CHAPTER VIII

AUTOGRAFT OR ALLOGRAFT AORTIC ROOT REPLACEMENT?

Autograft or allograft aortic root replacement?
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Abstract

Background: Limited information is available on outcome after autograft and allograft aortic root replacement. Therefore it may be difficult to make an objective choice between the 2 valve substitutes for patients who require aortic valve or root replacement. An evidence-based microsimulation model is used to calculate prognosis after autograft and allograft aortic root replacement.

Patients and Methods: Meta-analysis based data on outcome after autograft and allograft aortic root replacement were entered into a microsimulation model. For male patients at different ages (25-65 years) total life expectancy, event-free life expectancy and actual lifetime risks of experiencing valve-related events were calculated for both valve substitutes. The impact of valve-related events on outcome was calculated, and relative life expectancy compared to healthy age-matched individuals was assessed

Results: Estimated life expectancy after autograft and allograft aortic root replacement ranged from 27.4 and 27.0 years for a 25-year-old to 12.4 and 12.0 years for a 65-year-old male patient respectively. Event-free life expectancy was longer and lifetime event risk was smaller after autograft versus allograft aortic root replacement for young adult patients. Relative life expectancy after autograft and allograft aortic root replacement compared to healthy age-matched males was 56% and 55% at age 25 versus 89% and 86% at age 65. Valve-related events caused only a small decrease in relative life expectancy after autograft and allograft aortic root replacement (3.9% and 4.7% respectively at age 25).

Conclusions: Based on current evidence, for young adult patients calculated prognosis after aortic root replacement is slightly better with autografts compared to allografts. Relative life expectancy is markedly reduced compared to healthy age-matched Dutch males, especially in younger patients. The eradication of valve-related events results in only a small increase in relative life expectancy.

Key words: allograft, autograft, aortic root replacement, prognosis, microsimulation

Introduction

Autograft and allograft aortic root replacement (ARR) are both established surgical options for patients with aortic valve or root disease, associated with excellent hemodynamics, low thrombo-embolic rates, small endocarditis risk, and no need for anticoagulation. However, both valves have a limited durability. The autograft root is prone to dilatation, while allograft roots show a degenerative mode of failure that is clearly associated with younger patient age[1-4]. Also, the allograft that is usually implanted to reconstruct the right ventricular outflow tract in the autograft procedure has a limited life span[5, 6].

The choice between an autograft and allograft ARR is a complex one. It depends on multiple interrelated factors associated with the patient, the medical center, and the characteristics of the valve substitute. Moreover, evidence on the performance of autografts and allografts is limited, both with regard to size of the studies and the duration of follow-up in these studies.

This study describes the application a microsimulation model to calculate prognosis after ARR with autografts and allografts, and compare the outcome between the two valve substitutes.

Patients and Methods

Meta-analyses.

A previously reported meta-analysis of results after autograft ARR in adult patients[7] was updated with primary data from a large center in Oklahoma, USA[3]. In addition, a recent meta-analysis of outcome after cryopreserved aortic allograft ARR was used[8].

Events and outcome in all studies were defined according to Edmund's guidelines[9]. A combined estimate of events and outcome of these events was obtained by means of weighted pooling[10], or in case of few events per study, by direct pooling. For valvular thrombosis, thrombo-embolism, bleeding, endocarditis and non-structural valve deterioration (NSVD), annual occurrence rates were calculated. The incidence of structural valvular deterioration (SVD) requiring replacement or reintervention of the autograft, the allograft in pulmonary position after autograft procedure, and cryopreserved allograft in aortic position was described by a Weibull curve[11-13]. The parameters of the Weibull model were estimated using the pooled SVD data from the meta-analyses. Using data on the relationship between patient age and cryopreserved aortic allograft SVD from our own center and from Oklahoma, an age

parameter was estimated and added to the allograft Weibull model, allowing for age-specific calculations for SVD.

Microsimulation model

Figure 1 describes the microsimulation model that was previously developed to simulate the outcome of patients after aortic valve replacement (AVR) or ARR[7,8,14-16]. The basic assumption of the model is that a disease follows a course in time that can be adequately characterized by a number of discrete health states. After AVR or ARR the patient can either die as a result of the operation, or stay alive. If the patient stays alive, he or she remains at risk of developing valve-related events for the rest of his or her life. Eventually the patient will die of either valve-related or non-valve-related causes.

