (beta-testing). All testers were given specific instructions to focus on all aspects of the information portal, including information content, language, illustrations, design, and usability. Additionally, the patients/caregivers were also observed as they navigated the portal. The feedback from this beta-testing was the input for the final review and revision by the working group.

The product of this development process is a comprehensive patient information tool that corresponds with the preferences and needs expressed by patients and physicians and addresses the shortcomings identified in the surveys and interviews.

The implementation of the patient information portal in clinical care will take place as follows. Patients/caregivers that present to the cardiologist are invited to use the online information portal by the cardiologist who hands out a sketchpad during the consultation (Figure 1). This sketchpad offers a template for the cardiologist to provide a clear graphical representation of the patient's heart defect as well as any other relevant notes for the patient/caregiver. On the sketchpad, the cardiologist also indicates which of the predefined diagnoses are applicable to the patient. The patients/caregivers can then take their sketch sheet home and review the cardiologist's notes and drawings and visit the information portal using the link and personal private account details listed on the sketch sheet. When they do so, they enter a private information portal (Figure 2) with the following key characteristics.

Disease- and age-specific information

All information on the portal is compiled and presented specifically and separately for each congenital heart defect and target group (teenagers, adults, or parents/caregivers) with regard to both content and language.

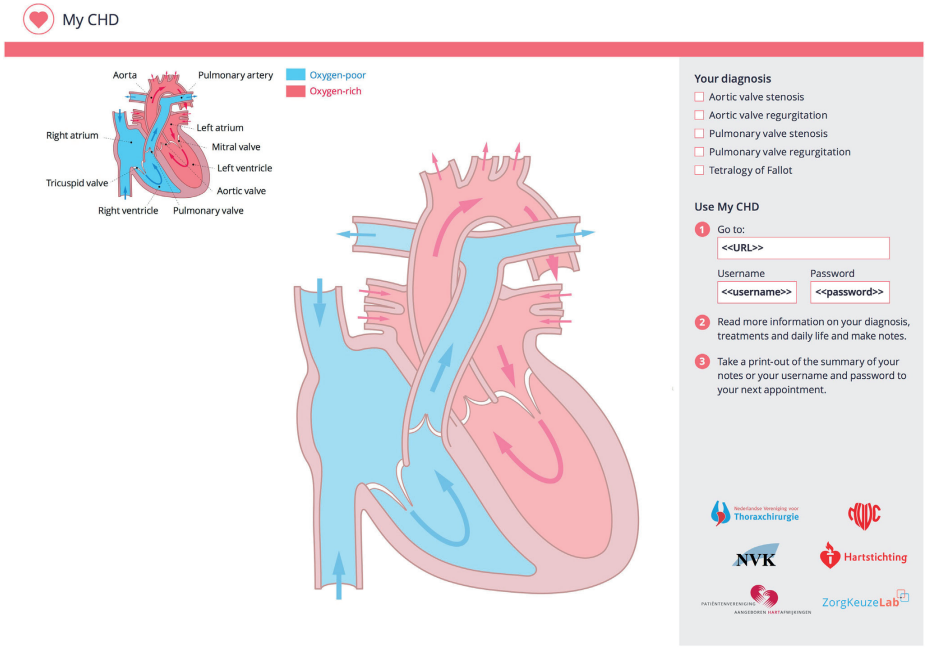

Figure 1. Sketchpad.

Upon their first visit to the website, users are prompted to select their target group and diagnosis (two simple multiple choice prompts). Based on the combination of these inputs, a tailored personal subportal is custom built for each user. Their personal subportal contains only the information that is relevant to them. In case of multiple congenital heart defects, all relevant information is automatically combined into a single tailored subportal for that unique combination of inputs.

Multi-faceted information based on patient/caregiver preferences

As patients/caregivers indicated a discrepancy between their own information needs and the information generally provided by physicians and other sources, the information provided by the portal is not based solely on what physicians think is important but rather represents both the clinical and the patient perspectives. Therefore, the information portal contains information on all aspects of disease that were found to be important to patients/caregivers and physicians in the surveys and interviews, such as diagnosis, treatment, prognosis, psychosocial aspects, and implications for daily life and future life planning.

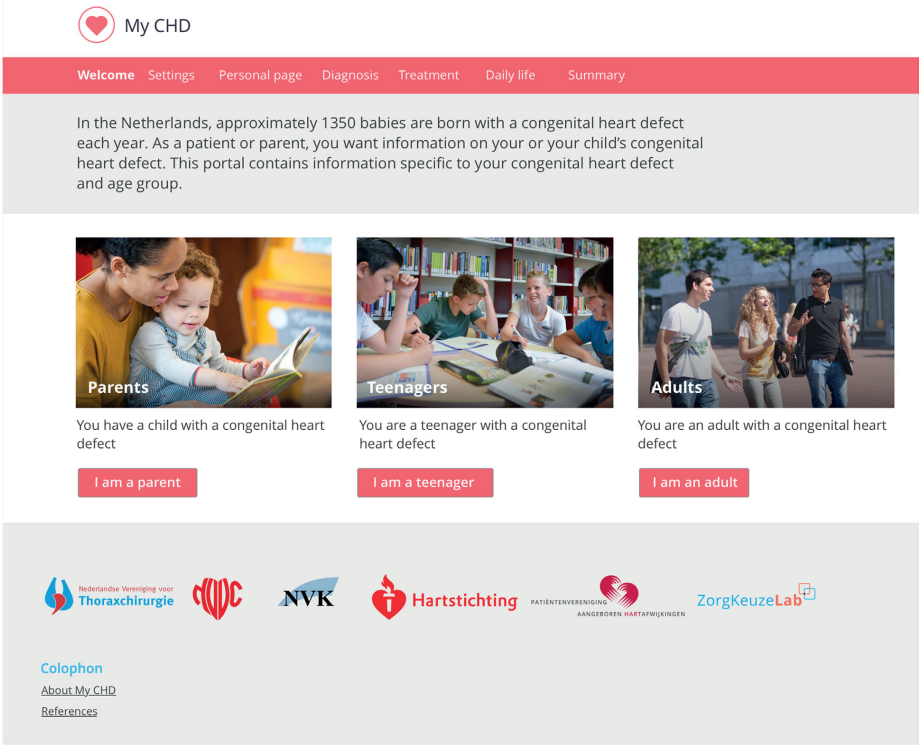

Figure 2. Screenshot of the pilot online patient information portal.

Format that is comprehensible and digestible

To maximize digestibility and comprehensibility, the information is fragmented into various frequently asked questions that correspond with the topics that patients/caregivers and physicians indicated to be important in the surveys and interviews. Comprehension is further enhanced by the liberal use of custom illustrations, designed to the specifications of the multidisciplinary working group by a professional medical illustrator. Additionally, a professional medical text writer was contracted to optimize the linguistics of the textual content for each target group separately to maximize comprehensibility, digestibility and attractiveness for users of all ages and education levels. Furthermore, to address the limited numeracy among the target audience, all numerical risks on the information portal are supported by risk visualizations, such as icon arrays.

Support patient/caregiver-physician communication

Patients/caregivers indicated that they are often unsure about which topics should be discussed with the physician. Throughout the information portal, we therefore provide numerous suggestions for important topics that should be discussed, as indicated by both physicians and patients/caregivers. Furthermore, there is a comment box on each

page of the information portal in which patients/caregivers are encouraged to note any questions they may have about the information on that page. These questions are then saved in their personal account. Users can view, edit, and/or print a summary of their questions and optionally discuss this with their physicians.

Physicians and other involved health-care providers are also provided with their own personal accounts for the information portal, so that they can use the information portal to aid in explaining or illustrating disease-related information to patients/ caregivers in the consulting room. Moreover, the sketchpad, as described above, is intended to further facilitate communication in the consulting room.

Evidence-based information

All information on the information portal is based on international guidelines and peer-reviewed published evidence where possible. Furthermore, all four centers for congenital cardiac surgery in the Netherlands have combined their prospective databases of early outcome after all congenital cardiac surgery performed in these centers in the past 10 years to allow conveyance of reliable, nationwide data on risks and recovery after contemporary cardiac surgery to patients/caregivers.

IMPLEMENTATION TRIAL

As the last phase of this pilot project, we are conducting a stepped-wedge cluster randomized [27, 28] implementation trial of the information portal in four large congenital cardiac centers in the Netherlands, which is ongoing as of writing.

The aim of this last phase of the pilot project is twofold:

- To gain insight into both the practical and cultural intricacies at each of the eight participating departments (departments of both adult and pediatric cardiology at each of the four participating centers) that need to be taken into account for effective implementation of the information portal and to subsequently develop individual implementation plans tailored to each of these departments and
- To evaluate the effect of the implementation of the information portal on patients and caregivers with regard to:
    - Disease-specific knowledge
    - Anxiety and depression
    - Mental quality of life
    - Patient/caregiver involvement and autonomy
    - Experiences with and views on patient information
    - Views on participation in decision-making
    - Decisional conflict.

Adult patients and caregivers of pediatric patients with congenital aortic and/or pulmonary valve disease and/or Tetralogy of Fallot that visit the outpatient clinic at one of the four participating centers are prospectively included. In total, at least 250 respondents will be included, 125 in the control group (no access to the information portal) and 125 in the intervention group (access to the information portal), all of whom will complete an online survey on the above topics 1 month after their visit to the outpatient clinic.

DISCUSSION AND FURTHER DEVELOPMENT

The present pilot project succeeded in developing and implementing a nationwide online, evidence-based, disease- and age-specific information portal for (caregivers of) patients with congenital heart disease, based on extensive input from all parties involved in congenital cardiac care in the Netherlands and addressing both patient and physician needs. Our extensive and meticulous nationwide multidisciplinary development process ensures broad nationwide acceptance into clinical practice by both patients/caregivers and health-care providers.

In various disease states, more informed and activated patients have been previously found to be associated not only with improved quality of life, treatment adherence, health behavior, and clinical outcome but also with more efficient health-care utilization and lower health-care costs.[4-16] The implementation trial, the final phase of the current pilot project, will shed light on the effect of the implementation of our pilot information portal on short-term psychosocial patient outcome. In the further development of the information portal, we will also focus specifically on clinical and long-term psychosocial effects as well as physician, implementation, and health-care service outcomes.

We are currently planning the further refinement and expansion of this information portal to all major forms of congenital heart disease, in which we aim to cover >90% of all cases of congenital heart disease. This full-scale project will build on all the knowledge, expertise, methods, framework, and infrastructure gained in the pilot project and will also be carried out in a multidisciplinary fashion. Additionally, focus groups with specific expertise will be employed when beneficial. This full-scale project will also include translations into other common languages, first and foremost English. We are also exploring innovative and interactive methods for improving patient participation, particularly in teenagers and adolescents.

Besides the further development of the current patient-tailored information portal, the full-scale project will also include the parallel development of a public information portal suited for broader use by patients and caregivers before a definitive diagnosis has been made, as well as their relatives and friends and the general public at large.

In the interest of sustainability, all relevant Dutch physician associations and patient associations have committed to a long-term partnership in this initiative. A multidisciplinary national working group in which each of these partners is represented will remain instated to oversee continuous review, updating, enhancement, and expansion of the information portal to ensure that we continue to provide up-to-date, evidence-based patient information of the highest standard.

Future partnerships and (conceptual) dissemination beyond the field of congenital heart disease and internationally may provide unique opportunities for further enhancing quality, expertise, and sustainability in this initiative.

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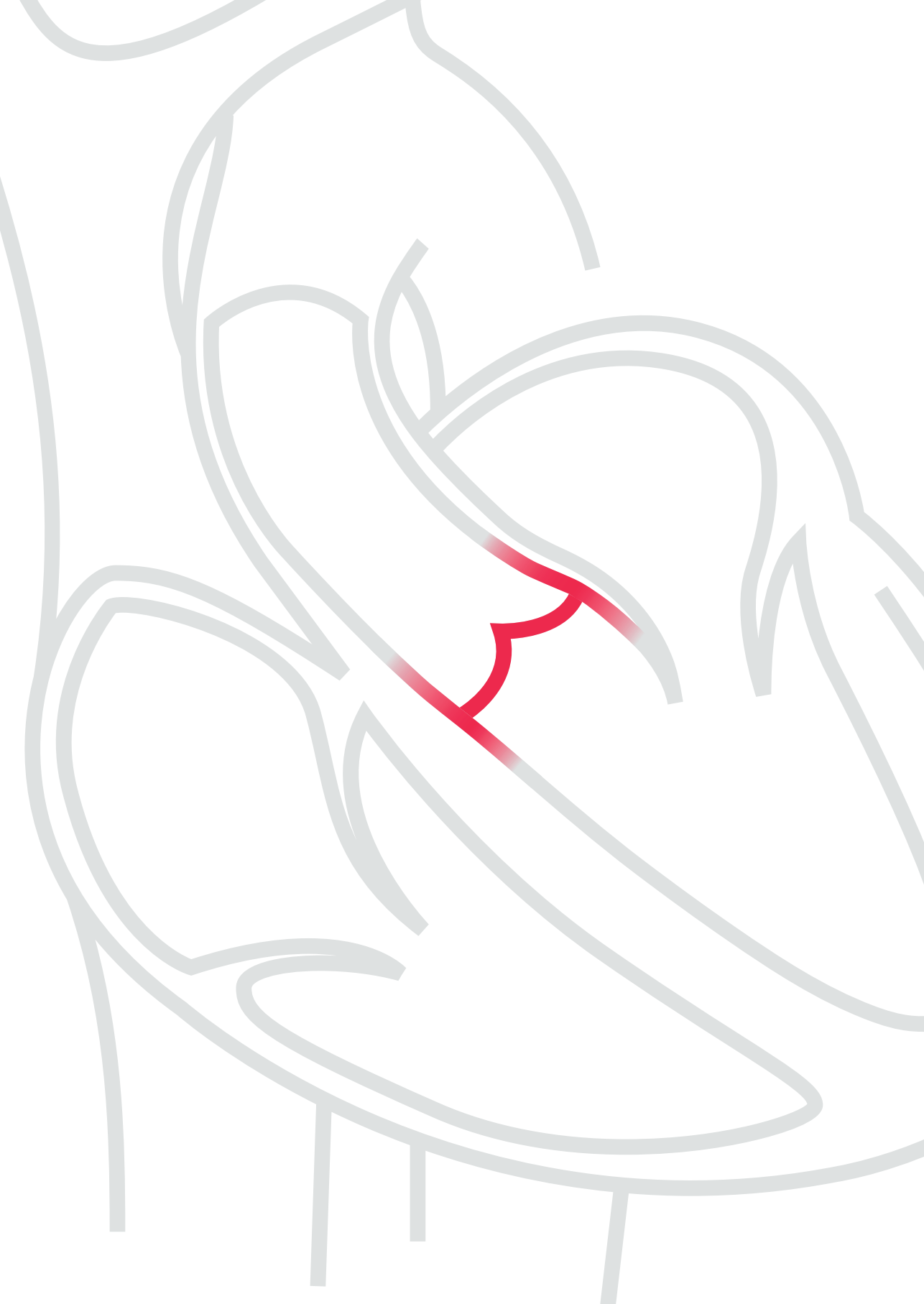

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Patient information portal for congenital aortic and pulmonary valve disease: a stepped-wedge cluster randomized trial

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ABSTRACT

Background

In response to an increased need for patient information in congenital heart disease, we previously developed an online, evidence-based information portal for patients with congenital aortic and pulmonary valve disease. To assess its effectiveness, a stepped-wedge cluster randomized trial was conducted.

