CHAPTER VII

PROGNOSIS AFTER AORTIC ROOT REPLACEMENT WITH CRYOPRESERVED ALLOGRAFTS IN ADULTS: META-ANALYSIS AND MICROSIMULATION BASED ESTIMATES

Prognosis after Aortic Root Replacement with Cryopreserved Allografts in Adults. Johanna J.M. Takkenberg, MD, Marinus J.C. Eijkemans*, MSc, Lex A. van Herwerden, MD, PhD, Ewout W. Steyerberg*, PhD, Mary M. Lane†, PhD, Ronald C. Elkins†, MD, J. Dik F. Habbema*, PhD, Ad J.J.C. Bogers, MD, PhD. *Submitted*

Abstract

Objectives Meta-analysis and microsimulation were employed to calculate age-specific long-term prognosis after allograft ARR based on limited current evidence.

Background ARR with cryopreserved allografts is associated with excellent hemodynamics, little endocarditis, low thrombo-embolic event rates and no need for anticoagulation. There is however concern regarding the long-term durability of this valve substitute, especially in younger patients.

Methods Our center's experience with cryopreserved allograft ARR in 165 adult patients was combined in a meta-analysis with reported and individual results of 4 other hospitals. Using this information, the microsimulation model predicted age and gender specific total, reoperation-free and event-free life expectancy (LE).

Results The pooled results comprised 629 patients with a total follow-up of 1860 patient years (range 0-12.8 yrs). Annual risks were 0.6% for thrombo-embolism, 0.05% for bleeding, 0.5% for endocarditis and 0.5% for nonstructural valve failure. Structural allograft failure requiring reoperation occurred in 15 patients and a patient age-specific Weibull function was constructed accordingly. Calculated total LE varied from 27 years in a 25-year-old to 12 years in a 65-year-old male; corresponding actual lifetime risk of reoperation was 89% and 35% respectively.

Conclusions Cryopreserved aortic allografts have an age-related limited durability. This results in a considerable lifetime risk of reoperation, especially in young patients. The combination of meta-analysis and microsimulation provides an appropriate tool for estimating individualized long-term outcome after AVR. It can be useful to obtain improved insight into factors that determine outcome, and can be easily adjusted in the light of new clinical evidence on outcome after AVR.

Abbreviations list

Aortic root replacement	ARR
Aortic valve replacement	AVR
Life expectancy	LE

Introduction

ARR with cryopreserved aortic allografts is an established surgical option for patients with aortic valve or root disease. It is associated with excellent hemodynamics, small endocarditis risk, low thrombo-embolic event rates and does not require anticoagulation. However, there is concern regarding long-term durability of this aortic valve substitute [1-3].

Since the introduction of the allograft as an aortic valve substitute, several changes have been made with regard to preservation and surgical techniques. Initially, fresh or antibiotically sterilized valves were implanted using the subcoronary implantation technique. Long-term results after AVR with fresh or antibiotically sterilized allografts that were mainly implanted using the subcoronary or "freehand" technique shows that after 20 years 35% of patients are free from re-do valve replacement and only 18% are still free from tissue failure [1]. Slightly better results were obtained in a large series of 804 patients who had AVR with either antibiotic sterilized (N=124) or cryopreserved (N=680) allografts that were implanted using predominantly the subcoronary implantation technique. Freedom from structural deterioration was 45% and 80% respectively after 15 years [4]. Both studies conclude that younger patient age is associated with increased structural valve failure rates. Most centers no longer use fresh or antibiotically sterilized allografts nor do they employ the subcoronary implantation technique. It is hypothesized that the use of cryopreservation methods and the root replacement technique will result in an improved durability of the valve substitute.

Unfortunately, most reported series on ARR with cryopreserved allografts are small and have a limited follow-up that does not allow insight into long-term failure of allograft roots beyond the first 10 years after operation. In addition, because of the small size of the studies, it is also hard to identify potential risk factors for allograft failure and to assess the impact they have on prognosis. The aim of this study was to estimate age-specific prognosis after ARR with a cryopreserved aortic allograft. We performed a meta-analysis to quantify a microsimulation model that estimates LE, and actual risks of events and reoperation in the individual patient.

Materials and methods

Meta-analysis

Rotterdam experience. All patients who received an allograft at our center were monitored prospectively over time by means of yearly telephone surveys and standardized echocardiography. Data were entered in the relational database Access for Windows 97 (Microsoft, Redmond, U.S.A.). Data from all 165 adult patients (≥16 years at time of operation) who underwent ARR with a cryopreserved aortic allograft between July 1989 and October 2000 was analyzed. ARR with reimplantation of the coronary arteries was the surgical technique used in all patients. Mean follow-up was 3.1 years (S.D. 2.5, range 0-10.1 years) and 99% complete at the closing date of the study (November 1, 2000). Cumulative survival was calculated using the Kaplan-Meier method. The Cox proportional hazards model was used to study the relationship between patient age (as a continuous variable) and structural valve failure.