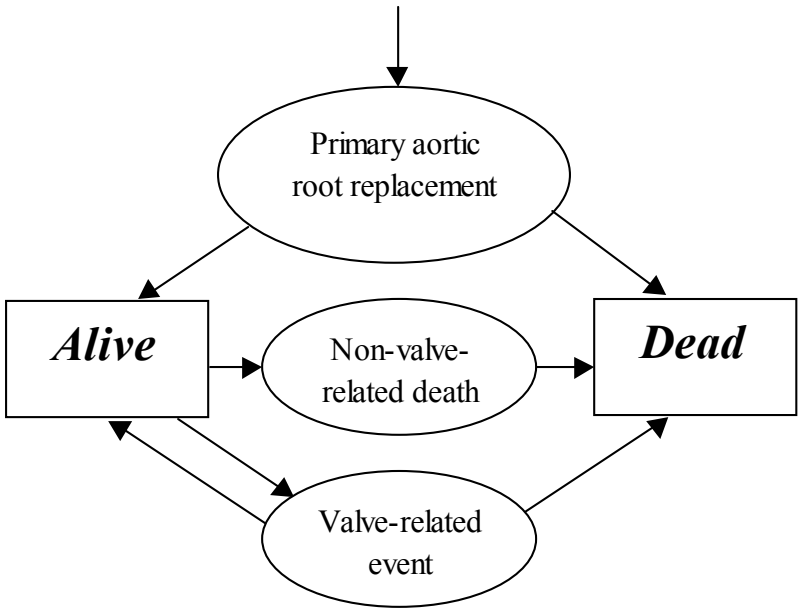

Figure 1. Schematic representation of different health states of a patient after autograft or allograft ARR as implemented in the microsimulation model.

From microsimulation conclusions can be drawn for a specific patient profile by performing calculations of random individual life histories of patients[12]. These calculations are repeated a number of times, thus producing a simulated or 'virtual' closed cohort of patients with similar characteristics. From this cohort, the mean outcome can be calculated and detailed insight can be obtained into the factors that affect outcome.

The information on event-incidence and event-related mortality after autograft and allograft ARR from the meta-analyses was entered into the microsimulation model. Ten thousand 'virtual' life histories were calculated for males at different ages by randomly

drawing the age of death from the Dutch general population life table. Since there is a higher mortality rate among patients after AVR compared to the general population that cannot solely be attributed to valve-related events[17-19], we multiplied the age and gender specific mortality hazard of the general population with an age and gender-related factor for excess mortality, based on previous work [7,11,15,20]. An overview of the final input of the microsimulation model including additional assumptions that were made with regard to the occurrence and lethality of valve-related events are displayed in the Appendix.

For male patients at five different ages (25, 35, 45, 55 and 65 years at the time of operation) total life expectancy, event-free life expectancy, and actual life time risks of the various valve-related events and reoperations were calculated for both valve substitutes. The impact of valve-related events on mortality was calculated by repeating the microsimulation calculations for the hypothetical case of total freedom from valve-related events. Relative life expectancy after autograft or allograft ARR (with and without valve-related events) compared to healthy age-matched individuals was calculated in order to investigate the impact of valve-related events.

To investigate validity of microsimulation-based estimates of outcome, estimated survival was compared to reported survival in the studies in the meta-analysis. In addition, estimated survival after autograft ARR was compared to reported survival after autograft AVR or ARR from Ross' pioneer experience[21]. Estimated survival after allograft root replacement was compared to reported survival after allograft AVR or ARR in 2 large dataset of patients who had AVR or ARR with fresh, antibiotic stored or cryopreserved allografts that were implanted using several different surgical techniques[1,2].

To investigate the effect of uncertainty in the parameter estimates on (event-free) life-expectancy, a one-way sensitivity analysis was performed. Parameters that were estimated using linearized annual occurrence rates (thrombo-embolism, bleeding, endocarditis and non-SVD) were ranged between 95% confidence limits, which were calculated using the method described by Breslow and Day for Poisson-distributed variables[22]. The estimates for operative mortality and SVD (ln sigma parameter of Weibull model) were ranged from half to double the baseline parameter values[23].

Results

Meta-analyses

Table 1 shows the pooled results of the autograft and allograft meta-analyses. Figure 2 displays the Weibull function for autograft SVD requiring reoperation. The parameters of this Weibull function were based on the 10 reported cases of autograft SVD from the meta-analysis (see Appendix). Estimated median time to autograft SVD was 23 years.

Table 1. Overview of pooled patient characteristics and outcome after ARR with autografts and cryopreserved allografts based on meta-analysis.

	Autograft	**Allograft**
Study period	1987-2000	1985-2000
Number of studies	5[3, 7, 27-29]	5[3, 8, 30-32]
Number of patients	534	629
Number of patient years	1574	1860
Mean age (range)	36 years (16-68 years)	51 years (13-77 years)
Male-to-female ratio	2.8	3.3
Concomitant CABG	3%	9%
Early mortality (N)	19 (3.6%)	59 (9.4%)
Late mortality (N)	9	36
Valve thrombosis (N)	0 (0%/patient year)	0 (0%/patient year)
Thrombo-embolism (N)	4 (0.3%/patient year)	11 (0.6%/patient year)
Late bleeding (N)	0 (0%/patient year)	1 (0.05%/patient year)
Endocarditis (N)	4 (0.3%/patient year)	11 (0.5%/patient year)
NSVD(N)	3 (0.2%/patient year)	10 (0.5%/patient year)
SVD (N)	10 (see Figure 2)	15 (see Figure 4)
Failure allograft in RVOT (N)*	8 (see Figure 3)	Not applicable