Methods

Adult patients and caregivers of pediatric patients with congenital aortic and/or pulmonary valve disease and/or tetralogy of Fallot who visited the outpatient clinic at any of the four participating centers in the Netherlands between 1/3/2016-1/7/2017 were prospectively included. The intervention (information portal) was introduced in the outpatient clinic according to a stepped-wedge randomized design. One month after outpatient clinic visit, each participant completed a questionnaire on disease-specific knowledge, anxiety, depression, mental quality of life, involvement and opinion/attitude concerning patient information and involvement.

Results

343 participants were included (221 control, 122 intervention). Cardiac diagnosis ($p=0.873$), educational level ($p=0.153$) and sex ($p=0.603$) were comparable between the two groups. All outcomes were comparable between groups in the intention-to-treat analyses. However, only 51.6% of subjects in the intervention group (n=63) reported actually visiting the portal. Among these subjects (as-treated), disease-specific knowledge ($p=0.041$) and mental health ($p=0.039$) were significantly better than in control subjects, while other baseline and outcome variables were comparable.

Conclusions

Even after being invited by their cardiologists, only half of the participants actually visited the information portal. Only in those participants that actually visited the portal, knowledge of disease and mental health were significantly better. This underlines the importance of effective implementation of online evidence-based patient information portals in clinical practice.

INTRODUCTION

Thanks to major advances in the treatment of congenital heart disease over the past decades, approximately 90% of patients now reach adulthood.[1] However, this has made congenital heart disease a chronic illness that represents a growing health burden among children and adults. For example, as of 2010 there were an estimated 2.4 million people living with congenital heart disease in the United States of America alone among a total population of approximately 309 million.[2]

The consequences of congenital heart disease for the individual patient are complex, time-varying and dependent on the specific defect(s), individual patient-related factors and treatment options and decisions. These consequences will have a significant impact on many aspects of patients' lives, both physical and psychosocial. Therefore, informing patients and their relatives in a complete, objective and understandable manner is essential and may optimize patient quality of life, lifestyle, health behaviour, treatment adherence, involvement and health care utilization.[3,4,5,6,7,8,9,10,11,12,13,14]

In response to an increased need for patient information in congenital heart disease in the Netherlands[15], where an estimated 65,000 people live with congenital heart disease, we previously developed a patient information portal for congenital heart disease in a nationwide initiative, starting with a pilot project aimed at a subgroup of congenital heart disease patients with aortic or pulmonary valve disease, including tetralogy of Fallot.[15,16]

To assess the effectiveness of this information portal, we conducted a stepped-wedge cluster randomized trial in four congenital heart disease centers in the Netherlands among (parents of) patients with congenital aortic or pulmonary valve disease, including tetralogy of Fallot.

METHODS

This study was approved by the institutional review board of the Erasmus University Medical Center (MEC-2015-584), registered in the Netherlands Trial Register (NTR6805) and written informed consent was obtained from all participants. The study is reported in accordance with the CONSORT guidelines.[17]

Participants

Participants were recruited from 4 congenital heart disease centers in the Netherlands, namely Erasmus University Medical Center (Rotterdam), Leiden University Medical Center (Leiden), Academic Medical Center (Amsterdam) and Radboudumc (Nijmegen).

All patients aged between 18 and 40 years and parents/caregivers of patients <18 years of age with congenital aortic stenosis/regurgitation, congenital pulmonary stenosis/regurgitation and/or tetralogy of Fallot who visited the pediatric or adult cardiology outpatient clinic at one of the participating centers during the study period were considered for inclusion. Subjects were only included if their aortic and/or pulmonary valve disease was of at least moderate hemodynamic severity (peak Doppler gradient ≥36 mmHg and/or ≥moderate regurgitation).[18,19] Mentally incompetent subjects and subjects that could not read or write Dutch were excluded. Subjects could only participate once, and were thus not recruited again at subsequent outpatient clinic visits after prior inclusion (no repeated measures). There were no restrictions on the moment during follow-up at which subjects could be included (e.g. at diagnosis, routine check-up, preoperative, postoperative, etc.).

Intervention

The intervention consisted of access to a previously developed evidence-based online patient information portal. The development of this portal has been previously described.[16] Practical introduction of the information portal in the outpatient clinic was tailored to the workflow at each participating department and all participating physicians and support staff were trained in its use. After introduction, subjects in the intervention group were invited to visit the portal by their treating pediatric or adult congenital cardiologist during the outpatient clinic consultation.

Subjects in the control group received standard care, without access to the information portal.

Trial design

The trial was conducted according to a prospective stepped-wedge cluster randomized design from 1 March 2016 to 1 July 2017 (Figure 1).[20] All 4 centers started in the control phase, in which enrolled subjects did not receive the intervention. Subsequently, each of the participating centers transitioned to the intervention phase at a different time point, according to a stepped-wedge randomized design.[20] All subjects enrolled during the intervention phase were invited to visit the information portal by their treating pediatric or adult congenital cardiologist during the outpatient clinic consultation. To ensure the accrual of sufficient control subjects, the first center transitioned to the intervention

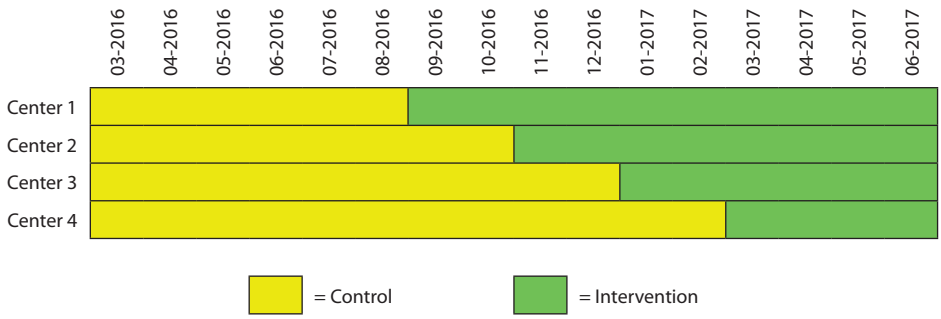

Figure 1. Stepped-wedge cluster randomized trial design. The four participating centers were randomly allocated as centers 1 through 4 as depicted in this figure and described in the methods section.

phase after at least 80% of the required total control group sample size had been accrued (1 September 2016). The dates for transition from control to intervention at each center were 2 months apart (1 September 2016, 1 November 2016, 1 January 2017 and 1 March 2017) and each of the four participating centers were randomly allocated to one of these four starting dates. Randomization was performed by an independent researcher by randomly drawing four cards listing the names of each of the four centers, with the order of the draw corresponding with the order in time of transition to intervention. Allocation concealment was achieved by placing each of the four cards in an opaque unmarked sealed envelope by a different independent researcher before random draw. Because of the nature of the intervention, it was not possible to blind investigators or participants to the allocation.

Outcomes

All participants completed a questionnaire 1 month after outpatient clinic visit. Age, sex and educational level were recorded as demographics in the questionnaire and diagnosis was extracted from the patient's medical record.

Primary outcome: Disease-specific knowledge

Disease-specific knowledge was assessed using a questionnaire developed specifically for the purpose of this study in a multidisciplinary working group consisting of a pediatric cardiologist (RAB), adult congenital cardiologist (APJvD), congenital cardiac surgeon (JK), patient (EvG), clinical psychologist (EMWJU) and epidemiologists (JRGE & JJMT). This questionnaire (Supplement 2) consisted of 7 multiple choice questions that test the subjects' knowledge of what their own (child's) personal condition is (2 questions), the implications of heart valve disease for lifetime risk of an operation (1 question), daily functioning (1 question) and work/career (1 question), the purpose of their regular check-ups (1 question) and symptoms that may indicate deterioration of their condition (1 question).

Secondary outcomes

Subjects' feeling about how well informed they were, experiences with patient information, preferences for involvement, anxiety, depression, health-related mental quality of life and satisfaction with the information portal (only intervention group) were assessed as secondary outcomes (further details in Supplement 1).

Sample size

We based our sample size calculations on data from a prior study by Korteland et al on a population of adult patients with heart valve disease who were facing heart valve replacement surgery.[21] Because this study did not assess our primary outcome using comparable methods (nor any other study to our knowledge), we based our calculations on the secondary outcome measure that was assessed in both studies, namely the Hospital Anxiety and Depression Scale (HADS). Based on the results of Korteland et al, we assumed a mean HADS of 10.5±7.9 in the control group and 7.7±6.7 in the intervention group. As there was no data available on intracluster correlation, we chose to take its possible effect on outcome into account by overpowering our study and thus basing our sample size on a power of 0.85 instead of 0.80. At a power of 0.85 and a 0.05 significance level, this led us to an estimated required sample size of 244 patients at a 1:1 sampling ratio (122 in the control arm and 122 in the intervention arm)

Statistical analysis

All outcomes were analyzed according to both the intention-to-treat and the as-treated principles.[20,22] Analyses were performed in the R statistical software (version 3.3.3, R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). Continuous data are presented as mean ± standard deviation or median (range) and categorical data (including Likert scales) are presented as proportions and/or counts. Comparison of baseline characteristics between groups was done using the Students t-test and Chi-square test where appropriate. For comparison of outcome measures between groups, linear regression models were used to analyze continuous outcomes (including summary scores) and ordinal regression models for ordinal outcomes (single Likert scales and Control Preferences Scale). All analyses of outcomes were adjusted for center and time effects using mixed models (random effect for center and fixed effect for calendar time).[20]

RESULTS

Between 1 March 2016 and 1 July 2017, 962 eligible subjects were asked to participate (542 control phase, 420 intervention phase), of which 343 gave written informed con-

sent and filled out the questionnaire (35.7% inclusion rate), 221 in the control group (standard care) and 122 in the intervention group (standard care + access to information portal) (Figure 2). Only 63 of the subjects in the intervention group (51.6%) reported actually visiting the information portal (as-treated intervention group). Baseline characteristics were comparable between the control group and both the intention-to-treat and as-treated intervention groups (Table 1). There were also no significant baseline differences between the subjects in the intervention group that visited the information portal (as-treated intervention group) and those who did not (Supplement 3).

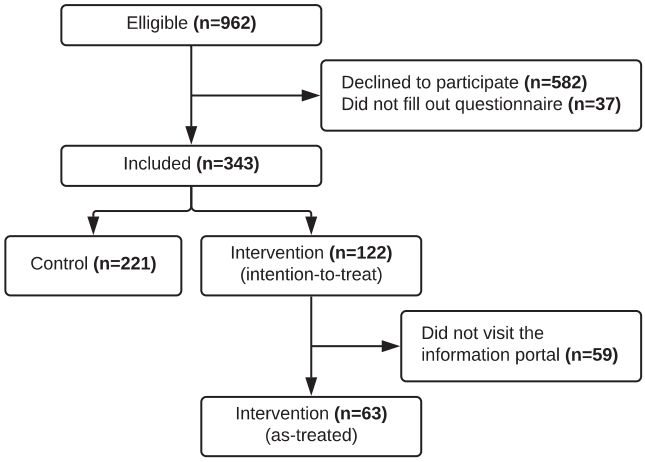

Figure 2. Flow diagram of inclusion.

Disease-specific knowledge

Disease-specific knowledge among the control and intervention groups are presented in Figure 3. All subjects answered at least 2 of the 7 disease-specific knowledge questions correctly. In the intention-to-treat analysis, there was no significant difference in disease-specific knowledge between the control and intervention groups (p=0.891). When only considering the 63 subjects that actually visited the information portal as the intervention group (as-treated analysis), disease-specific knowledge was significantly better in these subjects than in control subjects (p=0.041).

There were significant interactions between the intervention (intention-to-treat) and diagnosis (the positive effect of the intervention on disease-specific knowledge was greater in pulmonary valve disease/tetralogy of Fallot compared with aortic valve disease, p=0.009) and age group (greater positive effect among parents of pediatric patients compared with adult patients, p=0.009), but not with educational level (p=0.655), sex (p=0.189) or center (p=0.472).

Table 1. Baseline characteristics of the included subjects.

	Control	Intervention		p-value	
		Intention-to-treat	As-treated	Intention-to-treat	As-treated
	n=221	n=122	n=63		
Age group				0.395	0.984
Children	48.9% (108)	43.4% (53)	46% (29)		
Adults	51.1% (113)	56.6% (69)	54% (34)		
Male sex*	35.7% (79)	40.2% (49)	31.7% (20)	0.603	0.481
Diagnosis				0.873	0.438
PV disease	67% (148)	65.6% (80)	73% (46)		
ToF	46.2% (102)	38.5% (47)	47.6% (30)		
AV disease	29.9% (66)	32% (39)	25.4% (16)		
PV+AV disease	3.2% (7)	2.5% (3)	1.6% (1)		
Educational level*				0.153	0.613
Elementary	0.5% (1)	1.7% (2)	0% (0)		
Lower vocational	3.7% (8)	7.7% (9)	4.8% (3)		
Lower secondary	3.7% (8)	6% (7)	3.2% (2)		
Intermediate vocational	32% (70)	33.3% (39)	33.9% (21)		
Higher secondary	8.2% (18)	10.3% (12)	6.5% (4)		
Higher vocational	28.8% (63)	28.2% (33)	37.1% (23)		
University	23.3% (51)	12.8% (15)	14.5% (9)		

Data presented as "proportion (count)". *In the case of pediatric patients, sex and educational level relate to the parent that participated in the study. PV=pulmonary valve. ToF=tetralogy of Fallot. AV=aortic valve.

Secondary outcomes

Subjects in the intervention group did not feel more informed than control subjects in neither the intention-to-treat nor the as-treated analyses (Figure 4).

There was no association between how well informed subjects felt and their objective knowledge (β=0.137, p=0.083, adjusted for intervention [as-treated], time and center).

Contradictions in the information received from various sources were experienced by 14% of the control group ("Agree" 9%, "Strongly agree" 5%), which was comparable to the intervention group in both the intention-to-treat (12%; "Agree" 7%, "Strongly agree" 5%; p=0.241) and as-treated (15%; "Agree" 7%, "Strongly agree" 8%; p=0.928) analyses.

Anxiety, depression and preferences for involvement in own care and decision-making were comparable between control and intervention subjects in both the intention-to-treat and as-treated analyses (Table 2).