Literature search. We performed a literature search of the MEDLINE database using the PubMed search engine for the period starting from January 1995 until June 2000. This was done in order to obtain the most recent reports with the longest follow-up. Terms used for the search were MeSH terms and the text words “allograft”, “root”, “aortic valve” and “homograft”. All titles and abstracts were screened for study design (reports of clinical experience with cryopreserved allograft ARR), completeness of follow-up (>90%), surgical technique (root replacement with reimplantation of the coronary arteries), study size (N>40, reflecting the experience at that particular center), and patient age (age≥16 years at time of operation). The references of selected papers were cross-checked for other potentially relevant studies.

Data extraction and analysis. The selected papers were reviewed and patient characteristics and results of each study were tabulated in a spreadsheet. The authors of the papers were contacted for clarification and additional information, if necessary. Events and outcomes in all studies including our own were defined according to Edmund’s guidelines [5]. A combined estimate of outcome was obtained by means of weighted pooling [6], or in case of few events per study direct pooling. For valvular thrombosis, thrombo-embolism, bleeding, endocarditis and non-structural valve failure linearized annual occurrence rates were calculated. The incidence of structural valvular failure requiring replacement of the valve was described by a Weibull curve, which is a generalization of the exponential distribution that accommodates a changing risk over time [7-9]. The parameters of the Weibull model were

estimated using the pooled structural valve failure data from the meta-analysis. The center from Oklahoma [3] provided additional information on the relationship between patient age and structural valve failure in their dataset. This information was combined with the information on the relationship between patient age and structural valve failure from the Rotterdam dataset and an age parameter was estimated and added to the Weibull model, allowing for patient age-specific calculations for structural valve failure [10, 11].

Microsimulation model

The basic assumption of the microsimulation model is that a disease follows a course in time that is characterized by a number of discrete health states and disease related events. A schematic representation of these health states and events is given in Figure 1. After AVR with a cryopreserved allograft root, the patient can either die as a result of the procedure or stay alive. If the patient stays alive, he or she remains at risk for developing valve-related events for the rest of his or her life. Eventually this patient will die of either valve-related or non-valve-related causes.

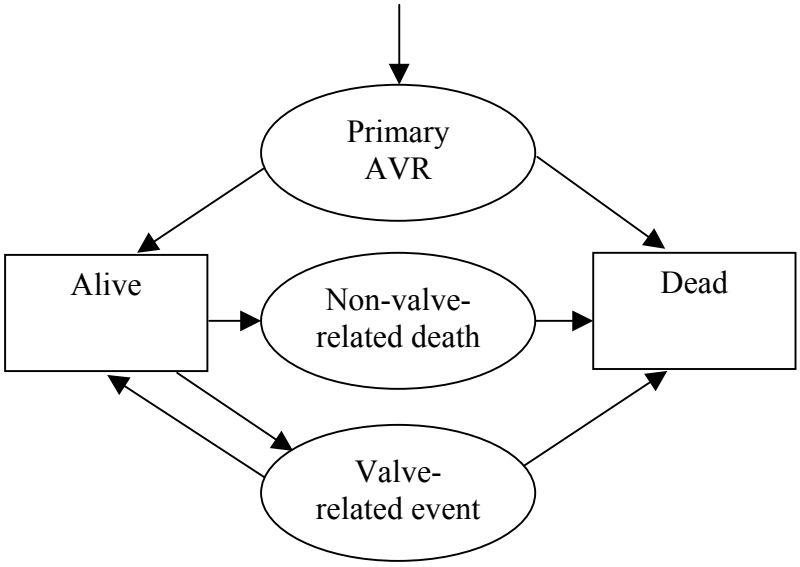

Figure 1. Schematic representation of different health states of a patient after ARR with a cryopreserved aortic allograft as implemented in the microsimulation model.

The information on outcome after allograft ARR from the meta-analysis was entered into the microsimulation model. For a given patient, characterized by gender and age, ten thousand 'virtual' life histories were calculated. Age of death due to non-valve related causes was randomly drawn from a life table that was based on the Dutch general population (http://www.cbs.nl). However, there is an excess mortality in patients after AVR compared to

the general population that cannot be explained solely by post-operative valve related events. This is for instance caused by sudden unexpected unexplained death and cardiac death, related to valve disease, cardiomyopathy and factors introduced by the type of valve substitute [12-14]. We therefore multiplied the age and gender specific mortality hazard of the general population with an age and gender related hazard ratio for excess mortality, based on previous work [15]. Other assumptions made were that bleeding risk increases with age (OR 1.0345/year) [16], operative mortality increases with age (2.6% at age 45 and increasing with OR 1.022/year) and also increases with each reoperation (OR 1.7 with each reoperation) [17, 18]. The lethality of valve-related events was estimated from our previous work and from recent literature, resulting in mortality rates of 10% after thrombo-embolism, 7% after bleeding and 25% after endocarditis [1, 19]. After structural or non-structural valve failure, the allograft was replaced by a mechanical prosthesis. If the patient survived the valve replacement with a mechanical prosthesis the hazards of valve-related events were changed accordingly, as was described previously [17]. If valve replacement was necessary after endocarditis, another allograft was implanted.

For males at different ages (25, 35, 45, 55 and 65 years) LE, reoperation-free LE, actual lifetime reoperation risk, event-free LE and actual lifetime event risk were calculated. The impact of valve-related events on mortality was assessed and loss of LE was compared to healthy age-matched individuals.