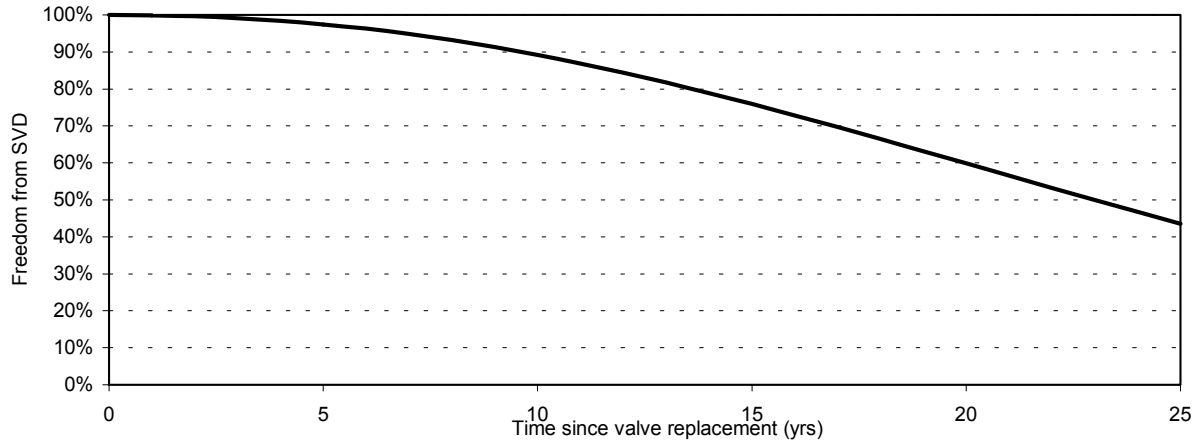

Figure 2. Meta-analysis-based estimated freedom from autograft SVD requiring reoperation, using a Weibull function.

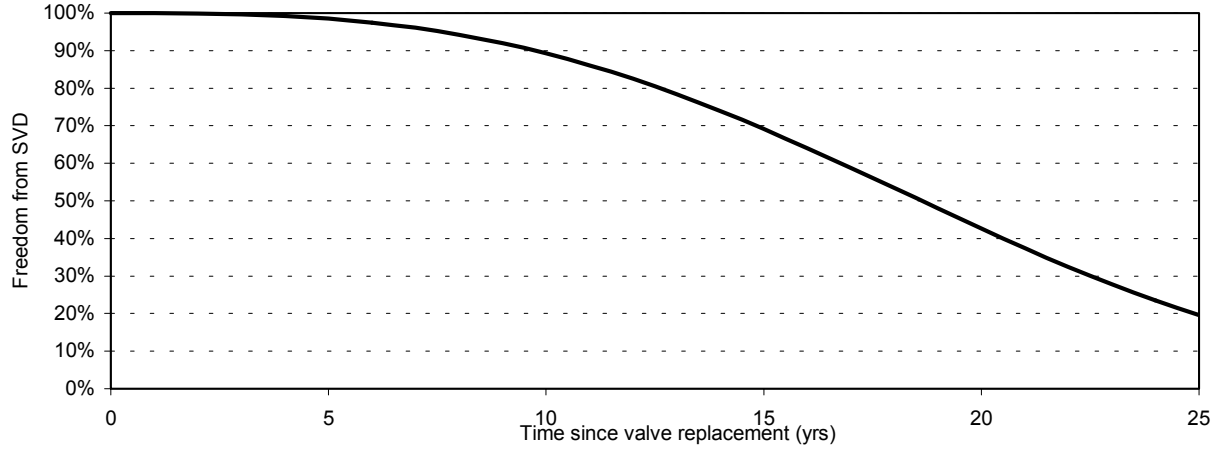

Figure 3. Meta-analysis-based estimated freedom from SVD of the allograft in the right ventricular outflow tract after the autograft procedure, using a Weibull function

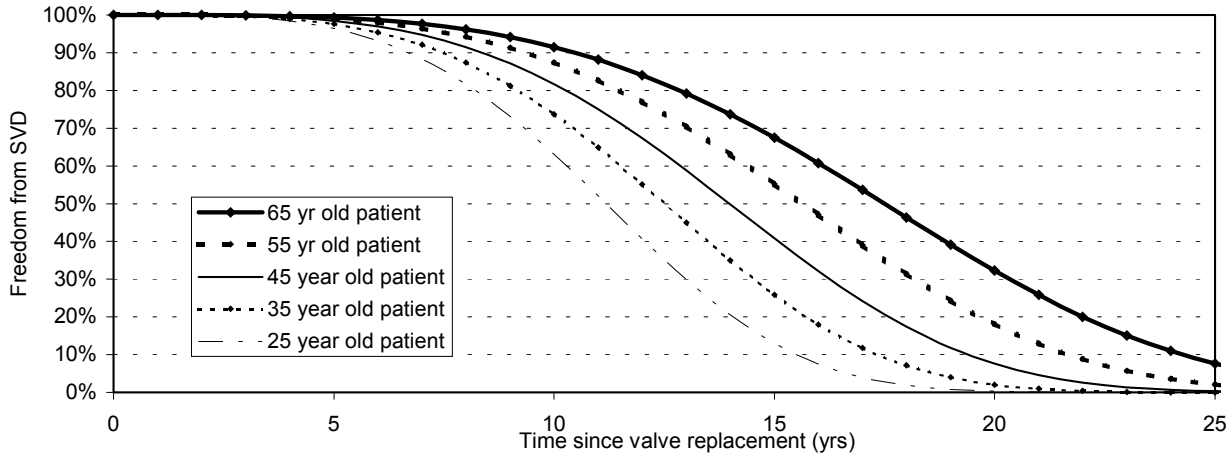

Figure 4. Meta-analysis-based estimated Weibull function of age-specific freedom from cryopreserved aortic allograft SVD requiring reoperation.