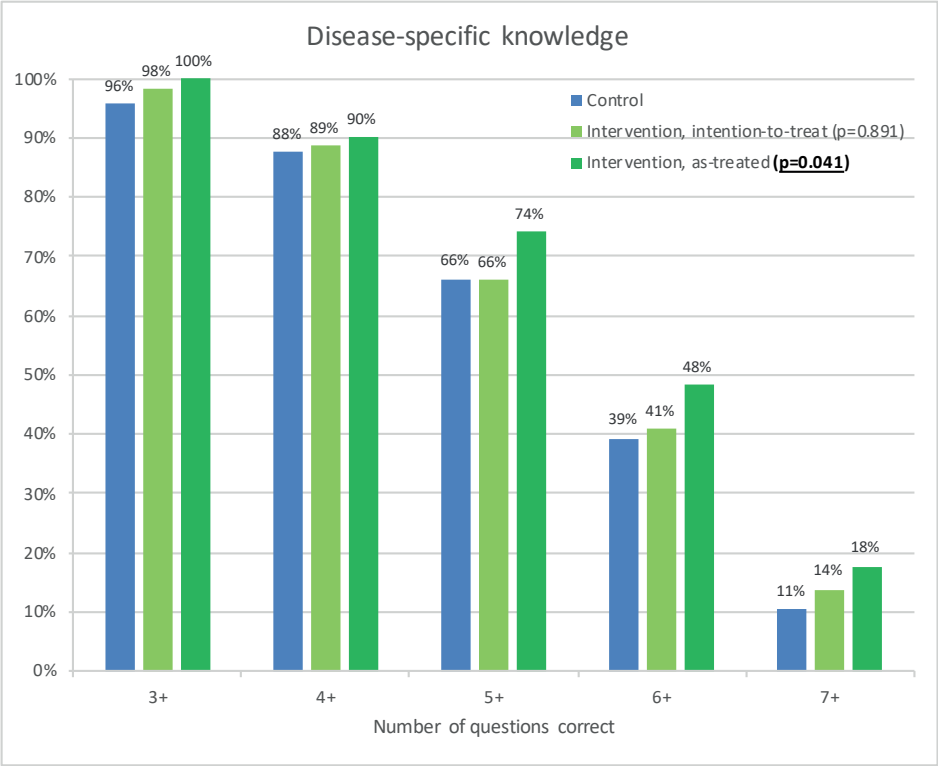

Figure 3. Disease-specific knowledge in the control and intervention groups (according to both the intention-to-treat and as-treated principles). All subjects answered at least 2 of the 7 disease-specific knowledge questions correctly. All significance tests were adjusted for center and time effects using mixed regression models (random effect for center and fixed effect for calendar time).

The total Mental Component Summary score of the SF-36 was also comparable between control and intervention subjects in both the intention-to-treat and as-treated analyses (Table 2). However, in the Mental Health subscale, intervention subjects reported significantly better quality of life than control subjects in the as-treated analysis (p=0.039).

The information portal received high ratings from the 63 subjects that visited it, for both contents (median rating on a 1-10 scale: 8, interquartile range 7-8) and design (median rating on a 1-10 scale: 8, interquartile range 7-8).

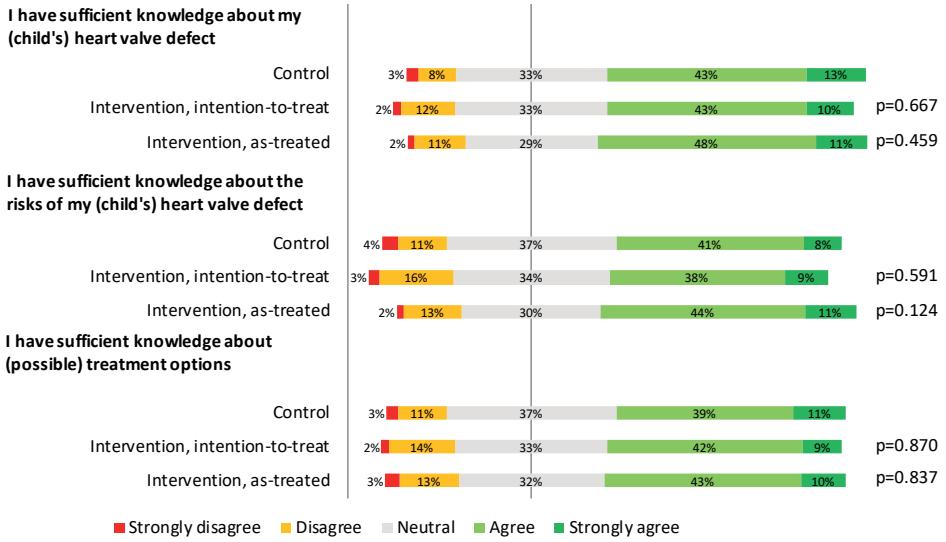

Figure 4. How well informed subjects felt in the control and intervention groups (according to both the intention-to-treat and as-treated principles). The graphs are centered on the response category "Neutral" (vertical grey line in the center of the graph). All significance tests were adjusted for center and time effects using mixed regression models (random effect for center and fixed effect for calendar time).

DISCUSSION

After the introduction of an information portal among patients with congenital aortic or pulmonary valve disease, including tetralogy of Fallot, only half of the participants invited by their cardiologist to visit the information portal actually visited the portal. Among those subjects that actually visited the information portal, disease-specific knowledge and mental health were significantly better at one month after outpatient clinic visit, while baseline characteristics and all other outcomes were comparable to control subjects and to intervention subjects that chose not to visit the portal. These findings demonstrate the potential effectiveness of an online evidence-based patient information portal in improving knowledge in patients with congenital heart disease, but also underline the crucial importance of effective implementation and active use of the portal.

Patients, parents and physicians alike have been previously demonstrated to experience substantial shortcomings in the way that patients and their parents are currently informed and involved.[15,16] Subsequently, patient/parent knowledge is limited, leading to suboptimal patient/parent involvement and substantial decisional conflict and valve-related anxiety.[15,16] In light of these shortcomings, our findings demonstrate the potential effectiveness of an online evidence-based patient information portal in improving

Table 2. Autonomy preference, anxiety and depression, mental quality of life and control preferences.

	Control	Intervention		p-value*	
		Intention-to-treat	As-treated	Intention-to-treat	As-treated
	n=221	n=122	n=63		
API	77.5 ± 8.1	78.0 ± 7.7	78.0 ± 7.9	0.594	0.815
Information seeking	88.7 ± 8.8	89.7 ± 7.7	90.4 ± 7.6	0.850	0.422
Decision-making	62.4 ± 13.7	62.8 ± 14.5	62.0 ± 14.8	0.250	0.970
HADS	7.4 ± 5.8	7.3 ± 5.9	7.65 ± 6.12	0.954	0.561
Anxiety	4.9 ± 3.4	4.6 ± 3.5	5.05 ± 3.97	0.962	0.225
Depression	2.5 ± 2.9	2.6 ± 2.9	2.57 ± 2.59	0.887	0.740
SF-36 MCS	75.5 ± 16.0	75.4 ± 16.9	75.8 ± 15.8	0.346	0.482
Vitality	65.3 ± 18.3	67.2 ± 19.3	67.0 ± 17.6	0.066	0.455
Social functioning	84.4 ± 20.4	83.0 ± 20.3	83.5 ± 18.9	0.663	0.657
Role-emotional	78.5 ± 23.0	76.1 ± 24.1	74.5 ± 24.5	0.953	0.444
Mental health	78.1 ± 16.2	78.9 ± 16.4	80.6 ± 15.4	0.160	**0.039**
CPS (The final treatment decision should be made by:)				0.829	0.738
Physician	0.5% (1)	0.0% (0)	0.0% (0)		
Physician, after considering patient opinion	14.3% (31)	12.2% (14)	14.3% (9)		
Physician and patient together	82.0% (178)	80.9% (93)	79.4% (50)		
Patient, after considering physician opinion	2.8% (6)	5.2% (6)	4.8% (3)		
Patient	0.5% (1)	1.7% (2)	1.6% (1)		

Data presented as "mean ± standard deviation" or "proportion (count)". *All significance tests were adjusted for center and time effects using mixed regression models (random effect for center and fixed effect for calendar time). API=Autonomy Preference Index. HADS=Hospital Anxiety and Depression Scale. SF-36 MCS=Short Form 36 Health Survey, Mental Component Scale, CPS=Control Preferences Scale

patient information, as subjects that used the information portal had significantly improved disease-specific knowledge and mental health.

However, our results also underline the importance of careful and effective implementation of such interventions, as only half of the subjects invited to use the information portal actually did so and an effect could only be demonstrated in those who did. The usage rate of our information portal (52%) is substantially higher than previously reported for patient information and decision support interventions (25-35%).[23] However, it remains suboptimal as it still leaves a large proportion of patients inadequately informed, as evidenced by their limited disease-specific knowledge. It remains unclear why one half of participants in the intervention group chose not to visit the information portal and the other half did, as we did not find any differences between these two groups in baseline characteristics and outcome measures other than knowledge and mental health. The observed lack of an association between how informed patients felt and their objective knowledge level may indicate that many patients may be unaware of

their knowledge deficits and, thus, do not see the need to seek additional information. Interventions aimed at helping such "unconsciously uninformed" patients gain insight into their own knowledge level may allow these patients to more reliably estimate how well informed they are and subsequently motivate them to seek additional information if they are inadequately informed. For instance, a short list of essential knowledge items (i.e. "What you should know about your heart defect") can be provided to patients or patients can be asked to take a short knowledge test before outpatient clinic visit, the results of which can then be reviewed together with their physician. Timing of information provision may be another important factor, as we included participants at all points during clinical follow-up (e.g. at diagnosis, at routine check-up, preoperative, postoperative, etc.). Providing information to patients at the right time when their information need is highest, for instance at diagnosis or surrounding interventions, may improve active use of the portal. Other patient barriers such as limited numeracy, anxiety, cultural factors and language barriers should also be considered in the conception, design and implementation of patient information interventions.[15,16,21,24]

Physician and healthcare system barriers should also be taken into account. A systematic review on the implementation of patient decision support interventions reports lack of physician training, disagreement with the contents of the intervention, physician views on patient involvement and time pressure as important barriers for physicians to motivate active use of the interventions among their patients.[23] We addressed many of these barriers during the introduction of the information portal with our extensive site initiation visits and center-tailored implementation plans, which may explain in part our relatively high usage rate compared with those previously described in the literature. [23] However, implementation may be further improved by more actively involving paramedical staff such as nurse practitioners, integration into the electronic patient record, employing waiting room tools such as computers or tablets and improving ease of use of the portal in the consulting room with the physician.

Furthermore, we found that the information portal was less effective among adult patients than among parents of pediatric patients. Informing, engaging and involving adolescents and young adults with congenital heart disease is a well described challenge in current practice, which often leads to suboptimal knowledge, poor health behavior and substantial loss to follow-up (up to 50% loss to follow-up during the transition from pediatric to adult care).[11,25,26] In this light, our findings may advocate a fundamentally different approach in informing adolescents and young adults. Although the language and contents of our information portal were tailored specifically to the needs of each age group (parents of pediatric patients, teenagers and young adults), the overall design and format of the portal were generally the same.[16] Employing innovative formats such

as video/animation, virtual reality, 3D modelling and serious gaming principles may prove more effective in engaging and informing adolescents and young adults and support successful transition from pediatric to adult care.

With regard to secondary effects of improved patient information and knowledge, in this study we found significantly improved mental health after use of the information portal, however we found no effect on other psychosocial outcomes. Our short follow-up duration (1 month) should be taken into account in the interpretation of these findings, as a longer follow-up or a longer exposure to the intervention may be required for a measurable effect on psychosocial outcomes to manifest. In prior studies, better informed and more activated patients have been found to be associated with improved quality of life, treatment adherence, health behavior and clinical outcome, but also with more efficient healthcare utilization and lower healthcare costs.[3,4,5,6,7,8,9,10,11,12,13,14,21,27] However, the relationship between improved patient knowledge of disease and anxiety remains unclear. Improving knowledge may not necessarily reduce anxiety, because while patients may find reassurance in knowing more about their condition, it may also give them more to worry about. Furthermore, besides the effect of improved knowledge, the sole availability of reliable information that patients trust, the format and design of the information and framing may each also have a direct effect on anxiety. This complex relationship is evidenced by inconsistent findings in prior studies regarding the effect of information portals and decision aids on anxiety.[21,28,29] Further investigation may provide insight into how we may best inform patients/parents to improve their knowledge and simultaneously reduce anxiety. Lastly, how improved patient information and knowledge relates to patient activation, involvement and concordance of treatment decisions with patient values remains to be elucidated.

Limitations

Although substantially higher than previously reported for comparable interventions, the limited usage rate of our information portal may have affected outcome and led to a limited sample size of our as-treated analyses. This study represents Dutch clinical practice and possible international differences in medical practice, culture and language should be taken into consideration. Results may differ for disease states other than aortic and pulmonary valve disease, which should be taken into account when interpreting our results. Although we found no center effect, the possible influence of any unobserved inter-provider differences in patient information should be taken into consideration. As this was a stepped-wedge cluster randomized study the inherent limitations of this study design, such as possible intracluster correlation, should be taken into account.[20]

CONCLUSIONS

After the introduction of an information portal among patients with congenital aortic or pulmonary valve disease, including tetralogy of Fallot, only half of the participants invited by their cardiologist to visit the information portal actually visited the portal. Among those subjects that actually visited the information portal, disease-specific knowledge and mental health were significantly better at one month after outpatient clinic visit, while baseline characteristics and all other outcomes were comparable. Thus, an online evidence-based patient information portal is potentially effective in improving knowledge in patients with congenital heart disease, although active use of the portal is crucial. There is an urgent need for efforts aimed at supporting effective implementation and use of information portals.

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SUPPLEMENTAL MATERIAL

Supplement 1. Secondary outcomes

Feeling informed

How well informed the subject felt about their (child's) heart defect (1 question), the risks thereof (1 question) and treatment options (1 question) was assessed using 5-point Likert scales (Supplement 2).

Experiences with patient information

Subjects were asked to indicate whether they had experienced contradictions in the information they received from various sources using a 5-point Likert scale (Supplement 2).

Preference for involvement

Preferences for involvement in own care and decision-making were assessed using the Autonomy Preference Index[30] and the Control Preferences Scale.[31,32] A higher score on the Autonomy Preference Index indicates a stronger preference for more involvement/ autonomy.

Anxiety and depression

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS).[31,32]

Health-related mental quality of life

Health-related mental quality of life was assessed using the Mental Component of the Dutch version of the Short Form 36 Health Survey (SF-36).[33,34] Total Mental Component raw scores as well as raw scores for each of its subscales were summed and transformed to a 0-100 scale.

Satisfaction with the information portal (only intervention group)

Subjects were asked to rate the contents (1 question) and design (1 question) of the information portal on a 1-10 scale (Supplement 2).