To investigate validity, calculated survival was compared to reported survival in 3 of the studies in the meta-analysis (Rotterdam, Brisbane, and Nieuwegein [2, 20]). In addition, calculated survival was compared to actual survival after allograft aortic valve or root replacement in 2 large dataset from Australia and the United Kingdom of patients who had aortic valve or root replacement with fresh, antibiotic stored or cryopreserved allografts that were implanted using several different surgical techniques[1, 21].

To investigate the effect of uncertainty in the parameter estimates on life-expectancy one-way sensitivity analyses were performed. For parameters that were estimated using linearized annual occurrence rates (thrombo-embolism, bleeding, endocarditis and non-structural valve failure) 95% confidence limits were calculated using the method described by Breslow and Day for obtaining confidence limits for estimating a Poisson-distributed variable[22]. The estimates for operative mortality and structural valve deterioration were ranged from half to double the baseline parameter values[23].

Results

Meta-analysis

Rotterdam experience. Pre-operative patient characteristics and outcome are displayed in Table I. Operative mortality was 6% (N=10; 9 non-valve-related, 1 due to right ventricular failure after a perioperative myocardial infarction caused by stenosis of the ostium of the reimplanted right coronary artery). During follow-up 16 more patients died (11 non-valve related, 1 due to a major bleeding and 4 suddenly, unexpected and unexplained). Cumulative survival was 72% at 7 years (95% CI 60-84%; Cox regression). Replacement of the allograft for structural valve failure was done in 7 patients at 4.4, 4.9, 5.6, 6.0, 6.4, 6.7 and 8.4 years postoperative. The mean age of these 7 patients at initial operation was 27 years (SD 6.6, range 18-37 years). Freedom from reoperation for structural valve failure was 81% (95% CI 65-97%) at 7 years. Younger patient age at operation was an important predictor of structural valve failure requiring reoperation (Hazard ratio 0.90; 95% CI 0.83-0.97; p=0.008; corresponding to a 10% decrease in hazard with each year of increasing age). Nonstructural valve failure requiring reoperation occurred in 3 patients. As mentioned above, 1 patient had a lethal bleeding. Two patients had a stroke at 2.5 and 3 years postop and 4 patients had one or more episodes of transient ischemic attacks (TIA). One patient developed an endocarditis with cerebral abscesses, and was treated with antibiotics. No valvular thrombosis or peripheral emboli were observed.

Literature search, data-extraction and pooling. The literature search yielded 77 papers of which only 4 met our inclusion criteria [2, 3, 20, 24]. The authors were contacted and 2 provided additional information. An overview of the patient characteristics and outcome from these 4 studies is displayed in Table I, together with the pooled results including pooled hazards for the different types of valve-related events.

Table I. Patient characteristics and outcome after allograft ARR from the 5 studies selected for the meta-analysis.

	Rotterdam (N=165)	Ann Arbor (N=71)	Oklahoma (N=115)	Brisbane (N=146)	Nieuwegein (N=132)	TOTAL (N=629)
Year of publication		1998[24]	1998[3]	1995[2]	1999[20]	
Study period	7/1989-11/2000	5/1989-1997	1986-1999	11/1985-1/1994	9/1989-5/1998	
Follow-up	Mean: 3.1 years	Mean: 2.5 years	Median: 3.5 years	--	Mean: 3.5 years	
Patient years	515	145	407	Estimated: 400	393	1860
Mean age (range)	48 (16-75)	62 (20-77)	51 (16-84)	Median 49(13-75)	51 (17-77)	51 (13-77)
M/F ratio	124/41	50/21	78/37	122/24	99/33	3.3
Pre-op NYHA class III/IV	46%	63%	--	--	65%	
Prior cardiac surgery	30%	30%	34%	9%	45%	
Active endocarditis	21%	28%	27%	--	48%	
Concomitant CABG	9%	21%	15%	--	5%	
Early mortality (N)	10 (6%)	12 (7%)	22 (19%)	3 (2%)	12 (9%)	59 (9.4%)
Late mortality (N)	16	4	6	4	6	36
Valve thrombosis (N)	0	0	0	0	0	0 (0.0%/pt yr*)
Thrombo-embolism (N)	6	0	0	4	1	11 (0.6%/pt yr*)
Late bleeding (N)	1	0	0	0	0	1 (0.05%/pt yr*)
Endocarditis (N)	1	2	4	2	2	11 (0.5%/pt yr*)
Non-structural valve failure (N)	3	2	0	1	4	10 (0.5%/pt yr*)
Structural valve failure (N)	7	0	5	3	0	See figure 2

-- = No information available, *pooled linearized annual occurrence rate

In Figure 2 the age-specific Weibull function derived from the pooled data on structural valve failure requiring reoperation is displayed. The formula for freedom from structural valve failure was $S(t) = e^{-(t/\sigma)^{\wedge}\beta}$, where S(t) indicates the probability of being free from structural valve failure at time t, and σ and β indicate the scale and shape parameters of the Weibull model. The value of σ depended on age: $\sigma = e^{2.234+0.0112*age}$, and the value of β was 3.669. The age parameter was estimated using combined information on the relationship between patient age and structural valve failure requiring reoperation from the Rotterdam and Oklahoma center [3]. In the Oklahoma dataset 5 patients required reoperation for structural valve failure at 4.7, 8.1, 8.5, 8.9 and 10.2 years after the initial operation. The mean age at the time of primary operation of these patients was 47 years (SD 6.8, range 37-55 years). The estimated value of the age parameter in the Weibull model (0.0112) resulted in an increase of the median time to structural allograft failure from 11.1 years in a 25-year old male to 17.5 years in a 65-year old (approximately 1.5 years with each 10 years increase in patient age).