Figure 3 shows the calculated freedom from reoperation and reintervention for SVD of the allograft implanted in the right ventricular outflow tract to replace the pulmonary valve in the autograft procedure. The parameters of this Weibull function were based on the 8 reported cases of SVD of the allograft in the right ventricular outflow tract after autograft procedure from the meta-analysis (Appendix). Estimated median time to reoperation or reintervention for SVD of the allograft in pulmonary position was 18.5 years. Figure 4 displays the age-specific Weibull function for cryopreserved allograft SVD requiring reoperation for patients aged 25 to 65 years at the time of operation. The parameters of this age-specific Weibull function were based on the 15 reported cases of SVD of the cryopreserved allograft in aortic position from the meta-analysis and are displayed in the appendix. Estimated median time to reoperation for allograft SVD ranged from 11.1 years in a 25-year-old to 17.5 years in a 65-year-old patient.

Microsimulation

Total life expectancy after autograft and allograft ARR is displayed in Figure 5 for male patients age 25 to 65 years at the time of operation.

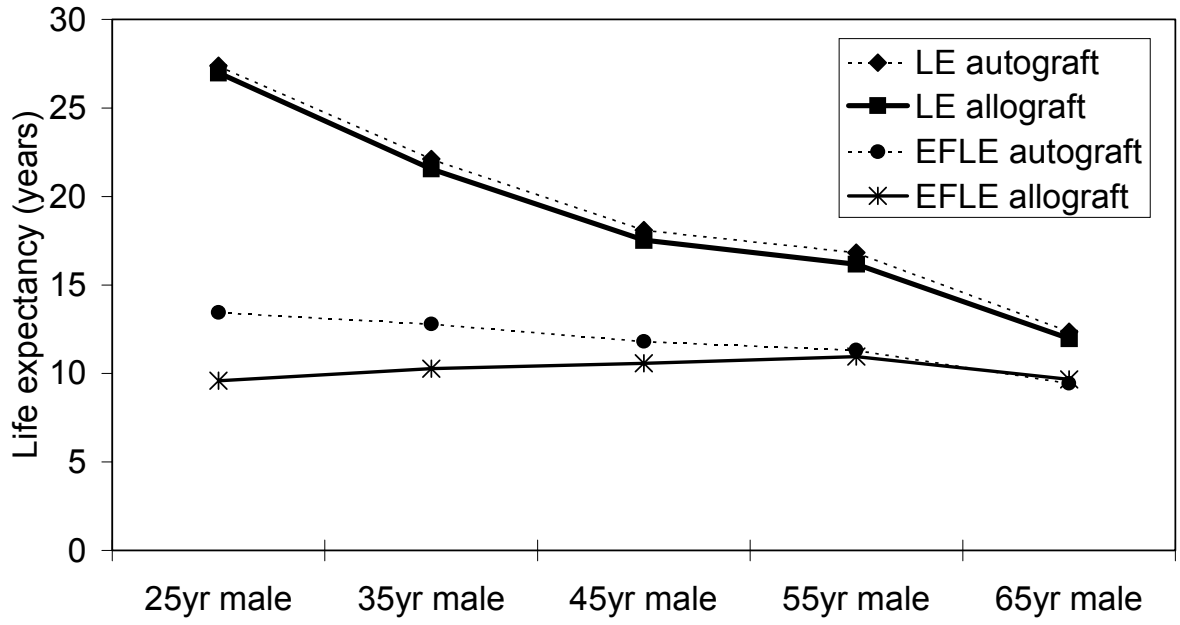

Figure 5. Life expectancy (LE) and event-free life expectancy (EFLE) of male patients at different ages (25-65 years at the time of operation) after autograft or allograft ARR.

For example, a 45-year-old male patient had an estimated life expectancy of 18.1 years after autograft ARR and 17.5 years after allograft ARR. Event-free life expectancy after autograft and allograft ARR is also displayed in Figure 5 for male patients aged 25 to 65 years at the time of operation. Especially in younger patients event-free life expectancy was markedly better after autograft ARR compared to allograft ARR. For example, event-free life expectancy of a 25-year-old male patient after autograft ARR was 13.4 years compared to 9.6 years after allograft ARR. The difference in event-free life expectancy decreased with increasing age of the patient, and was similar in patients over the age of 55 years.

In Figure 6 the actual lifetime risk of experiencing at least one major valve related event (Figure 6a) or at least one aortic valve reoperation (Figure 6b) after autograft and allograft ARR is displayed for male patients age 25 to 65 years at the time of operation. The lifetime event risk was considerable in young patients (in 25-year-old male patients 86% for autografts and 91% for allografts), and decreased with age. In the younger age groups autograft ARR was associated with a lower life time risk of at least one major valve-related event compared to allograft ARR, although the absolute risk difference disappeared with older age.