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Supplement 2. Questionnaires used in this study that have not been previously published (translated to English)

Disease-specific knowledge (primary outcome)

1 The heart has two outflow valves, the aortic valve and the pulmonary valve. Which valve is affected in your case?

☐ The aortic valve	(correct answer depends on the patients personal condition, as recorded by the (pediatric) cardiologist)
☐ The pulmonary valve	
☐ Both	
☐ I don't know	

2 My heart valve defect concerns a:

☐ Narrowing (stenosis)	(correct answer depends on the patients personal condition, as recorded by the (pediatric) cardiologist)
☐ Leakage (regurgitation)	
☐ Both	
☐ I don't know	

3 People who have been diagnosed with a heart valve defect: (only one answer possible)

☐ Usually do not need to undergo surgery.	(incorrect)
☐ Usually need to undergo 1 or multiple surgeries during their lifetime	(correct)

4 People with a heart valve defect usually do well in <u>daily functioning.</u>

☐ True	(correct)
☐ False	(incorrect)
☐ I don't know	(incorrect)

5 People with a heart valve defect <u>never</u> need to take this into account when considering <u>work/carreer</u>.

☐ True	(incorrect)
☐ False	(correct)
☐ I don't know	(incorrect)

6 What is the <u>most important</u> purpose of your check-ups?

- ☐ A routine check-up, without a specific purpose. (incorrect)
- ☐ Personal reassurance. (incorrect)
- ☐ To detect a deterioration in your condition. (correct)
- ☐ To continue treatment with the latest techniques. (incorrect)

7 Which of the following symptoms may indicate deterioration of your condition, in which case you should contact the cardiologist?

1. Shortness of breath
2. Getting exhausted sooner upon exertion
3. Fainting

- ☐ 1 and 2 (incorrect)
- ☐ 2 and 3 (incorrect)
- ☐ 1 and 3 (incorrect)
- ☐ All (1, 2 and 3) (correct)
- ☐ I don't know (incorrect)

Feeling informed (secondary outcome)

1. Do you feel like you have sufficient knowledge about your heart valve defect?

Strongly disagree 1 2 3 4 5 Strongly agree

2. Do you feel like you have sufficient knowledge about the risks of your heart valve defect?

Strongly disagree 1 2 3 4 5 Strongly agree

3. Do you feel like you have sufficient knowledge about the (possible) treatment options for your heart valve defect?

Strongly disagree 1 2 3 4 5 Strongly agree

Experiences with patient information (secondary outcome)

1. The information about my condition and the treatment options that I obtained from different care providers and/or other sources of information did not always correspond.

Strongly disagree 1 2 3 4 5 Strongly agree

Satisfaction with the information portal (secondary outcome, only intervention group)

1. How would you rate the website on a scale from 1 to 10 with regard to:

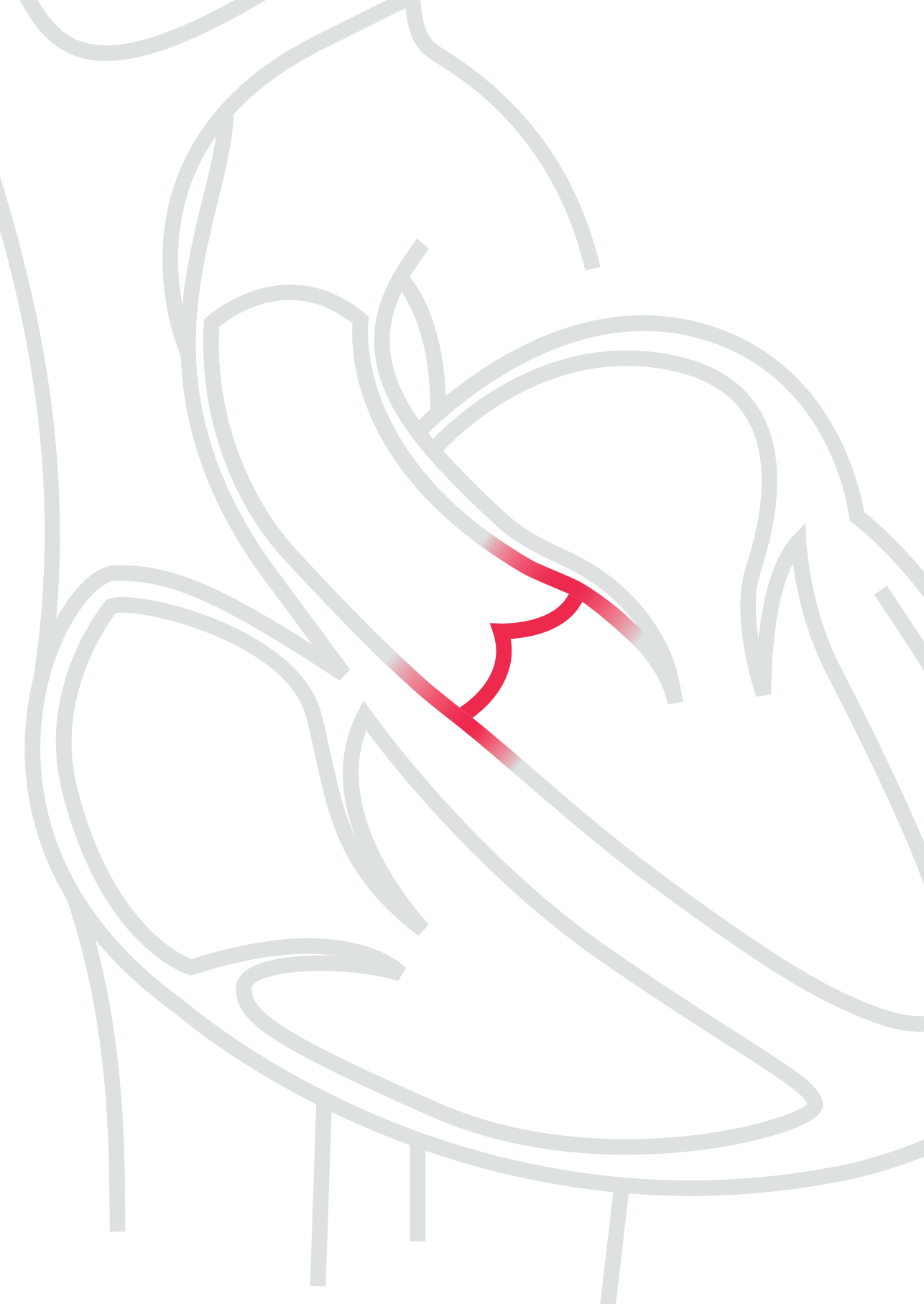
Contents: 1 2 3 4 5 6 7 8 9 10

Design: 1 2 3 4 5 6 7 8 9 10

Supplement 3. Baseline characteristics of the subjects in the intervention group who visited the information portal and those who did not.

	Intervention group:		p-value
	Did not visit portal	Visited portal	
	n=59	n=63	
Age group			0.679
Children	40.7% (24)	46% (29)	
Adults	59.3% (35)	54% (34)	
Male sex	49.2% (29)	31.7% (20)	0.146
Diagnosis			0.196
PV disease	57.6% (34)	73% (46)	
ToF	28.8% (17)	47.6% (30)	
AV disease	39% (23)	25.4% (16)	
PV+AV disease	3.4% (2)	1.6% (1)	
Educational level			0.083
Elementary	3.6% (2)	0% (0)	
Lower vocational	10.9% (6)	4.8% (3)	
Lower secondary	9.1% (5)	3.2% (2)	
Intermediate vocational	32.7% (18)	33.9% (21)	
Higher secondary	14.5% (8)	6.5% (4)	
Higher vocational	18.2% (10)	37.1% (23)	
University	10.9% (6)	14.5% (9)	

PV=pulmonary valve. ToF=tetralogy of Fallot. AV=aortic valve.



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GENERAL DISCUSSION

The aim of this thesis was to make sense of outcome after congenital left ventricular outflow tract surgery and improve evidence-based decision-making, patient information and patient involvement. In this chapter the results will be discussed in a broader perspective and implications for clinical practice and further research will be addressed. First, the results with regard to clinical outcome after surgery will be discussed, as well as the implications for decision-making. In light of clinical outcome, this chapter will then discuss methodology for accurate (patient-tailored) outcome modeling for meaningful and effective application in clinical practice, as well as methodology for reliable evaluation of the effect of clinical developments and innovations on outcome. Lastly, the conveyance of evidence on outcome to patients will be discussed in the context of patient information, patient involvement and informed shared decision-making.

CLINICAL OUTCOME

Subvalvular aortic stenosis

Thus far, outcome in patients with subvalvular aortic stenosis was not completely clear, due in part to the fact that data on outcome in these patients is scattered across an exceedingly large number of publications.[1-24] Furthermore, there is a large variation in outcome between individual patients, and there is little consensus which patient- and procedure-related factors play a role in this variation and how these factors may inform decision-making, as is also the case in many other disease states.

Chapter 2 was the first study to date aimed at aggregating all published evidence on clinical outcome in subvalvular aortic stenosis across numerous international patient series, and to investigate determinants of outcome in this setting.

Our results show that, although mortality rates are low after surgery for subvalvular aortic stenosis, there remains a substantial rate of reintervention. In light of the large variation in outcome between individual patients, we also succeeded in providing novel insights into the determinants of outcome. We identified that, among other factors, higher left ventricular outflow tract (LVOT) gradient (both pre- and postoperatively) and the presence of aortic regurgitation (either pre- or postoperatively) are associated with poorer postoperative hemodynamic results and a higher rate of reintervention. The distance between the subvalvular obstruction and the base of the aortic valve was also associated with outcome, however results were inconsistent across the included studies, which warrants further investigation of the prognostic value of this parameter. Unfortunately, it was not possible to quantify the associations between the aforementioned

prognostic factors and outcome in our study, due to methodological heterogeneity between the included studies.

Although there remains little consensus on the optimal timing of surgery in these patients**,** our findings may support decision-making and timing of intervention, as they may suggest that earlier intervention before the LVOT gradient progresses excessively and before aortic regurgitation develops may improve outcome after surgery, although this remains to be investigated in more detail.

In patients with discrete subvalvular aortic stenosis, more aggressive resection in the form of myectomy in addition to enucleation of the fibromuscular ridge has also been proposed to potentially reduce the recurrence rate and subsequently reoperations.[25,26] However, evidence on the benefit of routine myectomy in these patients is inconsistent.[27,28] Myectomy also increases the risk of complete atrioventricular block and its influence on aortic valve function remains unclear. Further investigation of the value of myectomy in reducing recurrence and subsequent reoperation is therefore warranted.

Thus, there are many patient- and procedure-related factors that influence outcome in these patients, as is also the case in most other cardiovascular diseases. Studies aimed at reliably quantifying the many associations between patient- and procedure-related factors and outcome in cardiovascular disease are therefore urgently needed to inform patient-tailored decision-making. In disease states with a relatively low incidence and with a relatively low occurrence rate of adverse outcome events, such as congenital left ventricular outflow tract disease, large multicenter registries may play an important role in these studies by providing the adequate sample size and methodological homogeneity necessary for such analyses, which is difficult to achieve in single-center studies. Although such registries are unfortunately not yet available for subvalvular aortic stenosis, for aortic valve disease the AVIATOR registry and the currently under development LEOPARD registry are promising initiatives in this light.[29,30]

Aortic valve disease

In aortic valve disease, when the valve requires replacement, all available aortic valve substitutes have their inherent drawbacks. Thus far, evidence on outcome after valve replacement has been fragmented across an exceedingly large number of publications on single-center series with varying results, and the data therein is often analyzed and presented in a manner that cannot be readily implemented in daily clinical practice, patient information and (shared) decision-making. In this light, Chapters 3-7 provide a unique insight into long-term outcome after aortic valve surgery. Our robust methods of systematic review and meta-analysis allow for effective amalgamation of all published

data on the subject, providing an exceptionally large sample size to draw inferences from and accounting for the heterogeneity encountered between individual publications. Moreover, as conventional methods for meta-analysis of long-term outcome provide results that may not be readily interpretable by clinicians and patients to an individual patient level (e.g. linearized occurrence rates), our application of novel methods of time-to-event meta-analysis and microsimulation provide an unprecedented insight into long-term outcome by providing results in a format that are more patient specific and readily interpretable by clinicians and patients alike (e.g. Kaplan-Meier estimates, lifetime risks of outcome events, life expectancy). This allows for more meaningful and direct implementation of this data into daily clinical practice, decision-making and patient information.

Outcome after aortic valve replacement

After mechanical aortic valve replacement in non-elderly adults (Chapter 4), there is a substantial lifetime risk of thromboembolism and of bleeding ranging from a combined risk of 53% for patients aged 20-30 years at surgery to 30% for patients aged 50-60 years. Also, although we found the long-term durability of mechanical prostheses to be excellent, as evidenced by not a single case of structural valve deterioration of modern bileaflet prostheses being reported in the reviewed literature, endocarditis and non-structural dysfunction still give rise to a risk of reintervention that is not to be neglected, ranging from a lifetime risk of 15% for patients aged 20-30 years at surgery to 8% for patients aged 50-60 years. Lastly, survival after mechanical aortic valve replacement is substantially impaired, particularly in younger patients, and little over 50% of the life expectancy of the age- and gender-matched general population. In children (Chapter 3), although lifetime estimates were not available, the linearized occurrence rate of reintervention was double the rate in adults (due in part to the additional risk of increasing patient-prosthesis mismatch over time in growing children), thromboembolism and bleeding rates were slightly lower and the endocarditis rate was comparable.

After bioprosthetic aortic valve replacement in non-elderly adults (Chapter 6), there is an exceptionally high rate of reintervention, with almost all patients aged 20-40 years at surgery expected to undergo one or more reinterventions during their lifetime and approximately 60-75% of patients aged 40-60 years at surgery. The overall reintervention rate is higher than after the Ross procedure (Chapter 5), even after taking the additional right ventricular outflow tract reinterventions associated with the Ross procedure into account, and also higher than after mechanical aortic valve replacement (Chapter 4). Rates of thromboembolism and/or bleeding are lower than after mechanical aortic valve replacement, with a combined lifetime risk of approximately 15-30% depending on age at surgery. However, this risk of thromboembolism and/or bleeding is certainly not zero

and higher than in the general population.[31] This risk is also higher than observed after the Ross procedure and aortic valve repair[32,33], even though bioprosthetic valve replacement, the Ross procedure and valve repair similarly aim to avoid the need for lifelong anticoagulation. This may be due in part to other indications for anticoagulation arising during follow-up after bioprosthetic aortic valve replacement, as two prior studies have reported that at approximately 10 years after bioprosthetic aortic valve replacement, 25% to 30% of patients require oral anticoagulation therapy, mostly due to atrial fibrillation.[34,35] Life expectancy is also impaired in these patients at approximately 60-75% of the life expectancy of the age- and gender-matched general population. In children, the use of bioprostheses is exceedingly rare, as there are no series encompassing more than 20 patients described in contemporary published literature.

Outcome after the Ross procedure (Chapter 5) in both children and non-elderly adults is characterized by a substantial reintervention rate, due in part to the additional risk of reintervention on the prosthesis in the right ventricular outflow tract when compared with other aortic valve substitutes. Consequently, almost all children and adults aged <40 years at surgery are expected to require reintervention during their lifetime and approximately 45-70% of patients aged 40-60 years at surgery. Nevertheless, the overall reintervention rate still appears to be lower than after bioprosthetic aortic valve replacement. Furthermore, lifetime risks of thromboembolism and bleeding are exceedingly low in both children and non-elderly adults, ranging from 5-7% depending on age at surgery, comparable to the risk in the age- and gender-matched general population.[31] In contrast to the outcome observed after mechanical and bioprosthetic aortic valve replacement, survival after the Ross procedure is excellent in both children and non-elderly adults despite the high reintervention rate, with a life expectancy of 90-95% of the life expectancy of the age- and gender-matched general population. Besides the lower rates of thromboembolism and bleeding, the favorable hemodynamics of the autograft in comparison with mechanical prostheses and bioprostheses may play a role in this observed survival difference, as suboptimal hemodynamics (i.e. patient-prosthesis mismatch) have been found to lead to significant excess mortality after both mechanical and bioprosthetic aortic valve replacement, particularly in younger patients.[36,37] However, the possible influence of patient selection and possible differences in patient characteristics and concomitant procedures performed at the time of surgery should also be taken into account in such comparisons.