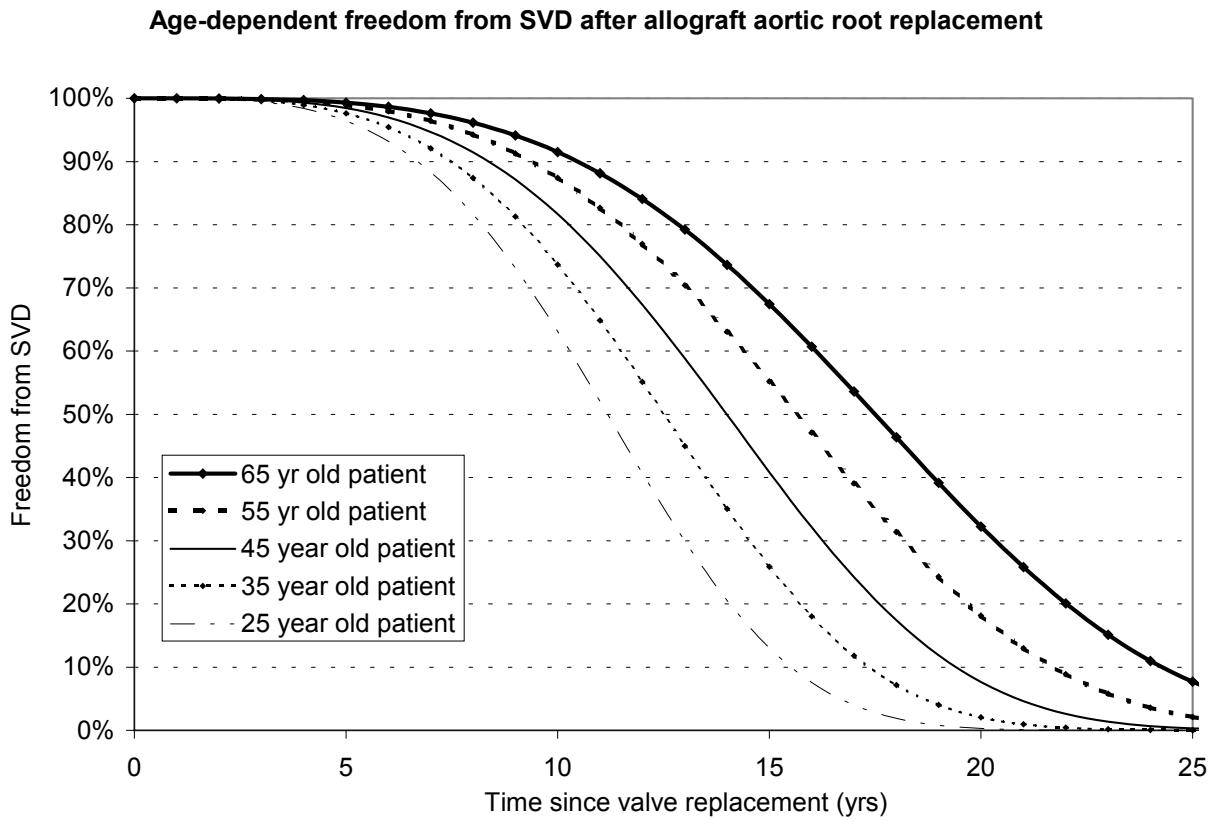

Figure 2. Weibull estimate of age-dependent freedom from structural valve deterioration (SVD) after ARR with a cryopreserved aortic allograft obtained from the pooled structural valve failure data from the meta-analysis.