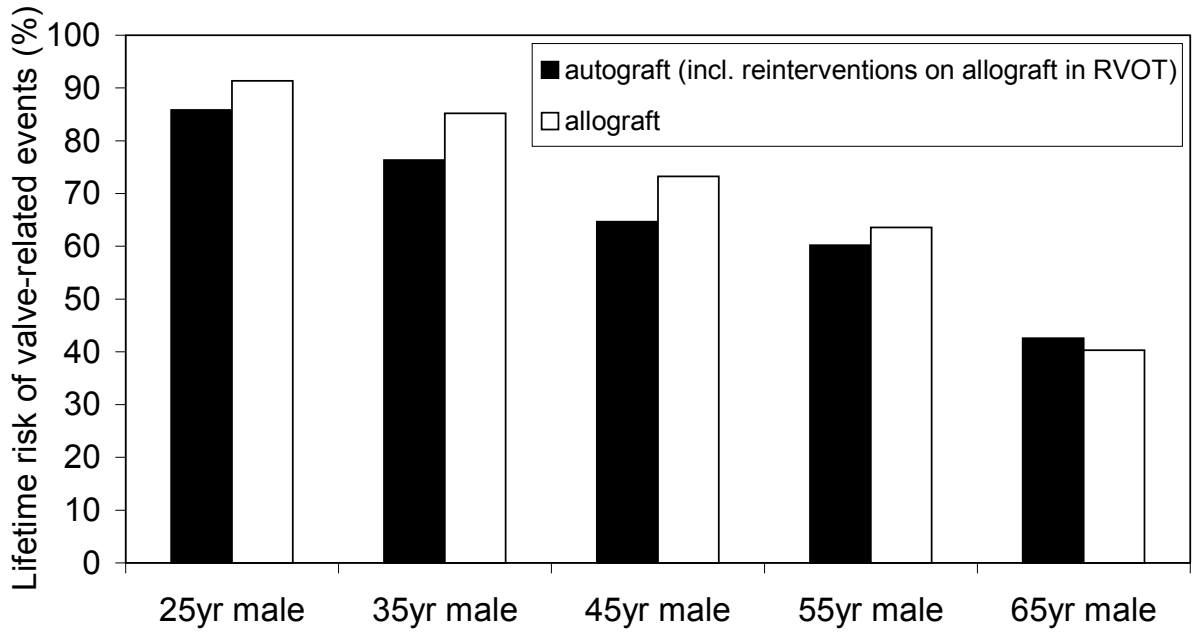

Figure 6a. Actual lifetime risk of experiencing at least 1 major valve-related event, for male patients at different ages (25-65 years at the time of operation).

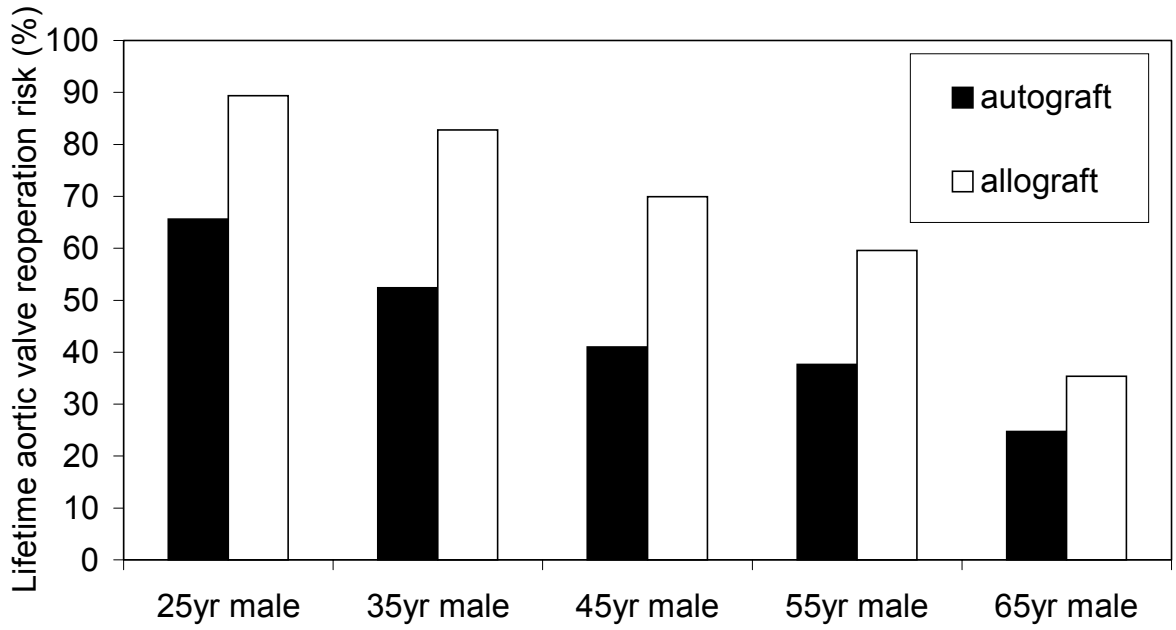

Figure 6b. Actual lifetime risk of experiencing at least 1 reoperation for SVD of the neo-aortic valve , for male patients at different ages (25-65 years at the time of operation).