Clinical prospects

From a clinical perspective, there are many developments within the field that may improve outcome in young adult patients requiring aortic valve replacement.

In patients undergoing mechanical aortic valve replacement, optimization of anticoagulation management may reduce complication rates. Studies have shown that, in patients treated with currently available anticoagulants, 25% of periodically measured International Normalized Ratio (INR) values lie outside of the target range.[38] More stable anticoagulation management through, for instance, pharmacological advances and self-management, may therefore reduce the rate of thromboembolic and bleeding complications. This may also translate to an improvement in survival in these patients, as there is evidence that, with optimal self-management anticoagulation, mechanical aortic valve replacement offers excellent late survival comparable to the general age-matched population and also comparable to patients undergoing the Ross procedure.[39] Lower dosing of anticoagulation may also prove promising in improving outcome. 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.[38,40,41] Additionally, advances in the design of mechanical valves may lead to reduced thrombogenicity and mechanical valves specifically designed with this in mind have emerged. One such novel mechanical valve prosthesis has received FDA-approval for anticoagulation management at a lower INR than recommended by the guidelines.[41] However, evidence on the effect thereof on clinical outcome remains to be awaited. Design improvements of novel mechanical prostheses should also focus on improving their hemodynamics, as patient-prosthesis mismatch currently remains a major problem that leads to significant excess mortality after both mechanical and bioprosthetic aortic valve replacement, particularly in younger patients.[36,37]

Lastly, besides clinical outcome, psychosocial outcome in patients with mechanical aortic valve prostheses remains suboptimal. After mechanical aortic valve replacement, non-elderly adult patients have been found to experience substantial valve-related impairments in quality of life due mostly to the valve sound, anticoagulation/INR management and fear of a reoperation (despite the excellent durability of mechanical prostheses).[42] These impairments in quality of life were more severe after mechanical aortic valve replacement than after the Ross procedure or aortic valve repair.[42] Non-elderly adult patients after mechanical aortic valve replacement also more frequently report that their valve prosthesis significantly affects their work, career and income, more frequently experience employment disability, and are overall less satisfied with their valve prosthesis when compared with patients with bioprostheses, pulmonary autografts or allografts.[43] Therefore, there is an urgent need for efforts aimed at improving psychosocial outcome in these patients, for instance through improvements in the design of mechanical protheses, postoperative clinical management, patient education and counseling, and shared decision-making.

With regard to bioprostheses further efforts aimed at reducing the exceedingly high rates of structural valve deterioration and subsequent reoperation in young adult patients are needed. There is still little evidence on the mechanism of increased structural valve deterioration in younger patients, although increased immune responsiveness, more active calcium metabolism and increased hemodynamic load have all been proposed to play a role[44-46], which warrants further investigation. Also, structural deterioration of aortic valve bioprostheses usually slowly develops and progresses over the course of several years, and thus the left ventricle is subjected to slowly deteriorating aortic valve function for an extended period of time. It currently remains unclear how this affects long-term cardiac function and survival.

In response, improvements in the design of modern bioprostheses have been proposed to improve durability, however clinical evidence of the hypothesized benefits provided by these modifications is inconclusive.[47-49] Lastly, similar to mechanical prostheses as discussed above, design improvements may also lead to improved hemodynamics, which may reduce patient-prosthesis mismatch and subsequently improve long-term survival.[36,37]

With regard to the Ross procedure there is increasing evidence that there are many factors that are associated with the large variation in reported clinical outcome.

Patient-related factors such as age, preoperative aortic regurgitation, preoperative aortic annulus dilatation, and underlying cause of disease have all been shown to be associated with the long-term durability of the procedure[50-53], which underlines the crucial importance of careful patient selection and patient-tailored decision-making in achieving optimal outcome after the Ross procedure. Further development of methods that allow for more accurate patient-tailored outcome modeling, for instance based on the methodology employed in this thesis, may prove valuable in this light (which will be further discussed later in this chapter).

Given the technical complexity of the procedure, variation in surgical technique and surgeon and center volume may also play a role in long-term autograft function. Further evaluation of modifications to surgical technique (such as subcoronary implantation, the inclusion technique, external prosthetic or pericardial support and annuloplasty) and perioperative management (such as strict early postoperative systemic blood pressure control) that are proposed to improve autograft durability may lead to the development of a more standardized and reproducible technique that provides a more durable result.

With regard to allograft deterioration, decellularization techniques are under ongoing development aiming to improve long-term durability by reducing the immune response that is thought to play a role in allograft deterioration (Chapter 8). However, accrual of larger patient series and longer follow-up are required to shed light on the proposed clinical benefit of decellularization.

There is growing interest in transcatheter aortic valve implantation (TAVI) as a primary intervention in increasingly younger and lower risk patients. However, to date, they have only been studied in elderly patients (even in the low-risk patient trials the mean age is >70 years)[54,55] and long term follow-up, which is of particular importance in younger patients, has yet to be accrued. In addition, its role as a prospective option for reintervention of failing surgical bioprostheses has also come into focus, however the effectiveness of valve-in-valve TAVI in younger patients, the feasibility of multiple sequential valve-in-valve TAVIs, and medium-to-long-term outcome after valve-in-valve TAVI remain to be investigated. Therefore, the future potential of TAVI in non-elderly patients remains uncertain. If TAVI proves valuable in this patient population, either as a primary intervention or in the setting of valve-in-valve TAVI after prior bioprosthetic aortic valve replacement or prior TAVI, the complexity of decision-making in these patients will increase considerably. Extensive decision analyses and decision models will then be required to shed light on the optimal (sequence of) procedure(s) for each individual patient, also taking patient values and preferences into account.

Considering the limitations of all currently available heart valve prostheses as discussed above, tissue engineering of heart valves is a promising development with the aim of providing a living autologous heart valve substitute that would ideally last a lifetime and reduce or even eliminate the long-term adverse outcomes of current prostheses. Although there is ever-growing interest in the development of such valves and much progress has been made in research in this field, it is still very experimental in nature, there are still many challenges to overcome and a clinically viable product has yet to be realized. Further, if and when a clinically viable tissue engineered valve is realized, it will also need to prove superior to currently available valve substitutes in the long-term with regard to both clinical outcome and cost-effectiveness. Thus, although ongoing developments are promising, the concept of "one valve for life" is not yet within reach.[56,57]

Lastly, continuous improvements in aortic valve repair techniques may increasingly provide options for native valve preservation in young adult patients, avoiding or postponing the need for valve replacement.[58] However, comparison of our findings with current literature on outcome after aortic valve repair is difficult, due to a sparsity of available outcome data, disparity in indications and a lack of standardization in data reporting.[32]

Collaborative initiatives, such as the AVIATOR international multicenter registry, may shed more light on whether the potential benefits of native valve-preservation translate to improved outcomes.[29,30,32]

Optimization of decision-making

With regard to decision-making, direct comparison of the various available valve prostheses in children and young adults is hampered by differences in patient characteristics and a lack of randomized, matched or adequately adjusted data. However, it is clear that each valve substitute provides vastly differing outcome profiles and that no valve substitute is consistently superior in all outcome measures.

Therefore, patients and physicians often face a difficult choice when aortic valve replacement is indicated. The difficulty of this decision has been demonstrated in a prior study among physicians, in which cardiologists and cardiac surgeons were asked to indicate their preference for a mechanical prosthesis or bioprosthesis for a number of patient profiles. There was an exceedingly wide variation in preferences between individual physicians: for a given patient with a specific patient profile, some physicians indicated that they would *always* choose a mechanical prosthesis while other physicians would *always* choose a bioprosthesis in the very same patient. This large individual variability in preferences has also been demonstrated among patients undergoing aortic valve surgery in trade-offs between quality of life and quantity of life.[59,60] This illustrates the complexity and value-sensitivity of decision-making in aortic valve disease.[61]

Clinical practice guidelines provide some guidance in the selection of a valve substitute, based largely on patient age. The 2017 United States and European guidelines for the management of valvular heart disease both recommend mechanical prostheses over biological alternatives for aortic valve replacement in adults younger than 50 to 60 years old. If anticoagulation is contraindicated or if the patient prefers a biological alternative, both guidelines recommend bioprostheses, and only the United States guidelines indicate that the Ross procedure may be considered.[62,63]

However, what underlies these recommendations is the interpretation of evidence according to the collective "outcome hierarchy" (i.e. the relative valuation of each possible outcome) of clinicians, investigators and policy makers. It is important to consider that individual patients' outcome hierarchies may differ strongly from those of clinicians, investigators and policy makers, and also with an exceedingly wide variation among individual patients, driven by personal values and life goals. Therefore, the choice for a certain treatment should be driven by individual patient values and preferences, besides

clinical and technical considerations. The guidelines therefore also highly recommend a shared decision-making process in prosthetic valve selection.[62,63]

In this light, development and clinical implementation of disease-specific value clarification methods that aid both patients and physicians in elucidating individual patient values may prove promising in promoting individualized value-based decision-making.[64] In a research setting, value clarification studies in this patient population may also provide much needed insight into what is really important to patients and thereby aid in shifting the focus of future research from investigator-motivated outcomes to more patient-centered outcomes.

OUTCOME MODELS FOR CLINICAL PRACTICE AND PATIENT-TAILORING

There is an ever-growing body of literature on patients with congenital left ventricular outflow tract disease. Nevertheless, in current daily clinical practice it often remains unclear to both physicians and (parents of) patients what the expected short- and long-term outcome is after surgical treatment. This is due in part to the fact that current evidence is fragmented across an exceedingly large number of publications and that the data therein is often analyzed and presented in a manner that cannot be readily implemented in daily clinical practice, patient information and shared decision-making. As a result, currently available evidence remains underutilized in practice.

The advanced meta-analysis and microsimulation methodology employed in Chapters 4-6 present a means for effective amalgamation of the ever-growing body of evidence and for reliable translation thereof to freedom-from-event estimates, lifetime estimates of event occurrence and life expectancy, outcome formats that are more readily interpretable and more meaningful to physicians and patients alike than traditional meta-analytic outcome formats such as linearized occurrence rates.

The microsimulation methodology employed in these studies, also provides an opportunity for individual patient-tailored outcome modeling, which would be a further development of the outcome models presented in Chapters 4-6. It is well known that outcome after cardiac surgery varies considerably among individual patients, dependent in part on patient- and procedure-related factors. For instance, in Chapter 2 we succeeded in identifying numerous patient characteristics associated with differences in clinical outcome in patients with subvalvular aortic stenosis, however quantitative analysis was not possible due to methodological heterogeneity between studies. Future

studies aimed at reliably and accurately quantifying such associations (also in valvular aortic disease and cardiovascular disease in general), in which large multicenter registries may play an important role, could provide the data necessary for incorporation of these associations into the existing microsimulation model. The microsimulation-based outcome estimates as presented in Chapters 4-6 could then be further tailored to patient-specific factors (such as underlying cause of disease, hemodynamics, symptoms, medical history, concomitant diseases, etc.) to more accurately represent what an individual patient can be expected to face after surgery.

Ideally, such patient-tailored outcome models could be incorporated into an open-access interactive online tool for clinicians, in which users can input patient characteristics and obtain patient-tailored outcome estimates in a clinically meaningful format. For patients, the modelled outcomes can be incorporated into online patient information portals such the one we developed and validated as described in Chapters 11 and 12. This may aid clinicians and patients in selecting the optimal treatment for each individual patient. This methodology may also provide similar opportunities in other areas of cardiovascular medicine in which long-term outcome modeling and subsequent evidence-based and value-sensitive decision-making remain a challenge.

Although microsimulation provides promising opportunities for long-term outcome modeling, it is limited by its dependence on a large quantity of high-quality comprehensive data as an input for parameterization of the model, with an increasing level of detail required as an increasing number of patient- and/or procedure-related factors are incorporated for patient-tailoring. The availability of such data with sufficient sample size is often limited in the setting of cardiac surgery, although large multicenter registries may prove valuable in this light as previously discussed. Additionally, due to the rapid developments in cardiac surgery over the past decades and the relatively favorable survival, the observed follow-up period in contemporary input data is often shorter than the modeled time-horizon, which requires assumptions to be made about evolution of event occurrence beyond the observed follow-up period. These factors all give rise to second-order uncertainty in the microsimulation model (i.e. uncertainty in the input parameters). Although such potential inaccuracies can only be effectively remedied through accrual of larger sample sizes, longer follow-up and more detailed data, they can be incorporated into the modeled outcome estimates through the use of probabilistic sensitivity analysis so that these potential inaccuracies in the input data are reflected in all generated outcome estimates, as was done in Chapters 5 and 6.

EVALUATION OF CLINICAL DEVELOPMENTS AND INNOVATIONS

Randomized controlled trials are often considered the gold standard for the evaluation of the efficacy of novel therapies in comparison with standard of care.[65]

However, randomized controlled trials are not always feasible due to clinical, ethical, logistic or financial reasons. Moreover, depending on trial design, the generalizability of results to the target population in large is often limited in comparison to other study designs, which may hamper inferences on effectiveness (i.e. performance under 'real-world' circumstances) rather than efficacy.

Unfortunately, in the absence of randomized controlled trials, observational studies by design introduce bias in comparisons between treatment groups, as a result of confounding due to an inherent imbalance of covariates between groups.[66]

Considering the limitations of all currently available surgical options and the subsequent need for innovation, there is an urgent need for methodology that allows for reliable evaluation of the effectiveness of these innovations in improving on the current standard of care when randomized controlled trials are not feasible.

In this light, Chapter 8 succeeds in reliably evaluating an innovation in the Ross procedure, namely decellularization of the pulmonary allograft, in comparison with standard pulmonary allografts in an observational study. This was done employing propensity score analysis as conceptualized by Rosenbaum and Rubin, which offers the possibility for correction for the imbalance in measured covariates between treatment groups in an observational study.[67] This provided us the unique opportunity for a direct comparison between the novel decellularized allografts and standard cryopreserved allografts in a large observational cohort of patients undergoing the Ross procedure.

Our comparison shows that decellularized and standard cryopreserved pulmonary allografts, when used for right ventricular outflow tract reconstruction in the Ross procedure, both provide comparably excellent clinical and hemodynamic outcome up to 5 years postoperatively. Longer follow-up is necessary to shed light on the proposed benefits of allograft decellularization.