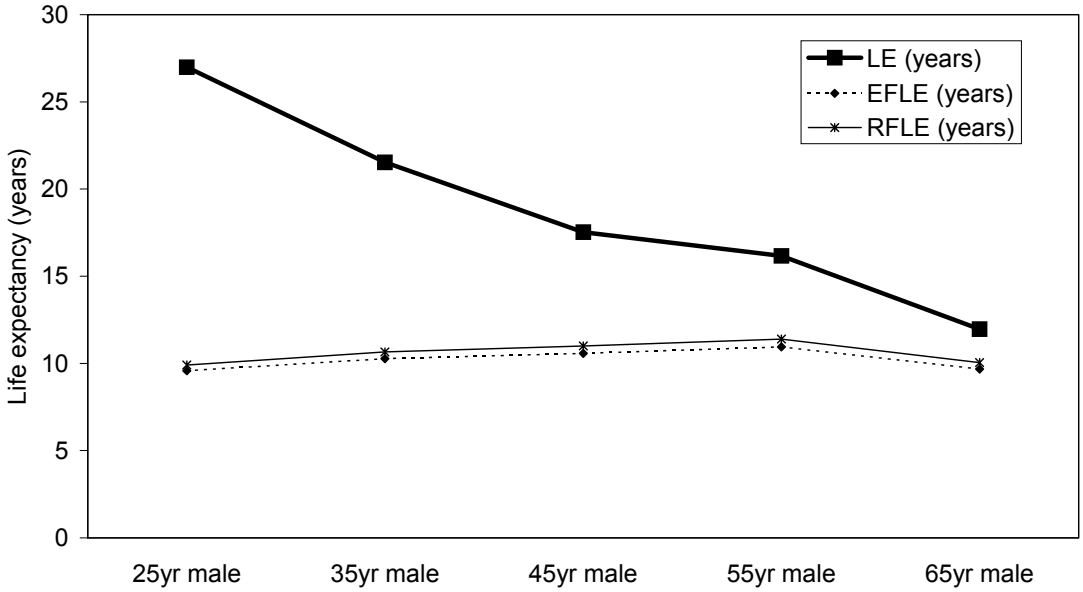

Figure 3a. Total life expectancy (LE), event-free life expectancy (EFLE), and reoperation-free life expectancy (RFLE) for males at different ages, based on the microsimulation model.

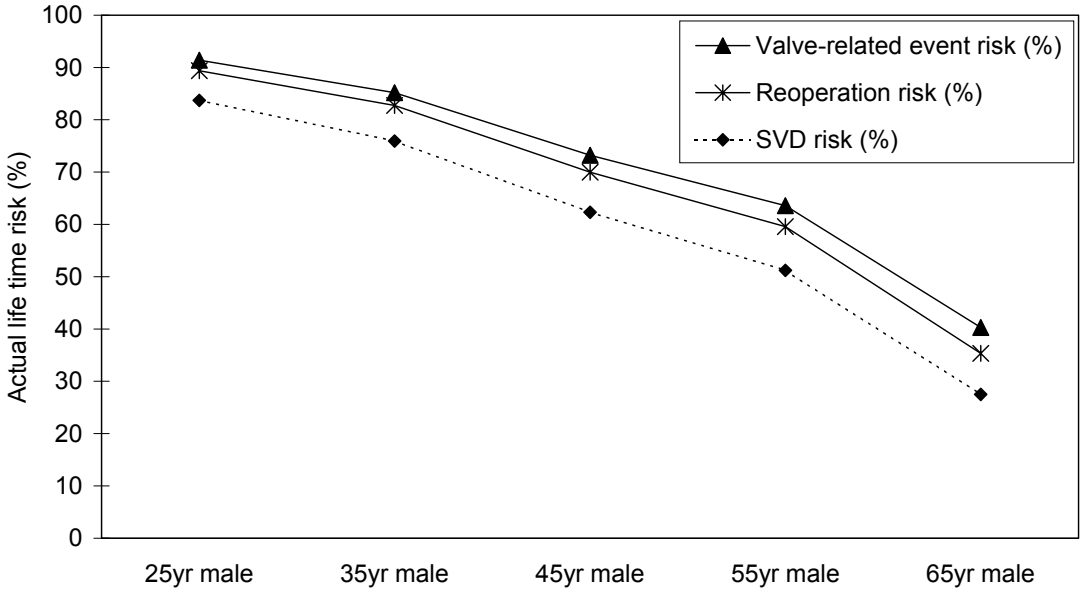

Figure 3b. Actual lifetime event risk, actual lifetime reoperation risk and actual life time structural valve failure (SVD) risk for males at different ages, based on the microsimulation model.

Microsimulation

Total LE, event-free LE, reoperation-free LE, actual lifetime event risk, and actual lifetime reoperation risk based on the microsimulation model and its assumptions is illustrated for males in different age groups in Figure 3a and 3b. For example, for a 45 year old male patient total LE was 17.6 years, event-free LE 13.8 years, reoperation-free LE 14.6 years, actual life-time event risk 46%, and actual life-time reoperation risk 39%.

In Figure 4 age-specific life time causes of death after ARR with a cryopreserved aortic allograft are displayed for males in different age groups, illustrating the importance of the individual factors that cause mortality after operation in patients at different ages.

Figure 5 shows the relative LE for patients in different age groups compared to healthy age-matched individuals, illustrating the impact of heart valve disease on total LE. For example, a 55-year-old male patient has a mean LE of 16.2 years, compared to 21.5 years in a healthy age-matched male in the general Dutch population. This 25% reduction in LE is mainly due to excess mortality caused by the heart valve disease (a reduction of 3.8 years) and to a minor extent to valve-related events (1.5 years).

Calculated cumulative 5-year-survival for a 51-year-old patient was 86%, while reported 5-year-survival from 3 studies in the meta-analysis varied from 83-93% [2, 20]. Long-term calculated survival for a 50-year-old male was 56% at 15 years postoperative, while overall survival in the Australian dataset was 60% at 15 years (95% CI 54-66 years) postoperative for patients with a similar mean age who received an allograft using several preservation and implantation techniques. In addition, 20-year calculated survival for a 50-year old patient was 34%, while 20-year reported cumulative survival of patients with a mean age in the United Kingdom dataset was 35% (95% CI 31-39%).

One-way sensitivity analyses showed that varying the individual parameters had little effect on the total LE in all age groups. This is displayed in Table II. The most pronounced effect was seen for structural valve failure in the youngest age group. Here, doubling and halving the hazard of structural valve failure did result in a considerable shift in event-free LE.