Figure 7 illustrates the effect of valve-related events on relative life expectancy of male patients after autograft and allograft ARR compared to age-matched Dutch males. Life expectancy of patients after autograft and allograft ARR was markedly reduced (for example 45% for both valve types at age 25) compared to age-matched males, especially in the younger age groups. This reduction in life expectancy decreased with increasing patient age to 11% for autograft and 14% for allograft ARR at age 65. The hypothetical situation of total freedom from valve-related events resulted in a small increase in life expectancy of approximately 3-5%.

Calculated survival after autograft ARR for a 36-year-old male patient (mean age of autograft patients in meta-analysis) was 91% at 7 years, while observed survival in the meta-analysis ranged from 85% to 96% at 7 years postoperative. Twenty-year calculated survival after autograft ARR was 60%, while reported 20-year actuarial survival after autograft AVR or ARR was 61% (95% CI 53-69%)[21]. Calculated survival after allograft aortic root for a 51-year-old male patient (mean age of allograft patients in meta-analysis) was 83% at 7 years, while observed survival in the meta-analysis ranged from 72% to 85% at 7 to 8 years postoperative. Twenty-year calculated survival after allograft ARR was 35%, while reported

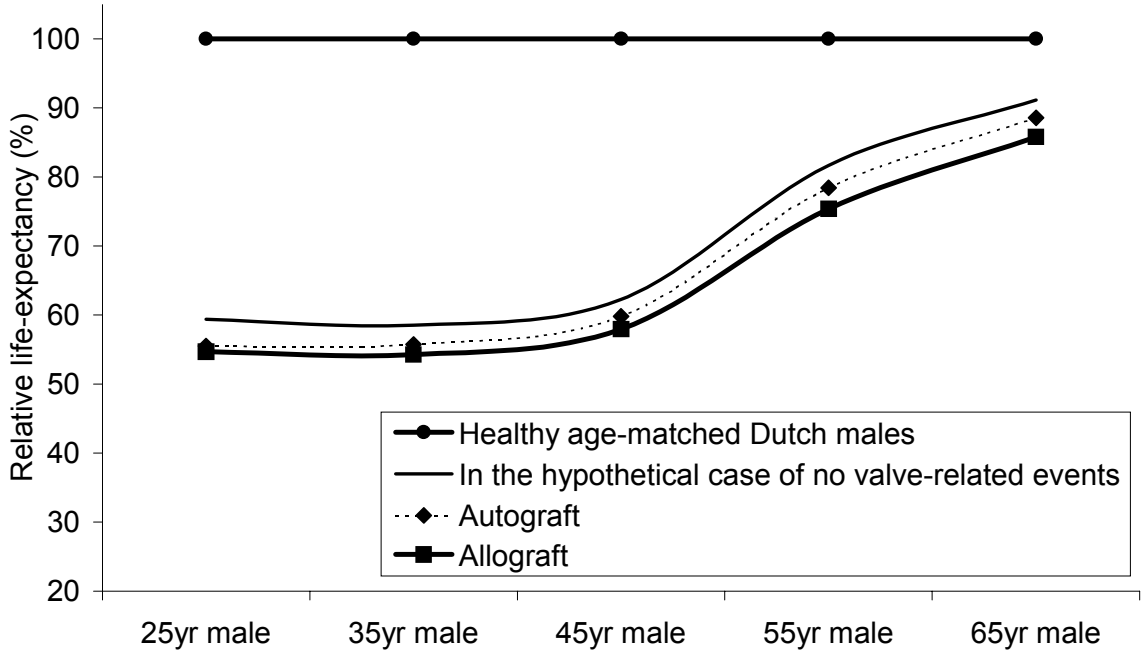

Figure 7. Relative life expectancy (%) of male patients at different ages (25-65 years at the time of operation) compared to healthy age-matched Dutch males.

20-year cumulative survival after allograft AVR or ARR was 35% (95% CI 31-39%)[1] and 42% (95% CI 34-50%)[2].

Table 2 displays the results of the sensitivity analyses for patients aged 25, 45 and 65 years at the time of operation. Varying the individual estimates of valve-related events had little effect on total life expectancy. Varying operative mortality and SVD caused the largest change in life expectancy. The effect on event-free life expectancy of varying the baseline estimates of valve-related events was most pronounced for SVD, especially in the younger age groups. For example, by varying the baseline hazard for allograft SVD the event-free life expectancy of a 25-year-old male patient ranged from 9.7-15.0 years after autograft ARR and from 5.1-16.4 years after allograft ARR. Also, for autograft patients variation of the baseline hazard of pulmonary allograft SVD resulted in a considerable shift in event-free life expectancy. For example, event-free life expectancy of a 25-year-old male patient ranged from 8.2 years after doubling the baseline hazard, to 16.9 years after halving the hazard for pulmonary allograft SVD.

Table 2. Results of sensitivity analyses. Life expectancy (LE) and event-free life expectancy (EFLE) are displayed in years for patients aged 25, 45 and 65 years at the time of operation.