In the absence of the results of a randomized controlled trial, this propensity score analysis represents the most reliable evidence on the effectiveness of this novel therapy to date. In other clinical settings in which randomized controlled trials may be ethically or practically unfeasible, this methodology provides a unique opportunity to draw in-

ferences that would otherwise not be possible in observational studies. However, the limitations of propensity score analyses should always be carefully considered. Most importantly, contrary to randomization, propensity score analyses can only balance groups based on observed covariates, while unobserved or unknown covariates (some of which may be prognostically important) will remain unbalanced between groups, which may introduce bias.[68] Also, propensity score matching may reduce generalizability of the results of analyses, by producing matched subpopulations that may not be representative for the entire unmatched "real-world" target population of interest. This is particularly the case if the matched subpopulation is only a small proportion of the unmatched patient population.[69]

Our robust methods of longitudinal data analysis allowed us to accurately analyze echocardiographic hemodynamic allograft function over time. In contrast to the clinical outcome events that are most frequently analyzed in studies on aortic and pulmonary valve substitutes, hemodynamic allograft function is not discrete, but rather subject to gradual changes over time (longitudinal outcome). As such, there is a wealth of valuable information in serial echocardiographic measurements of hemodynamic allograft function taken at various points in the follow-up of each patient. Methods for longitudinal data analysis, such as the mixed models we used, provide a means to take full advantage of the valuable information that lies in the temporal pattern of longitudinal outcomes within each patient, rather than analyzing these outcomes as a "snapshot" at a specific time in follow-up.[70] Although such methodology is highly complex, it is becoming increasingly available to the broader scientific community in the form of user-friendly statistical software packages.

In the assessment of these novel decellularized pulmonary allografts in the Ross procedure, because the incidence of clinical outcome events is relatively low in this clinical setting and these events tend occur mostly after many years of follow-up rather than early in the follow-up, longitudinal analysis of echocardiographic allograft function may reveal a benefit of the novel therapy long before a detectable clinical benefit manifests. In many other clinical settings, such use of novel methodology for accurate and reliable analysis of precursors to clinical events may also provide similar means for drawing earlier inferences on treatment innovations.

In the broader perspective of published literature, evaluation of surgical innovations over the years often requires the possibility for comparisons between separate study cohorts. Although a certain degree of methodological heterogeneity among individual studies is unavoidable, we must aim to keep methodological heterogeneity to a minimum to increase comparability between reports. Further collaborative implementation of and

wide adherence to methodological and reporting guidelines, such as those reported by Akins and colleagues with regard to studies on cardiac valve interventions in 2008[70], are instrumental in this light. Establishment of large multicenter registries may further aid in improving methodological homogeneity.

It should always be considered that novel treatment options may not provide a "one-size-fits-all" solution that is universally superior for all patients, especially not in the increasingly complex and heterogeneous patient population in the field of cardiac surgery. Careful patient selection and consideration of patient values and preferences are therefore of utmost importance in the evaluation and clinical application of novel therapies as well.

Lastly, with the growing importance of efficiency and sustainability in health care expenditures, the cost-effectiveness of novel therapies should always be considered. Consequently, (early) health technology assessment will play an increasingly important role in how we evaluate ongoing developments in care. The methodology for long-term clinical outcome modeling employed in this thesis, as previously discussed in this chapter, provides unique opportunities in this light by providing the possibility for accurate patient-tailored long-term outcome modeling, which represents the basis for reliable health technology assessment.

PATIENT INFORMATION AND INVOLVEMENT

Considering the important implications of treatment decisions on patients' lives, it is essential to inform patients and their relatives in a complete, objective, and understandable manner.

In various disease states, more informed and activated patients have been previously found to be associated not only with improved quality of life, treatment adherence, health behavior, and clinical outcome but also with more efficient healthcare utilization and lower healthcare costs.[71-83] However, as evidenced by Chapter 9 of this thesis, there are substantial shortcomings in patient information and decision-making in congenital aortic valve surgery, as reported by patients, parents and physicians alike. Patient knowledge is severely limited due to the limited availability, reliability and comprehensibility of patient information. Furthermore, the provided information often does not meet the patients' information needs. When treatment decisions need to be made, patient activation and involvement are suboptimal and there is substantial decisional conflict and valve-related anxiety.

Unfortunately, adequately informing patients is no easy task. For instance, if we are to communicate outcome after surgery in the form of event risk estimates (such as those we estimated in Chapters 3-6) with patients, how well can patients interpret these numerical risks? As found in Chapter 9, the understanding of numerical risks is severely impaired among congenital aortic valve patients and their parents. Only approximately 50% of subjects were found to have an adequate understanding of numerical risks. As this poses a major challenge in risk communication, risk visualizations (such as icon arrays, bar charts and pie charts) have been proposed to improve the understanding of numerical risks. However, their effectiveness had not previously been investigated in the setting of conveyance of the precise magnitude of absolute risks, such as the setting we face in communicating treatment outcome estimates with patients. In Chapter 10 we therefore explored the understanding of the precise magnitude of absolute numerical risks in the broader general population and investigated the effectiveness of risk visualizations in improving this understanding. We found that in the general population, only 60% of subjects have an adequate understanding of the precise magnitude of absolute numerical risks (comparable to 50% in our patient population) and that risk visualizations do not improve this understanding. This study was, to our knowledge, the first to investigate the effectiveness of risk visualizations in supporting the verbatim communication of single absolute risks (as is often necessary in cardiac surgery). Our findings in this setting are in contrast to those of prior studies that focused on the conveyance of gist knowledge (i.e. understanding of the general risk message) and/or comparisons/trade-offs of multiple risks, in which a beneficial effect of risk visualizations was often found.[84,85] Our findings challenge the currently prevailing dogma that risk visualizations are universally beneficial[84,85] and suggest that their effectiveness may rather be dependent on the setting in which they are applied, although our study has yet to be replicated for external validation.

Thus, there are substantial shortcomings in patient information and involvement and important challenges in patient communication.

This underlines the need for innovative solutions, such as the online evidence-based patient information portal we developed (Chapter 11) and validated in a stepped-wedge cluster randomized trial (Chapter 12). In this study, although the information portal was received well by physicians and (parents of) patients alike and received consistently high ratings from users, only half of the participants invited by their cardiologist to visit the information portal actually visited the portal. Among those subjects that actually visited the information portal, disease-specific knowledge and mental health were significantly better at one month after outpatient clinic visit than in control subjects that did not have access to the portal. This demonstrates that an online evidence-based

patient information portal is potentially effective in improving knowledge in patients with congenital heart disease, although active use of the portal is crucial.

The above shows that, although this thesis provides the basis for much needed improvements in patient information, there are still many challenges in adequately informing patients and implementing tools such as the information portal into clinical practice.

For instance, although the usage rate of our information portal (52%) was higher than previously reported for other patient information and decision support interventions (25-35%)[86], it still leaves a large proportion of patients unsatisfactorily informed and it remains unclear why so few patients make use of patient information tools. An interesting finding in our study (Chapter 11) was that there was no association between how informed patients felt subjectively and their objective knowledge level. This may indicate that many patients may be unaware of their knowledge deficits and, therefore, do not see the need to seek additional information. Efforts aimed at helping such "unconsciously uninformed" patients gain insight into their own knowledge level may therefore support more active use of patient information interventions and subsequently improve patient knowledge.

Additionally, identification of the moments at which the information need is greatest among patients may allow for more effective timing of information interventions, which may lead to increased usage and knowledge uptake.

Moreover, employing innovative media formats such as video/animation, virtual reality, 3D modeling and serious gaming principles may prove more effective in engaging and informing patients, particularly adolescents and young adults.

Implementation and effectiveness of patient information interventions may be further improved by deeper integration into the healthcare system by, for instance, more active involvement of paramedical staff such as physician assistants and nurse practitioners, integration into electronic patient record systems, employing waiting room tools such as computers or tablets, etc.

It also remains to be elucidated what the secondary effects of improved knowledge are on patient activation, involvement, concordance of treatment decisions with patient values, long-term quality of life, health behaviors.

Besides their effects on patients, patient information interventions probably also have an effect on physicians and how they communicate with patients by providing a stimu-

lus and support in more actively informing and involving their patients. Thus, part of the potential effectiveness of patient information interventions may lie in these physician effects rather than solely in isolated patient effects. Future studies on physician effects of patient information interventions may therefore be valuable in informing design and implementation considerations in the interest of improving on their role as physician-support tools, thereby potentially increasing the net positive effects on patients.

With the growing importance of efficiency and sustainability in health care expenditures, the effect of patient information interventions on health care systems should also be considered, as more activated patients have been previously found to be associated with significantly lower healthcare costs.[87] By potentially improving patient knowledge and activation, patient information interventions may therefore not only improve patient outcome, but also lead to more efficient healthcare utilization and lower healthcare costs, although this remains to be investigated.

When it comes to risk communication, we have shown that there is a need for support in the verbatim communication of individual absolute risks, as is the case in the communication of estimates of treatment outcome such as those provided by this thesis. Our findings suggest that this need may be unmet by currently widely used forms of risk visualization. As this was the first study to our knowledge to investigate the effectiveness of risk visualizations in the particular setting of verbatim communication of individual absolute risks, replication of our study in different countries and languages is warranted and may provide insights into potential cultural, societal and language-related factors that may be of influence on the effectiveness of these risk visualizations. It should also be investigated whether risk visualizations may be more effective in real-world healthcare settings among actual patients with a vested interest in understanding the risk information as opposed to general population samples presented with a hypothetical scenario. The increasing digitalization of patient information over the years also provides the opportunity for the use of novel digital media formats, for instance (narrated) animations, which may further aid in conveying risks to subjects and prove more effective than classical static two-dimensional risk visualizations. Finally, the effectiveness of risk visualizations in verbal risk communication also remains to be investigated.

CONCLUSIONS AND PROSPECTS

This thesis provides novel insights into long-term outcome after congenital left ventricular outflow tract surgery through the use of innovative methods of advanced meta-analysis, microsimulation, propensity score analyses and longitudinal data analysis. It

also demonstrates that there is an urgent need for improvements in patient information and involvement and provides the basis for interventions and initiatives that have the potential to substantially improve patient knowledge, empowerment, involvement, psychosocial outcome and health behavior. Further developments building upon the work in this thesis, as proposed above, may offer us a means for more patient-tailored outcome modeling, provide a platform for making this information readily available to both clinicians and patients in an understandable and meaningful format, and advance our knowledge and skills on how we can better inform patients and tailor our treatments to the individual patient, taking personal values and preferences into account. It is imperative that we keep trying to make more sense of outcome after surgery to both clinicians and patients in the interest of achieving optimal outcome for each individual patient.

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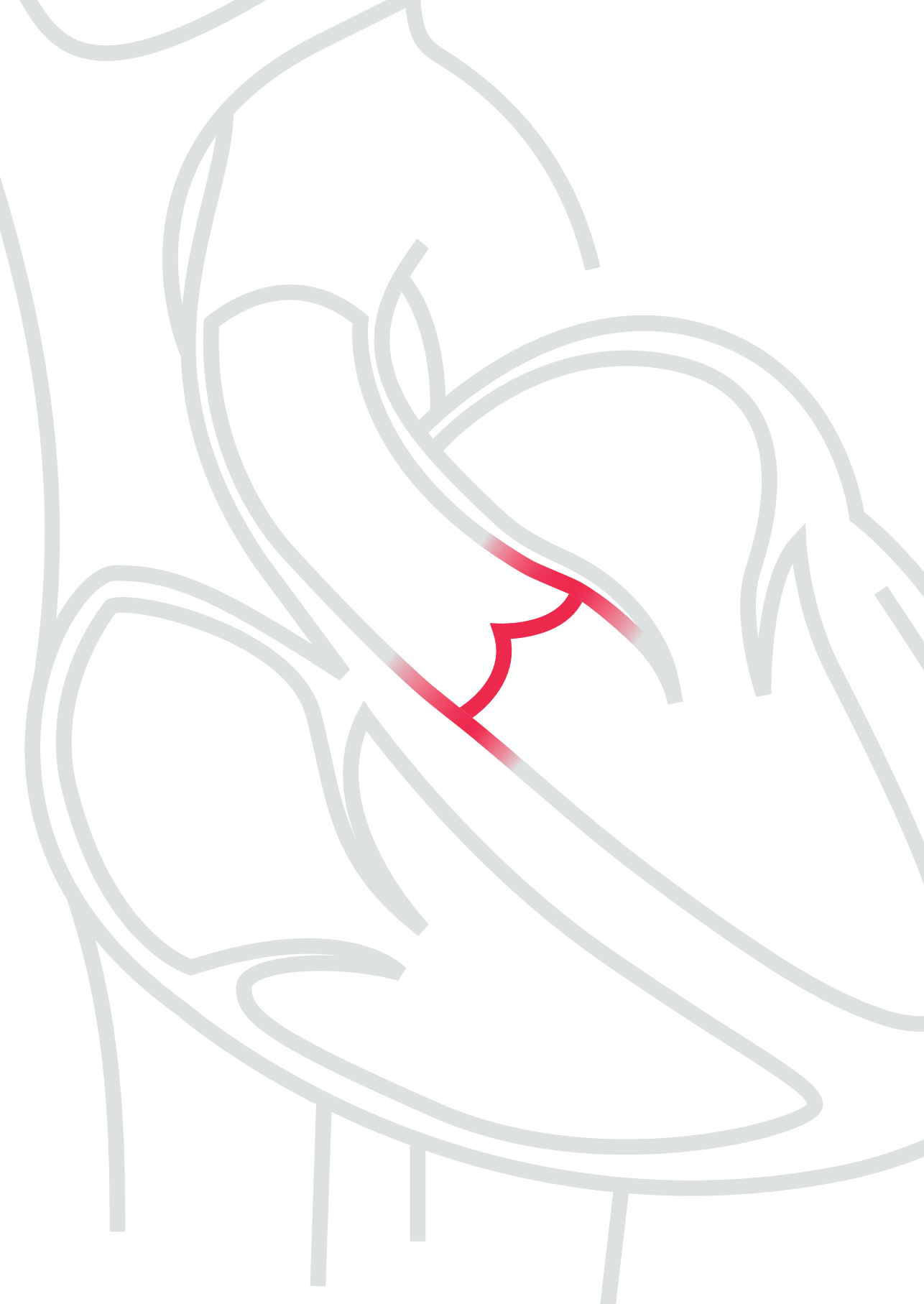

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SUMMARY

Chapter 1 is a general introduction to this thesis, in which the background, aims, research questions and outline of this thesis are described.

Chapter 2 provides an overview of the natural history of pediatric subvalvular aortic stenosis, of outcome after surgery and of factors associated with prognosis. This systematic review includes 24 studies, encompassing a total of 809 natural history and 1476 surgical patients. This chapter shows that approximately half of patients diagnosed with subvalvular aortic stenosis require surgery and that after surgery, although mortality is low, there is a substantial reintervention rate. This chapter illustrates the prognostic value of left ventricular outflow tract gradient, the presence of aortic valve regurgitation and the distance between the subvalvular obstruction and the aortic valve, which underlines the importance of these factors in surgical decision-making. There is a need for further studies on the optimal timing of surgery based on these factors.

Chapter 3 provides an overview of outcome after pediatric aortic valve replacement (AVR). In this systematic review and meta-analysis, 34 publications reporting on 42 cohorts were included: 26 concerning the Ross procedure (2409 patients), 13 concerning AVR with a mechanical prosthesis (696 patients), and 3 concerning AVR with an allograft (224 patients). There were no studies on bioprostheses that met our inclusion criteria. This chapter illustrates that all currently available aortic valve substitutes are associated with suboptimal results in children, reflecting the urgent need for reliable and durable repair techniques and innovative replacement solutions for this challenging group of patients.