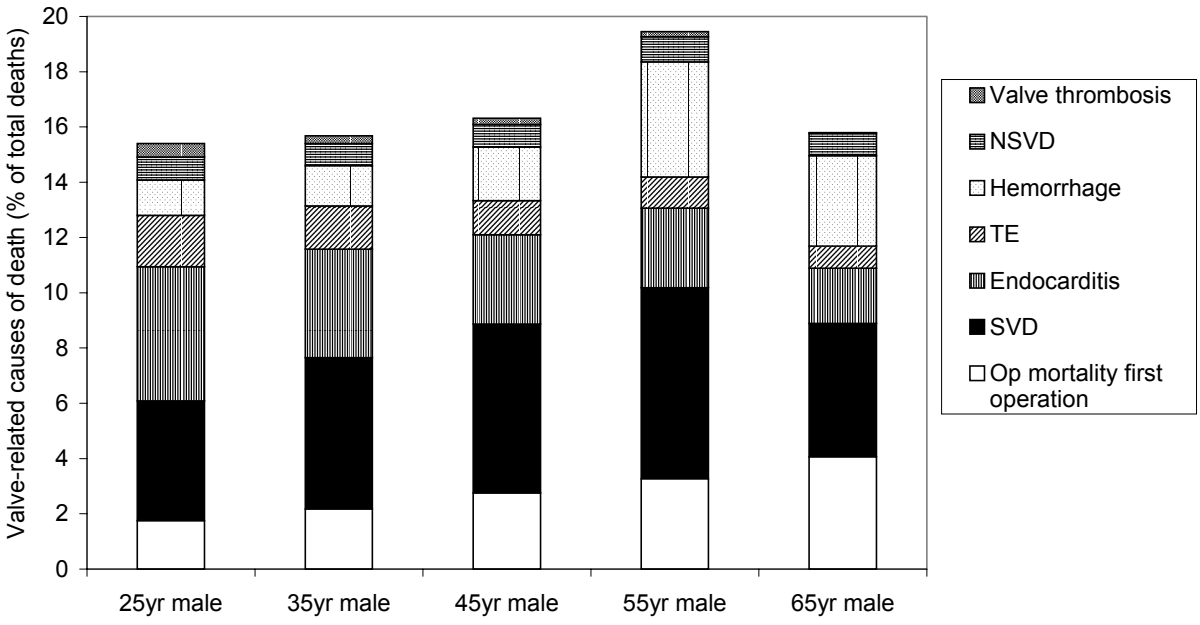

Figure 4. Age-specific distribution of valve-related causes of death (%) after ARR with a cryopreserved aortic allograft for males at different ages. Results are projected from the microsimulation model, which assumes that failed allografts will be replaced with mechanical valves which will produce events not directly associated with allograft usage but nevertheless part of the lifetime risk.

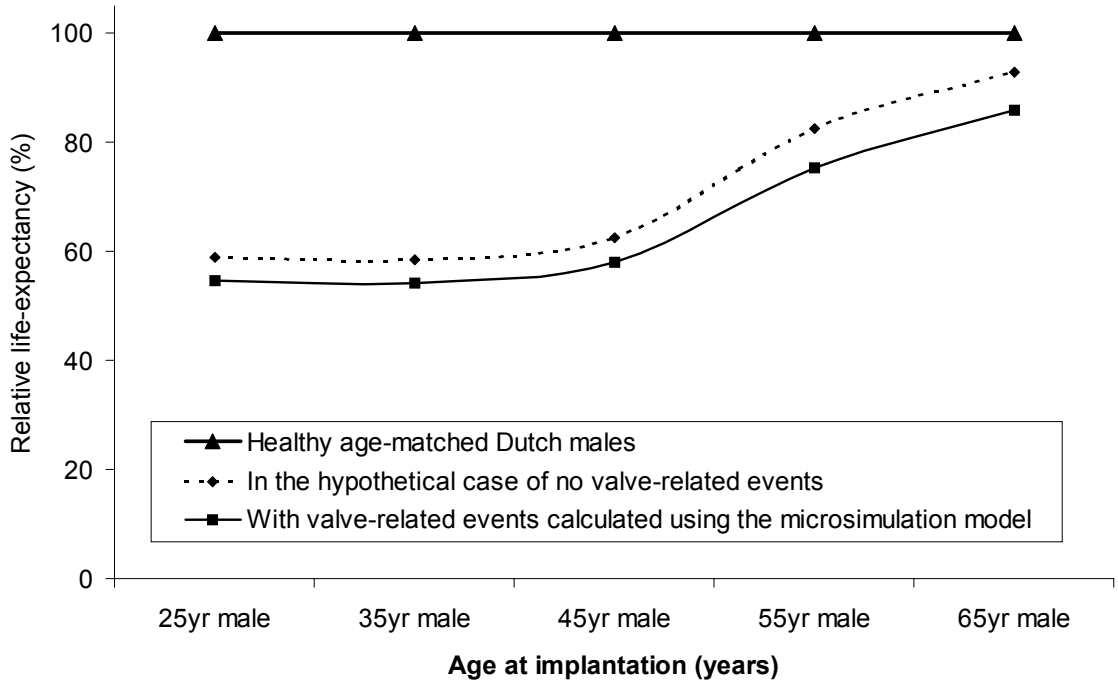

Figure 5. Relative LE (%) in patients at different ages after ARR with cryopreserved aortic allografts in comparison with age-matched healthy male individuals.