	Autograft		Allograft	
	LE (years)	**EFLE (years)**	**LE (years)**	**EFLE (years)**
Baseline estimate				
Age 25	27.4	13.4	27.0	9.6
Age 45	18.1	11.8	17.5	10.6
Age 65	12.4	9.4	12.0	9.7
Operative mortality				
Age 25	26.9-27.6	13.2-13.5	26.5-27.2	9.4-9.7
Age 45	17.6-18.4	11.5-12.0	17.1-17.8	10.3-10.7
Age 65	11.9-12.6	9.1-9.6	11.5-12.2	9.3-9.9
SVD aortic valve				
Age 25	26.4-28.0	9.7-15.0	26.8-27.5	5.1-16.4
Age 45	17.6-18.3	9.0-12.9	17.1-18.1	6.1-14.7
Age 65	12.0-12.5	7.6-10.0	11.2-12.3	6.6-11.0
SVD allograft RVOT				
Age 25	27.1-27.5	8.2-16.9	Not applicable	Not applicable
Age 45	17.9-18.2	7.8-13.7		
Age 65	12.3-12.4	6.9-10.4		
NSVD				
Age 25	27.3-27.4	13.0-13.6	27.0-27.0	9.4-9.7
Age 45	18.0-18.1	11.5-11.9	17.5-17.6	10.3-10.8
Age 65	12.3-12.4	9.2-9.5	11.9-12.0	9.4-9.8
Endocarditis				
Age 25	26.9-27.6	12.9-13.7	26.7-27.2	9.4-9.7
Age 45	17.9-18.2	11.4-12.0	17.4-17.6	10.3-10.7
Age 65	12.2-12.4	9.2-9.6	11.9-12.0	9.4-9.8
Thrombo-embolism				
Age 25	27.3-27.5	12.9-13.7	26.9-27.1	9.3-9.8
Age 45	18.0-18.1	11.4-12.0	17.5-17.6	10.3-10.8
Age 65	12.3-12.4	9.2-9.6	11.9-12.0	9.4-9.9
Bleeding				
Age 25	27.4-27.4	13.4-13.4	27.0-27.0	9.5-9.6
Age 45	18.1-18.1	11.8-11.8	17.5-17.5	10.4-10.6
Age 65	12.4-12.4	9.4-9.4	12.0-12.0	9.5-9.7

Discussion

The perfect aortic valve substitute is easy to implant, has excellent hemodynamics, lifelong durability, and zero risk of thrombosis, thrombo-embolism, NSVD and endocarditis. Unfortunately, we are still in search of this valve substitute. Autografts and allografts were introduced in the 1960's as an alternative to mechanical valves and stented bioprostheses[24, 25]. Although implantation of autografts and allografts is technically more challenging, there are major advantages over mechanical prostheses and stented bioprostheses with regard to hemodynamic profile, endocarditis and thrombo-embolic event rates. On the down side, both autografts and allografts have a limited durability[1-4]. Currently, reported evidence of autograft and allograft SVD is limited. Reported series are relatively small, with a limited follow-up. Also, surgical and preservation techniques vary between centers. In order to overcome these challenges, we employed meta-analysis and microsimulation (calculate long-term outcome based on current mid-term results).

Our analyses suggest that prognosis is slightly better after autograft versus allograft ARR in the younger age groups. This is mainly due to the better durability of the autograft compared to the allograft root, especially in younger patients. In addition autograft ARR was associated with lower thrombo-embolic, endocarditis, and NSVD event rates compared to allograft ARR. On the other hand, outcome after autograft ARR may be negatively influenced by SVD of the allograft in the right ventricular outflow tract. Current evidence on the durability of the allograft in the right ventricular outflow tract is very limited but appears to be better compared to the durability of allografts in aortic position[5]. This is confirmed by the estimated freedom from allograft SVD in this study. Median time to pulmonary allograft valve deterioration was 18 years, while median time to aortic allograft valve deterioration was 11.1 years in a 25-year-old and 17.5 years in a 65-year-old patient. There was no evidence of an effect of patient age on SVD of the allograft in the right ventricular outflow tract. This is not surprising, since the estimates of SVD of the allograft in pulmonary position are based on only 8 cases. No evidence of mortality resulting from deterioration of the allograft in the right ventricular outflow tract could be detected from the meta-analysis. Therefore we assumed a 2% mortality rate related to deterioration of the pulmonary allograft. For patients aged 25 years at the time of the primary operation, SVD of the allograft in pulmonary position requires reintervention in approximately 54%. This has an important impact on event-free life expectancy. Therefore, improvement of the durability of the valve substitute in the right

ventricular outflow tract would also improve event-free survival after the autograft procedure considerably.

When carefully examining the shape of the autograft and allograft aortic root SVD curves, there appears to be a major difference in the mode of failure between the two valve substitutes. Autograft aortic roots are prone to dilatation, which causes aortic regurgitation and may require reoperation fairly soon after the initial operation. This hazard does not (yet) increase considerably with time. No evidence for degeneration or calcification or a relation to patient age is (yet) observed. On the other hand, cryopreserved aortic allograft roots have a degenerative mode of deterioration with or without calcification that does show an increase in hazard over time and has an evident relation to patient age. The surgical consequences of these different modes of failure with regard to the difficulty of the following reoperation may very well indirectly influence the choice for a particular valve substitute for future patients. We acknowledge that the Weibull estimates for autograft and allograft SVD are based on a limited number of observations (10 and 15 respectively) during a limited follow-up time (maximum of 12.2 and 12.8 years). Therefore, there is a considerable amount of uncertainty with regard to these estimates. Since SVD is the most important valve-related factor with regard to outcome, a relatively small change in the estimates of SVD may cause important changes in patient prognosis as is evidenced by the results of the sensitivity analyses.