Chapter 4 provides an overview of outcome after mechanical AVR in non-elderly adults. In this systematic review, meta-analysis and microsimulation study, 29 publications were included, encompassing a total of 5728 patients. This chapter 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 reintervention. 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.

Chapter 5 provides an overview of outcome after the Ross procedure in both children and non-elderly adults. In this systematic review, meta-analysis and microsimulation study, 99 publications were included, encompassing a total of 13129 patients. This chapter demonstrates that, through excellent survival and avoidance of the burden of

anticoagulation, the Ross procedure provides a unique opportunity for patients whose preferences do not align with the outcome provided by mechanical valve replacement and for growing children who also benefit from autograft diameter increase along with somatic growth. On the downside, almost all pediatric and many adult Ross patients will require a reintervention in their lifetime.

Chapter 6 provides an overview of outcome after bioprosthetic AVR in non-elderly adults. In this systematic review, meta-analysis and microsimulation study, 19 publications were included, encompassing a total of 2686 patients. This chapter demonstrates that AVR with bioprostheses in young adults is associated with high structural valve deterioration and reintervention rates, and low, though not absent, hazards of thromboembolism and bleeding. Foremostly, most patients will require one or more reinterventions during their lifetime and survival is impaired in comparison with the age- and sex-matched general population. Prosthesis durability remains the main concern in these patients.

Chapter 7 is an expert review that discusses contemporary evidence on clinical and psychosocial outcome after AVR and aortic root surgery in non-elderly adults. This chapter illustrates that treatment for non-elderly aortic valve and aortic root disease patients needs to be tailored to the individual patient, considering both clinical and psychosocial outcomes as crucial factors to reach a treatment decision that best reflects the individual patient's values and goals in life.

Chapter 8 compares the durability of novel fresh decellularized pulmonary allografts with that of standard cryopreserved pulmonary allografts when used for right ventricular outflow tract reconstruction in patients undergoing the Ross procedure. In this propensity score-matched analysis of a prospective observational cohort, out of a total of 144 fresh decellularized allograft and 619 standard cryopreserved allograft patients, 94 propensity score-matched pairs were obtained. Analysis of clinical outcome and longitudinal echocardiographic analyses show that, up to 5 years of follow-up, fresh decellularized and standard cryopreserved allograft used for right ventricular outflow tract reconstruction in the Ross procedure are associated with comparably excellent clinical and hemodynamic outcome. Longer follow-up will shed light on the long-term performance of decellularized allografts.

Chapter 9 assesses the current state of patient information and decision-making in congenital aortic and pulmonary valve disease in the Netherlands. This survey includes 62 adult patients, 11 parents of pediatric patients and 35 physicians (pediatric cardiologists, adult congenital cardiologists and congenital cardiac surgeons) in the Netherlands. This chapter reveals substantial shortcomings in our current practice of patient information

and decision-making that underline the need for innovative solutions, such as careful implementation of patient information tools and shared decision-making in the care path.

Chapter 10 investigates the effectiveness of risk visualizations in conveying verbatim knowledge of single absolute risks among the general population. In this randomized investigator-blinded survey, 393 randomly sampled members of the general Dutch population were asked to complete risk conversion tasks and randomized to support of these risk conversion tasks by either icon arrays, pie charts, bar graphs or no visualization. This chapter, in contrast to prior studies that all focus on the conveyance of gist knowledge (i.e. understanding of the general risk message) or comparisons/trade-offs of multiple risks, demonstrates that risk visualizations do not improve conveyance of verbatim knowledge of single absolute risks, irrespective of age, education level, risk magnitude, risk format and form of risk visualization. Risk visualizations may therefore be less suitable for settings in which detailed conveyance of single absolute risks is the main objective (as is often the case in cardiac surgery), although their effect on user experience and perception of risk communication and subsequent patient activation and participation remains to be elucidated.

Chapter 11 discusses our nationwide Dutch initiative for the development of an online evidence-based patient information portal for congenital heart disease in response to an increasing need for patient information and the shortcomings identified in **Chapter 9**. It describes our systematic methodology for successful multidisciplinary development of an online patient-tailored information portal that presents evidence-based disease- and age-specific medical and psychosocial information about diagnosis, treatment, prognosis, and impact on daily life in a manner that is comprehensible and digestible for patients and that meets the needs expressed by both patients and physicians.

Chapter 12 assesses the effectiveness of the patient information portal we developed (as described in **Chapter 11**) in improving patient knowledge and psychosocial outcome. This stepped-wedge cluster randomized trial among 343 (parents of) patients from four participating centers for congenital heart disease in the Netherlands shows that only half of the participants invited by their cardiologist to visit the information portal actually visited the portal. Among those subjects that actually visited the information portal, disease-specific knowledge and mental health were significantly better at one month after outpatient clinic visit, while baseline characteristics and all other outcomes were comparable. Thus, this chapter demonstrates that an online evidence-based patient information portal is potentially effective in improving knowledge and psychosocial outcome in patients with congenital heart disease, although active use

of the portal is crucial. It underlines the urgent need for efforts aimed at supporting effective implementation and active use of patient information support tools.

Chapter 13 is the general discussion of this thesis. It discusses the results presented in this thesis and their implications. It also answers the research questions and proposes future research.

NEDERLANDSE SAMENVATTING

hoofdstuk 1 betreft een algemene introductie van dit proefschrift. In dit hoofdstuk wordt de achtergrond van dit proefschrift beschreven en worden de doelen en onderzoeksvragen uiteengezet.

Hoofdstuk 2 geeft een overzicht van het natuurlijk beloop van subvalvulaire aortastenose in kinderen, van de resultaten van chirurgie en van factoren die geassocieerd zijn met prognose. Deze systematische review van 24 studies omvat in totaal 809 patiënten waarvan het natuurlijke beloop is beschreven en 1476 patiënten waarvan de chirurgische uitkomsten zijn beschreven. Dit hoofdstuk laat zien dat ongeveer de helft van patiënten met subvalvulaire aortastenose een operatie nodig hebben. Na de operatie is de mortaliteit laag, hoewel er een substantieel risico is op reoperatie. Dit hoofdstuk belicht de prognostische waarde van linker ventrikel uitstroombaan gradiënt, de aanwezigheid van aortaklepinsufficiëntie en de afstand tussen de subvalvulaire obstructie en de aortaklep en benadrukt daarmee het belang van deze factoren in chirurgische besluitvorming. Verder onderzoek is nodig naar de optimale timing van chirurgie op basis van deze factoren.

Hoofdstuk 3 geeft een overzicht van de resultaten van aortaklepvervanging (aortic valve replacement, AVR) in kinderen. In deze systematische review en meta-analyse zijn 34 publicaties meegenomen die 42 cohorten omvat: 26 waarvan betrekking hebben tot de Ross procedure (2409 patiënten), 13 tot AVR met een mechanische klepprothese (696 patiënten), en 3 tot AVR met een menselijke donorklep (224 patiënten). Er waren geen publicaties over bioprotheses in kinderen die voldeden aan onze inclusiecriteria. Dit hoofdstuk laat zien dat alle huidige mogelijkheden voor aortaklepvervanging in kinderen suboptimale resultaten bieden. Er is derhalve een dringende behoefte aan betrouwbare en duurzame technieken voor aortaklepreparatie en innovatieve oplossingen voor aortaklepvervanging in deze uitdagende groep patiënten.

Hoofdstuk 4 geeft een overzicht van de resultaten van AVR met een mechanische klepprothese in jongvolwassenen. Deze systematische review, meta-analyse en microsimulatie studie van 29 publicaties omvat in totaal 5728 patiënten. Dit hoofdstuk laat zien dat de uitkomst na mechanische AVR bij jongvolwassenen wordt gekenmerkt door suboptimale overleving en een aanzienlijk levenslang risico op complicaties gerelateerd aan antistolling, maar ook op reoperatie. Jongvolwassen patiënten die een aortaklepvervanging moeten ondergaan hebben recht op inzicht in evidence-based schattingen van de voor- en nadelen van zowel mechanische klepprotheses als van biologische alternatieven in een gezamenlijk besluitvormingsproces.

Hoofdstuk 5 geeft een overzicht van de resultaten van de Ross procedure bij zowel kinderen als jongvolwassenen. Deze systematische review, meta-analyse en microsimulatie studie van 99 publicaties omvat in totaal 13129 patiënten. Dit hoofdstuk laat zien dat de Ross procedure uitstekende overleving biedt en de complicaties van antistolling vermijdt, waardoor de Ross procedure een unieke mogelijkheid biedt voor patiënten wiens voorkeuren niet overeenkomen met de resultaten van mechanische AVR en tevens voor groeiende kinderen die ook profiteren van toename van de autograft diameter naarmate het kind groeit. De keerzijde van de medaille is wel dat bijna alle kinderen en een groot deel van de volwassenen die de Ross procedure ondergaan in de loop van hun leven een reoperatie nodig zullen hebben.

Hoofdstuk 6 geeft een overzicht van de resultaten van AVR met een bioprothese in jongvolwassenen. Deze systematische review, meta-analyse en microsimulatie studie van 19 publicaties omvat in totaal 2686 patiënten. Dit hoofdstuk laat zien dat er na AVR met bioprotheses in jongvolwassenen een hoog risico op structurele klepdegeneratie en reoperatie is, en hoewel het risico op tromboembolieën en bloedingen laag is, is deze niet afwezig. De meeste patiënten die op jongvolwassen leeftijd AVR met een bioprothese ondergaan zullen in de loop van hun leven een of meerdere reoperaties nodig hebben en hun overleving is verminderd in vergelijking met de algemene bevolking. De duurzaamheid van bioprotheses blijft bij deze patiënten de grootste zorg.

Hoofdstuk 7 is een expert review waarin het huidige bewijs voor klinische en psychosociale uitkomsten na AVR en aortawortelchirurgie in jongvolwassenen wordt besproken. Dit hoofdstuk illustreert dat de behandeling van aortaklep- en aortawortelpathologie in jongvolwassenen moet worden afgestemd op de individuele patiënt, waarbij zowel klinische als psychosociale uitkomsten overwogen moeten worden in besluitvorming, om zo te komen tot een behandeling die het beste overeenkomt met de waarden en doelen van de individuele patiënt.

Hoofdstuk 8 vergelijkt de duurzaamheid van nieuw ontwikkelde verse gedecellulariseerde donorkleppen met die van standaard gecryopreserveerde donorkleppen in het kader van rechter ventrikel uitstroombaan reconstructie tijdens de Ross procedure. In een prospectief observationeel cohort van patiënten die de Ross procedure ondergingen werden in 144 patienten verse gedecellulariseerde donorkleppen gebruikt en in 619 werden standaard gecryopreserveerde donorkleppen gebruikt. Middels propensity score-matching werden uit deze totale cohort 94 patiënten uit elke groep geselecteerd die qua patiëntkenmerken vergelijkbaar waren. Analyse van klinische resultaten en longitudinale echocardiografische analyses toonden aan dat, tot 5 jaar na de operatie, verse gedecellulariseerde en standaard gecryopreserveerde donorkleppen vergelijkbare uit-

stekende klinische en hemodynamische resultaten bieden. Langere follow-up zal nodig zijn om een uitspraak te doen over de lange termijn prestaties van gedecellulariseerde donorkleppen.

In **Hoofdstuk 9** brengen wij de huidige status van patiënten informatievoorziening en besluitvorming bij congenitale aorta- en pulmonalisklepaandoeningen in Nederland in kaart. Dit onderzoek omvat 62 volwassen patiënten, 11 ouders van pediatrische patiënten en 35 artsen (kindercardiologen, volwassen congenitaal cardiologen en congenitaal hartchirurgen) in Nederland. Dit hoofdstuk onthult substantiële tekortkomingen in onze huidige praktijk van patiënten informatievoorziening en besluitvorming. Er is derhalve een dringende behoefte aan innovatieve oplossingen hiervoor, zoals de ontwikkeling van hulpmiddelen voor patiëntinformatie en gezamenlijke besluitvorming en zorgvuldige implementatie daarvan in het zorgpad.

Hoofdstuk 10 onderzoekt de effectiviteit van risicovisualisaties in het bevorderen van het exacte begrip van absolute risicogetallen onder de algemene bevolking. In deze gerandomiseerde enquête werd aan 393 willekeurig geselecteerde leden van de algemene Nederlandse bevolking gevraagd om risicogetallen om te rekenen. De deelnemers werden willekeurig ingedeeld in 4 groepen: in één groep werden de rekenopdrachten ondersteund door pictogrammen, in een andere groep door cirkeldiagrammen, in een derde groep door staafdiagrammen en in de laatste groep werd de rekenopdracht niet ondersteund door een risicovisualisatie. In tegenstelling tot eerdere studies die allemaal gericht waren op globaal risicobegrip of op vergelijkingen van meerdere risico's, toont dit hoofdstuk aan dat, als het gaat om het exacte begrip van absolute risico getallen, het gebruik van risicovisualisaties het begrip niet bevordert, ongeacht leeftijd, opleidingsniveau, de grootte van het risico, het tekstuele format van het risico en het type risicovisualisatie. Risicovisualisaties zijn daarom mogelijk minder geschikt voor situaties waarin gedetailleerde/exacte communicatie van absolute risico's het doel is (zoals vaak het geval is in de hartchirurgie), hoewel het effect op gebruikerservaring en patiëntbetrokkenheid nog onderzocht moet worden.

Hoofdstuk 11 bespreekt ons landelijke Nederlandse initiatief voor de ontwikkeling van een online evidence-based patiënteninformatieportaal voor aangeboren hartafwijkingen in respons op een toenemende behoefte aan patiëntinformatie alsook de tekortkomingen daarin die zijn geïdentificeerd in **Hoofdstuk 9**. Het beschrijft onze systematische methodologie voor succesvolle multidisciplinaire ontwikkeling van een online patiënt-specifiek informatieportaal dat evidence-based ziekte- en leeftijdsspecifieke medische en psychosociale informatie over diagnose, behandeling, prognose en

impact op het dagelijks leven presenteert op een manier die begrijpelijk en verteerbaar is voor patiënten en die voldoet aan de behoeften van zowel patiënten als artsen.
Hoofdstuk 12 onderzoekt de effectiviteit van het door ons ontwikkelde patiënten informatieportaal (zoals beschreven in **Hoofdstuk 11**) in het verbeteren van kennis en psychosociale uitkomsten van patiënten. Uit deze stepped-wedge cluster gerandomiseerde studie onder 343 (ouders van) patiënten uit vier deelnemende Nederlandse centra voor aangeboren hartafwijkingen blijkt dat slechts de helft van de deelnemers die door hun cardioloog werden uitgenodigd om het informatieportaal te bezoeken, het portaal daadwerkelijk hebben bezocht. Bij de deelnemers die het informatieportaal daadwerkelijk bezochten, waren ziekte-specifieke kennis en geestelijke gezondheid significant beter één maand na het bezoek aan de polikliniek, terwijl de patiëntkenmerken en alle andere uitkomsten vergelijkbaar waren. Dit hoofdstuk laat dus zien dat een online evidence-based patiënten informatieportaal potentieel effectief is in het verbeteren van kennis en psychosociale uitkomsten bij patiënten met een aangeboren hartaandoening, hoewel actief gebruik van het portaal van essentieel belang is. Het onderstreept de dringende behoefte aan initiatieven en innovaties gericht op het ondersteunen van de effectieve implementatie en het actief gebruik van dergelijke hulpmiddelen voor patiënten informatie.