Table II. Summary of sensitivity analyses

Parameter	**Baseline estimate*** **(favorable-unfavorable)**	**LE in years** **(favorable-unfavorable)**	**Event-free LE in years** **(favorable-unfavorable)**
Operative mortality	2.6% (1.3-5.2%)	17.5 (17.8-17.1)	10.6 (10.7-10.3)
Median time to SVD (yrs)			
25-year-old	11.1 (22.2-5.6)	27.0 (27.5-26.8)	9.6 (16.4-5.1)
35-year-old	12.5 (25.0-6.3)	21.5 (22.1-21.2)	10.3 (16.1-5.6)
45-year-old	14.0 (28.0-7.0)	17.5 (18.1-17.1)	10.6 (14.7-6.1)
55-year-old	15.6 (31.2-7.8)	16.2 (16.8-15.5)	10.9 (14.1-6.6)
65-year-old	17.5 (35.0-8.7)	12.0 (12.3-11.2)	9.7 (11.0-6.6)
Thrombo-embolism	0.6 (0.3-1.07)	17.5 (17.6-17.5)	10.6 (10.8-10.3)
NSVD	0.5 (0.24-0.92)	17.5 (17.6-17.5)	10.6 (10.8-10.3)
Endocarditis	0.5 (0.25-0.9)	17.5 (17.6-17.4)	10.6 (10.7-10.3)
Bleeding	0.05 (0.001-0.28)	17.5 (17.5-17.5)	10.6 (10.6-10.4)

***** Baseline estimates and plausible ranges are expressed as % per patient year for a 45-year-old patient, except for operative mortality that is expressed in %, and SVD (=structural valve deterioration requiring reoperation) where the median time to SVD according to the Weibull model is given in years for patients at different ages; NSVD = non-structural valve deterioration requiring reoperation.

Discussion

Scarce information on structural valvular deterioration after ARR with cryopreserved aortic allografts is yet available. We therefore investigated whether long-term outcome after ARR with a cryopreserved aortic allograft can be estimated by combining a meta-analysis of both published and individual mid-term results [25] with microsimulation [26].

There is evidence for a strong effect of patient age on the durability of the aortic allograft [1, 4, 27]. Increased rates of structural valvular deterioration are associated with younger patient age. This could be explained by a stronger immune response against the allograft [28], by higher strains posed on the allograft due to the more active life style in young adults, or to non-viability of cryopreserved allografts resulting in the failure of repair processes [29]. Our study confirms the strong effect of patient age, and adds an important new fact: Although allografts are overall more durable than stented porcine bioprostheses, the effect of patient age on structural valve failure after allograft ARR closely resembles the effect of patient age on structural valve failure of a stented porcine bioprosthesis as was described previously using a similar age-dependent Weibull model [18]. This suggests that the dominant mechanisms underlying valve deterioration may be quite similar in these 2 valve types.

In the microsimulation model structural valvular deterioration is the most important cause of reoperation. In a 25-year old male patient it results in a huge lifetime reoperation risk of 89%, while in a 65-year old male patient this is reduced to 35%. This illustrates the need for improvement of the available valve substitutes, and well as the need for an objective clinical decision support system that allows selection of the most appropriate aortic valve substitute in the individual patient. It is obvious from our findings that in young adults other aortic valve substitutes should be seriously considered. The estimates of age-dependent freedom from structural valve failure in the model are based on 15 cases from studies with a mean follow-up of less than 4 years. This is an important limitation of the model. It is necessary to obtain more information on the relation between patient age and structural valve deterioration rates in order to estimate this relationship more accurately. Note that the 35% lifetime risk of reoperation in a 65-year-old patient is probably an overestimate of the true risk of reoperation. This is caused by the limited information on the relationship between patient age and structural valve deterioration rates on which the Weibull model is based and by the microsimulation model assumption that all patients with structural valve deterioration are reoperated. In true life a lot of older patients with structural valve deterioration will probably be less often reoperated on compared to younger allograft recipients.

Although valve-related events are common after ARR with a cryopreserved aortic allograft, they do not play a major role in reduction of total LE. As can be seen in figure 6, mortality is mainly caused by non-valve-related events and loss of LE compared to healthy age-matched individuals is mainly determined by excess mortality caused by cardiac disease secondary to the heart valve disease. The reduction of LE due to excess mortality is most pronounced in younger patients and decreases with age. This could be caused by a more aggressive form of aortic valve disease in the younger patients that requires replacement of the valve relatively early in life. On the other hand, in the older age groups a selection process takes place, and only the most vital patients with a relatively long LE are considered for AVR. An interesting finding in Figure 4 is that thrombo-embolism and bleeding are relatively important causes of valve related mortality in the younger patient groups. This is related to the fact that these patients require early replacement of their allograft and according to the microsimulation model then receive a mechanical prosthesis. In addition, the high mortality rate of endocarditis in the model (25%), results in the relatively large contribution of this valve-related event to mortality in general.