The choice between an autograft and an allograft for the replacement of the aortic root does not have a major impact on life expectancy of patients. Valve-related events are only of limited influence on relative life expectancy, especially in the younger age groups. It implies that improvement of the current aortic valve substitutes will only result in a small improvement of life expectancy. Why life expectancy of patients after AVR or ARR is considerably reduced compared to the healthy age-matched population, can only be speculated upon and requires extensive further investigation.

The methods that were employed in this study have several limitations that should be taken into account. The input of the microsimulation model is based on pooled short-term and mid-term data from different centers, surgeons and patients. A constant hazard was assumed for several valve-related events, although these factors may in fact be dependent on age and time. Also, the assumption was made that in case of reoperation the autograft was replaced by an allograft, and the allograft was replaced by a mechanical valve (with the exception of reoperation for endocarditis where the allograft was replaced by another allograft root). The choice for a particular aortic valve substitute in case of reoperation may have an important effect on prognosis and requires further investigation. The excess mortality hazards of patients

after AVR compared to the general age- and gender-matched population were obtained from previous work on survival after implantation with mechanical monoleaflet prostheses and stented bioprostheses[15,20]. These excess mortality estimates were validated using reported long-term experiences with autografts and allografts for the replacement of the aortic valve or root, and good agreement was found[1,2,21]. Therefore they are likely to be a good reflection of reality. Finally, it should be noted that survival after AVR or ARR does not only depend on age and gender, but also on many other factors like the presence of coronary heart disease and pre-operative NYHA class[19,26]. These factors were not yet taken into account in the microsimulation model.

In conclusion, microsimulation offers an objective tool to study expected outcome after autograft or allograft ARR in the individual patient. Of course our results are only applicable to those patients in whom both valve types are a good option. Based on current evidence, for young adult patients the use of an autograft to replace the aortic root is associated with slightly better calculated outcome compared to an allograft.

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Appendix: Input microsimulation model

Operative mortality

2.6% at age 40, increasing with age (OR 1.022/year) and with each reoperation (OR 1.7).

Valve related events after autograft ARR

Valve thrombosis: none. Thrombo-embolism: Linearized annual occurrence rate (LOR) 0.3%/patient year, mortality rate 7%. Bleeding: none. Endocarditis: LOR 0.3%/patient year, direct mortality rate 25%, reoperation rate 100%, valve replacement by allograft root. NSVD: LOR 0.2%/patient year, direct mortality rate 0%, reoperation rate 100%, valve replacement by allograft root. SVD: Weibull function with the following parameters: $\beta = 2.162$ and $\Sigma = 27.237$, direct mortality rate 0%, reoperation rate 100%, valve replacement by allograft. These estimates were based on 10 reported cases of autograft SVD from the meta-analysis, occurring at 0.2, 0.8, 1,3, 1.8, 1.8, 2.7, 4.5, 5.0, 6.0, and 6.7 years after the initial operation. Deterioration of the allograft in the right ventricular outflow tract: Weibull function with the following parameters: $\beta = 2.911$ and $\Sigma = 21.126$, direct mortality rate 2%, reintervention 100%. These estimates were based on 8 reported cases of pulmonary allograft SVD from the meta-analysis, occurring at 0.8, 2.1, 3.1, 4.7, 8.1, 8.5, 8.9, and 10.2 years after the initial operation. In cases where autograft reoperation preceded deterioration of the allograft in pulmonary position it was assumed that the allograft in pulmonary position was automatically replaced by a new allograft during the replacement of the autograft.

Valve related events after cryopreserved allograft ARR

Valve thrombosis: none. Thrombo-embolism: LOR 0.6%/patient year, direct mortality rate 10%. Bleeding LOR 0.05%/ patient year, direct mortality rate 7% at age 40 and increasing with age (OR 1.0345/year). Endocarditis: LOR 0.5%, direct mortality rate 25%, reoperation rate 100%, valve replacement by allograft root. NSVD: LOR 0.5%/patient year, direct mortality rate 0%, reoperation rate 100%, valve replacement by bileaflet mechanical valve. SVD: age-dependent Weibull function with the following parameters $\beta = 3.669$, $\Sigma = 27.237$ and age 0.0112, direct mortality rate 0%, reoperation rate 100%, replacement by bileaflet mechanical valve. These estimates were based on 15 reported cases of autograft SVD from the meta-analysis, occurring at 2.7, 4.4, 4.7, 4.7, 4.9, 6.0, 6.4, 6.5, 6.7, 7.5, 8.1, 8.4, 8.5, 8.9, and 10.2 years after the initial operation.

Excess mortality

Hazard ratio for mortality for selected age groups compared to general Dutch population

Age (years)	HR Males	HR Females
25	8	7
35	6	7
45	3.6	4.2
55	1.5	2.8
65	1.1	2.2
75	1	1.3

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