Hoofdstuk 13 is de algemene discussie van dit proefschrift. In dit hoofdstuk worden de resultaten van dit proefschrift en de implicaties van deze resultaten bediscussieerd. Tevens worden de onderzoeksvragen beantwoord en worden er voorstellen voor verder onderzoek gedaan.

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PHD PORTFOLIO

Name PhD student:	Jonathan R.G. Etnel
Erasmus MC department:	Cardiothoracic Surgery
Research school:	Cardiovascular Research School (COEUR)
PhD period:	September 2014 - September 2016
Promotors:	Prof. dr. J.J.M. Takkenberg
	Prof. dr. A.J.J.C. Bogers

Academic education

2010-2013	Bachelor of Science (BSc) in Medicine, Erasmus MC, Rotterdam, The Netherlands
2016-2019	Master of Science (MSc) in Medicine, Erasmus MC, Rotterdam, The Netherlands

PhD training	ECTS
In-depth courses	
2014	
NIHES Erasmus Summer Program	
Principles of Research in Medicine and Epidemiology	0.7
Master Class: Advances in Epidemiologic Analysis	0.4
Methods of Clinical Research	0.7
Fundamentals of Medical Decision Making	0.7
Master Class: Advances in Genomic Research	0.4
The Practice of Epidemiologic Analysis	0.7
COEUR course Vascular Clinical Epidemiology	1.5
2015	
NIHES Erasmus Summer Program	
Logistic Regression	1.4
Master Class: Advances in Epidemiologic Analysis	0.4
Survival Analysis	1.4
Master Class: Advances in Genomic Research	0.4
Markers and Prediction Research	0.7
COEUR course Congenital Heart Disease	1.5
Basic course on R	1.4
2016	
NIHES Erasmus Winter Program	
Advanced Analysis of Prognosis Studies	0.7
2014-2016	
COEUR symposia	2.0

Compulsory PhD courses		
2015		
	Research Integrity Course	0.3
	CPO-Course on Patient Oriented Research	0.3
Conferences		
2015		
	Heart Valve Society Annual Meeting, Monaco	0.9
2016		
	Association for European Pediatric and Congenital Cardiology Biennial Psychosocial Meeting, Rotterdam	0.6
	Heart Valve Society Annual Meeting, New York	0.9
	Association for European Pediatric and Congenital Cardiology Annual Meeting, Rome	1.2
	Society for Medical Decision Making Annual North American Meeting, Vancouver	1.2
2018		
	Association for European Pediatric and Congenital Cardiology Biennial Psychosocial Meeting, Leicester	0.9
	Heart Valve Society Annual Meeting, New York	0.9
	Dutch Association for Thoracic Surgery Biannual Meeting, Utrecht	0.6
	Society for Medical Decision Making Annual European Meeting, Leiden	0.6
Conference presentations		
2015		
	Heart Valve Society Annual Meeting, Monaco	0.6
2016		
	Association for European Pediatric and Congenital Cardiology Biennial Psychosocial Meeting, Rotterdam	0.6
	Heart Valve Society Annual Meeting, New York	0.6
	Association for European Pediatric and Congenital Cardiology Annual Meeting, Rome	0.6
	Society for Medical Decision Making Annual North American Meeting, Vancouver	1.2
2017		
	MedStar Health Cardiovascular Education Program, Washington D.C.	0.6
2018		
	Association for European Pediatric and Congenital Cardiology Biennial Psychosocial Meeting, Leicester	0.6
	Heart Valve Society Annual Meeting, New York	1.2
	Dutch Association for Thoracic Surgery Biannual Meeting, Utrecht	0.6
	Society for Medical Decision Making Annual European Meeting, Leiden	0.6

Teaching		
2014		
	Supervision of 2nd year medical students in writing a systematic review	0.6
2015		
	Supervision of 2nd year medical students in writing a systematic review	0.6
	Supervision of 3rd year medical students in writing a systematic review	0.6
	Supervision of 3rd year TU Delft students for Medical Delta minor	0.6
	Lecture minor congenital heart disease	0.6
2016		
	Lecture minor congenital heart disease	0.6
	Supervision of 3rd year medical students in writing a systematic review	1.8
	Supervision of Erasmus University College students	0.6
	Supervision of 3rd year TU Delft students for Medical Delta minor	0.6
2019		
	Lecture minor congenital heart disease	0.6
	Supervision of 3rd year medical students in writing a systematic review	1.2
	Lecture COEUR course	0.6
2020		
	Lecture COEUR course	0.6
Meetings		
Various dates		
	Scientific meetings Department of Cardiothoracic Surgery, Erasmus MC	3.0
	Biannual meetings of the CVON Bicuspid Aortic Valve Consortium	1.2
Peer reviewer international scientific journals		
	European Heart Journal	1.0
	Heart	0.5
	Annals of Thoracic Surgery	1.0
	European Journal for Cardio-Thoracic Surgery	0.5
	Patient Education and Counseling	1.0
Conference abstract reviewer		
2020		
	Society for Medical Decision Making 18th Biennial European Conference	0.5
Total ECTS		**48.9**

LIST OF PUBLICATIONS

1. Patient information portal for congenital aortic and pulmonary valve disease: a stepped-wedge cluster randomized trial
   Etnel JRG, Bons LR, De Heer F, Robbers-Visser D, Van Beynum IM, Straver B, Jongbloed MRM, Kiès P, Slieker MG, Van Dijk APJ, Kluin J, Bertels RA, Utens EMWJ, The R, Van Galen E, Mulder BJM, Blom NA, Hazekamp MG, Roos-Hesselink JW, Helbing WA, Bogers AJJC, Takkenberg JJM
   Open Heart. In press.

2. Prosthesis-patient mismatch after mitral valve replacement: a systematic review and meta-analysis
   Tomsic A, Arabkhani B, Schoones JW, **Etnel JRG**, Ajmone Marsan N, Klautz RJM, Palmen M
   J Card Surg. In press.

3. Do risk visualizations improve the understanding of numerical risks? A randomized, investigator-blinded general population survey.
   Etnel JRG, De Groot JM, El Jabri M, Mesch A, Nobel NA, Bogers AJJC, Takkenberg JJM.
   Int J Med Inform. 2020 Mar;135:104005.

4. Outcome after surgical repair of tetralogy of Fallot: A systematic review and meta-analysis
   Romeo JLR*, **Etnel JRG***, Takkenberg JJM, Roos-Hesselink JW, Helbing WA, Van de Woestijne P, Bogers AJJC, Mokhles MM
   J Thorac Cardiovasc Surg. 2020 Jan;159(1):220-236.e8.
   **Shared first authorship*

5. Outcomes after surgery for functional tricuspid regurgitation: a systematic review and meta-analysis.
   Veen KM, **Etnel JRG**, Quanjel TJM, Mokhles MM, Huygens SA, Rasheed M, Oei FBS, Ten Cate FJ, Bogers AJJC, Takkenberg JJM.
   Eur Heart J Qual Care Clin Outcomes. 2020 Jan 1;6(1):10-18.

6. Clinical and quality of life outcomes after aortic valve replacement and aortic root surgery in adult patients <65 years old.
   Gökalp AL*, De Heer F*, **Etnel JRG**, Kluin J, Takkenberg JJM.
   Ann Cardiothorac Surg. 2019 May;8(3):372-382.
   **Shared first authorship*

7. Sildenafil for bronchopulmonary dysplasia and pulmonary hypertension: a meta-analysis.
   Van der Graaf M, Rojer LA, Helbing W, Reiss I, **Etnel JRG**, Bartelds B.
   Pulm Circ. 2019 Feb 26:2045894019837875.

8. Bioprosthetic Aortic Valve Replacement in Nonelderly Adults: A Systematic Review, Meta-Analysis, Microsimulation.
   Etnel JRG, Huygens SA, Grashuis P, Pekbay B, Papageorgiou G, Roos-Hesselink JW, Bogers AJJC, Takkenberg JJM.
   Circ Cardiovasc Qual Outcomes. 2019 Feb;12(2):e005481.

9. What Is the Potential of Tissue-Engineered Pulmonary Valves in Children?
   Huygens SA, Rutten-van Mölken MPMH, Noruzi A, **Etnel JRG**, Corro Ramos I, Bouten CVC, Kluin J, Takkenberg JJM.
   Ann Thorac Surg. 2019 Jun;107(6):1845-1853.

10. Bioprosthetic aortic valve replacement in elderly patients: Meta-analysis and micro-simulation.
    Huygens SA, **Etnel JRG**, Hanif M, Bekkers JA, Bogers AJJC, Rutten-Van Mölken MPMH, Takkenberg JJM.
    J Thorac Cardiovasc Surg. 2019 Jun;157(6):2189-2197.e14.

11. The Ross Procedure: A Systematic Review, Meta-Analysis, and Microsimulation.
    Etnel JRG*, Grashuis P*, Huygens SA, Pekbay B, Papageorgiou G, Helbing WA, Roos-Hesselink JW, Bogers AJJC, Mokhles MM, Takkenberg JJM.
    Circ Cardiovasc Qual Outcomes. 2018 Dec;11(12):e004748.
    **Shared first authorship*

12. Patient and physician view on patient information and decision-making in congenital aortic and pulmonary valve surgery.
    Etnel JRG, Helbing WA, Roos-Hesselink JW, The R, Bogers AJJC, Takkenberg JJM.
    Open Heart. 2018 Nov 10;5(2):e000872.

13. Fresh decellularized versus standard cryopreserved pulmonary allografts for right ventricular outflow tract reconstruction during the Ross procedure: a propensity-matched study.
    Etnel JRG, Suss PH, Schnorr GM, Veloso M, Colatusso DF, Balbi Filho EM, Costa FDAD.
    Eur J Cardiothorac Surg. 2018 Sep 1;54(3):434-440.

14. Decellularized versus standard pulmonary allografts in the Ross procedure: propensity-matched analysis.
da Costa FDA*, **Etnel JRG***, Charitos EI, Sievers HH, Stierle U, Fornazari D, Takkenberg JJM, Bogers AJJC, Mokhles MM.
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15. 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.
Eur Heart J. 2017 Dec 1;38(45):3370-3377.
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16. Decellularized allografts for right ventricular outflow tract reconstruction in children
da Costa FDA, **Etnel JRG**, Torres R, Balbi Filho EM, Torres R, Calixto A, Mulinari LA.
World J Pediatr Congenit Heart Surg. 2017 Sep;8(5):605-612.

17. Development of an online, evidence-based patient information portal for congenital heart disease
Etnel JRG, van Dijk APJ, Kluin J, Bertels RA, Utens EMWJ, Van Galen E; Regina The, Bogers AJJC, Takkenberg JJM.
Front Cardiovasc Med. 2017 May 1;4:25.

18. Systematic review and meta-analysis of music interventions in hypertension treatment: a quest for answers.
Kühlmann AYR, **Etnel JRG**, Roos-Hesselink JW, Jeekel J, Bogers AJJC, Takkenberg JJM.
BMC Cardiovasc Disord. 2016 Apr 19;16(1):69.

19. Drug therapy in the prevention of failure of the Fontan circulation: a systematic review.
Oldenburger NJ, Mank A, **Etnel JRG**, Takkenberg JJM, Helbing WA.
Cardiol Young. 2016 Jun;26(5):842-50.

20. Outcome after aortic valve replacement in children: a systematic review and meta-analysis.
Etnel JRG, Elmont LC, Ertekin E, Mokhles MM, Heuvelman HJ, Roos-Hesselink JW, de Jong PL, Helbing WA, Bogers AJJC, Takkenberg JJM.
J Thorac Cardiovasc Surg. 2016 Jan;151(1):143-52.e1-3.

21. Does exercise training improve cardiopulmonary fitness and daily physical activity in children and young adults with corrected tetralogy of Fallot or Fontan circulation? A randomized controlled trial.
    Duppen N, **Etnel JRG**, Spaans LG, Takken T, Van den Berg-Emons RJ, Boersma E, Schokking M, Dulfer K, Utens EM, Helbing W, Hopman MT.
    Am Heart J. 2015 Sep;170(3):606-14.

22. Paediatric subvalvular aortic stenosis: a systematic review and meta-analysis of natural history and surgical outcome.
    Etnel JRG, Takkenberg JJM, Spaans LG, Bogers AJJC, Helbing WA.
    Eur J Cardiothorac Surg. 2015 Aug;48(2):212-20.

BOOK CHAPTERS

1. Tricuspid valve disease: surgical outcome
   Veen KM, **Etnel JRG**, Takkenberg JJM
   Chapter in: Practical Manual of Tricuspid Valve Diseases. Soliman O.I., Ten Cate F.J. (eds). 2018. 305-327.

ABOUT THE AUTHOR

Jonathan Richard Gregory Etnel was born in Paramaribo, Suriname on February 18th, 1992. At the age of one he moved together with his parents to St. Maarten, Netherlands Antilles. After graduating from secondary school (Cum laude, Valedictorian, VWO, Curriculum Nature & Health, Milton Peters College, Philipsburg, St. Maarten), he moved to Rotterdam, The Netherlands to start Medical School at the Erasmus University Rotterdam in 2010. During his medical studies he was active in numerous clinical and administrative student teams at various hospitals, he tutored senior secondary school students (HAVO & VWO) for their final exams in Biology and he also did volunteer work in the organization of international medical internships and training courses. He quickly developed an affinity for the field of Cardiothoracic Surgery and after an elective in Cardiovascular Disease in the second year of his studies, he started working at the Department of Cardiothoracic Surgery, Erasmus MC as a research associate. In the third year of his studies he enrolled in the minor Congenital Heart Disease. During this minor he conducted a research project under supervision of prof. dr. W.A. Helbing of the Department of Pediatric Cardiology and prof. dr. J.J.M. Takkenberg of the Department of Cardiothoracic Surgery. After the minor, he continued his extracurricular research in the field of congenital heart disease and cardiac surgery parallel to his medical studies, which ultimately resulted in a PhD position at the Department of Cardiothoracic Surgery, Erasmus MC under supervision of prof. dr. J.J.M. Takkenberg and prof.dr. A.J.J.C. Bogers in 2014 after obtaining his Bachelor of Science in Medicine in 2013. After two years of full-time PhD research, he resumed his medical studies in 2016 with his clinical internships, while continuing his PhD research in parallel. In 2018 he received the Young Investigator Award from the Association for European Pediatric and Congenital Cardiology. In August 2018 he graduated as a Medical Doctor and in September 2018 he started working as a resident at the Department of Cardiothoracic Surgery, Erasmus MC, while continuing his PhD research in parallel. In September 2020 he started his training to become a cardiothoracic surgeon at Erasmus MC.

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