Comparison of survival as calculated with the microsimulation model showed a good agreement with reported short and long-term outcome after allograft aortic valve or root replacement [1, 2, 20, 21]. This indicates that survival calculated using the model is an accurate reflection of true LE after AVR. It is more difficult to compare structural valve failure outcome as calculated with the model to reported long-term durability of aortic allografts. Since surgical technique may affect outcome [30], we chose to include in the meta-analysis only reports on the experience with ARR, which is now the most commonly used surgical technique. An overview of different reports on allograft AVR using a variety of preservation and surgical techniques [31] shows an actuarial freedom from allograft failure varying from less than 20% to over 80% at 15 years postoperative. This reflects the numerous factors that play a role in the process of allograft structural failure [31, 32]. It is therefore difficult to make a straightforward comparison between the structural valve failure outcome of the microsimulation model and reported results with allografts that were implanted with different preservation and operative techniques. However, the Weibull model estimates of 15-year freedom from structural valve failure with cryopreserved aortic allografts are in good agreement with the reported 15-year freedom from structural valve failure in a subset of patients who had ARR with fresh or antibiotic sterilized allografts [1]. It suggests that the rate of structural valvular deterioration may not be very different between “homovital” or antibiotic sterilized versus cryopreserved allograft roots. This is supported by observations in

a recent update of a large series from O'Brien in Australia, where it is shown that long-term durability of allografts implanted with the subcoronary technique is similar in antibiotic stored and cryopreserved valves [21].

Microsimulation solves a number of problems that are encountered when using standard statistical methods to analyze outcome after cardiac surgery. While standard statistical techniques of outcome analysis provide information on a group level, microsimulation allows detailed insight into the outcome of patients according to age and gender. In addition it provides not only actuarial but also actual outcome after AVR. When the outcome is death, there is no difference between actuarial and actual estimates. However, when the outcome measure is a non-fatal complication actual estimates may be considered more meaningful than actuarial ones [33]. Microsimulation generates a large amount of virtual patient histories after AVR thus creating a virtual closed cohort of patients of patients with a certain age and gender. Because the life history of each patient in the population is known from the time of operation until the time of death, it is easy to quantify the (time to) occurrence of each of the events and the associated lethality. In addition microsimulation allows insight into repeatedly occurring events, enables hazards to vary over time, and deals adequately with competing risks. These are all clear advantages over the standard statistical techniques of outcome analysis. Therefore in our opinion microsimulation may provide a useful and valid statistical tool for estimating individualized long-term outcome after AVR. However, the microsimulation model is a simplification of real life, requires several structural assumptions, and highly depends on the quality of the input. These issues will be considered below.

Limitations to this study are first of all the limitations related to the meta-analysis. In a perfect world we would use a "super data set" with detailed and complete information on each patient including long-term follow up [13] to feed the microsimulation model. However, such data is not available yet for allograft ARR and therefore information on patients with different characteristics who were operated by different surgeons in different institutions was pooled. Although no clear heterogeneity was noted, patient age, the percentage of patients with pre-operative active endocarditis, and early mortality did vary among the reports in the meta-analysis. Other limitations to this study relate to the structural assumptions and simplifications that were implied by the microsimulation model. By structuring the clinical problem using microsimulation, simplification of reality can not be avoided. To date, the microsimulation model only considers age and gender when calculating prognosis, while a number of other factors are also important determinants of outcome, for example the need for concomitant

coronary artery surgery, etiology of the aortic valve disease, heart rhythm and left ventricular function [14, 34]. Therefore, it is yet unable to make predictions taking in account all these important additional risk factors. We estimated operative mortality in the microsimulation model to be 2.6% for a 45-year-old elective patient undergoing first time cardiac surgery, while in the meta-analysis pooled operative mortality was substantially higher. However, the very high operative mortality in some of the studies in the meta-analysis reflected the high percentage of patients with active endocarditis, higher NYHA-class, and prior cardiac surgery. Also, a constant hazard was assumed for thrombo-embolism, bleeding, endocarditis and non-structural valve failure. This risk may in fact depend on age and time since implantation. Further, if the virtual patient required reoperation following structural or non-structural valve deterioration, the allograft was by definition replaced by a mechanical valve. Finally, and as mentioned above, the age-specific Weibull function that describes the relation between patient age and structural valve failure was based on a limited number of observations and hence uncertain.

In conclusion, applying microsimulation to pooled results of outcome after ARR with cryopreserved aortic allografts allows a detailed insight into the factors that cause post-op morbidity and mortality. Joint effort is necessary to improve and regularly update the input of the microsimulation model in order to provide valid estimates of prognosis after ARR with cryopreserved aortic allografts in the future. The addition of other valve substitutes to the model would allow comparison of the performance of different valve substitutes in the individual patient and may be a useful tool for obtaining improved insight into the factors that determine outcome after AVR. An internet-based version of the model will become available in the near future for easy-access use by clinicians.

Acknowledgements

We thank Richard L. Prager, M.D. and LaWaun Hance, PA-C, for providing us with additional information on their study [24]. We further like to thank Mrs. Ada Matser- van den Berg and Mrs. Marijke Rozema for their excellent secretarial assistance.

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