CHAPTER VI

ESTIMATING EVENT-FREE LIFE EXPECTANCY AFTER AUTOGRAFT AORTIC ROOT REPLACEMENT IN ADULTS: APPLICATION OF META-ANALYSIS AND MICROSIMULATION

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Abstract

Background: Autograft aortic root replacement is an established therapeutic option for young adults with aortic valve disease. Unfortunately, most series are small with a limited follow-up. Meta-analysis and microsimulation modeling were used to predict long-term outcome based on currently available mid-term data.

Methods: We combined our center's experience with autograft aortic root replacement in 85 adult patients in a meta-analysis with reported results of 3 other hospitals. The outcomes of this meta-analysis were entered in a microsimulation model, calculating (event-free) life expectancy after autograft aortic root replacement.

Results: The pooled results comprised 380 patients with a total follow-up of 1077 patient years (range 0-11.4 yrs). Mean age was 37 years (range 16-68 yrs). Male/female ratio was 2.7. Operative mortality was 2.6% (N=10), during follow-up 6 more patients died. Linearized annual risk estimates were 0.5% for thrombo-embolism, 0.3% for endocarditis and 0.4% for nonstructural valve failure. Structural autograft failure requiring reoperation occurred in 6 patients, and a Weibull function was constructed accordingly. No other valve-related events were observed. Using this information, the microsimulation model predicted age and gender specific mean, reoperation-free and event-free life expectancy.

Conclusions: Based on current evidence the calculated average autograft related reoperation-free life expectancy is 16 years. The combination of meta-analysis and microsimulation provides a promising and powerful tool for estimating long-term outcome after aortic valve replacement. It can be useful in patient counseling, to determine the preferred treatment strategy for the individual patient.

Introduction

In 1967 Ross was the first to describe the use of the pulmonary autograft in aortic valve replacement [1]. Autograft aortic root replacement, also known as the modified Ross procedure, was introduced in 1986 [2] and has become an established therapeutic option for young adults with aortic valve disease. Recently, several centers have reported excellent mid-term results [3-7], and our center shares this experience [8]. There is however concern on the long-term durability of the autograft root [9,10] but based on current evidence from the relatively small reported series with a limited follow-up it is difficult to draw conclusions on longer-term outcome. In this paper we introduce the combined use of meta-analysis and Monte Carlo type microsimulation [11] as a method to predict life expectancy and event-free life expectancy after autograft aortic root replacement.

Materials and Methods

Meta-analysis

Rotterdam experience. All patients who receive a human tissue valve (autograft or allograft) at our center are monitored prospectively over time by means of yearly telephone surveys and standardized serial echocardiography. Data are entered in a relational database (Microsoft Access for Windows 97, Redmond, U.S.A.). Data from all 85 adult patients (≥16 years at time of operation) who underwent an autograft procedure between November 1988 and February 2000 were analyzed. Aortic root replacement with reimplantation of the coronary arteries and replacement of the pulmonary valve with a cryopreserved pulmonary allograft was the surgical technique used in all patients. Mean follow-up was 4.2 years (SD 2.6; total follow-up 358 patient years) and 99% complete at the closing date of the study (June 1, 2000). Cumulative survival was calculated using the Kaplan-Meier method [12].

Literature search. We performed a literature search of the PUBMED and MEDLINE databases for the period starting from January 1996 until September 1999. This was done in order to obtain the most recent reports with the longest follow-up. Terms used for the search were both MeSH terms and the text words “autograft”, “root”, “aortic valve” and “Ross”. All titles and abstracts were screened for study design (reports of clinical experience with autograft aortic root replacement), completeness of follow-up (>90%), surgical technique (modified Ross or autograft procedure), study size (N>40; reflecting the experience at that particular center), etiology of valve disease similar to our patient population (not with

predominant rheumatic valve disease), and patient age (16 years and older). The references in the remaining papers were cross-checked for other potentially relevant studies.

Data extraction and analysis. The selected published papers were reviewed and patient characteristics and results of each study were tabulated in a spreadsheet. The authors of the selected published 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 [13]. Heterogeneity between the different studies was investigated by means of sensitivity analysis. A combined estimate of outcome was obtained by means of direct pooling, since the studies were small and there were only few events. For valvular thrombosis, thrombo-embolism, bleeding, endocarditis and non-structural valve failure linearized annual event rates were calculated. The risk 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 [11,14,15]. The parameters of the Weibull model were estimated using the pooled structural valve failure data from the meta-analysis.

Microsimulation model

The basic assumption of the simulation model is that a disease follows a course in time that can be adequately characterized by a number of discrete states. After aortic valve replacement with an autograft 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. A schematic representation of these health states and events is given in Figure 1.

In microsimulation or Monte Carlo-type simulation one calculates random life histories of the course of disease for individual patients with predefined characteristics. These calculations are repeated many times, producing a simulated or 'virtual' population of patients. The outcomes of this population are then averaged with respect to expected time till death or other outcome. An attractive feature of microsimulation is that it has memory, for example it can adjust operative mortality of the left-sided valve taking into account whether the patient has had previous aortic valve replacements.

The information on outcome after autograft aortic root replacement from the meta-analysis was entered into the microsimulation model. Ten thousand 'virtual' life histories were calculated for males and females. The age of death due to of non-valve related causes

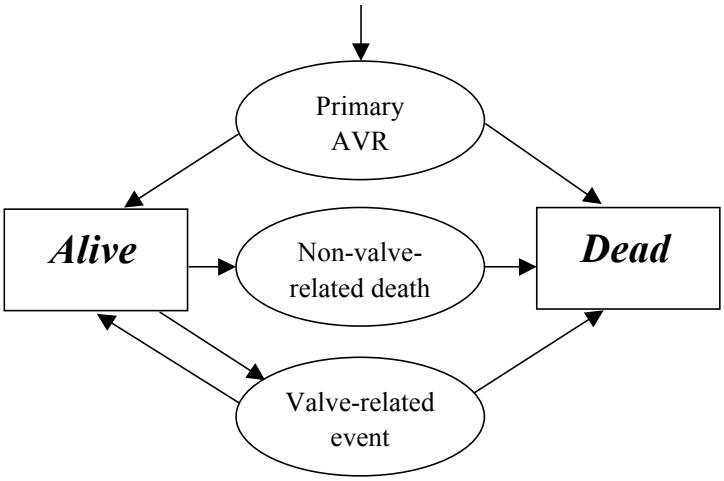

Figure 1. Schematic representation of different health states of a patient after autograft aortic root replacement as implemented in the microsimulation model.

was randomly drawn from the Dutch general population life table. However, there is an excess mortality in patients after aortic valve replacement 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 valve replacement devices [16,17]. 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 [18]. Other assumptions made were that operative mortality increases with age (Odds ratio 1.022/year) and also increases with each reoperation (Odds ratio 1.7 with each reoperation).

For males and females in 5 different age groups (20-30 years, 30-40 years, 40-50 years, 50-60 years and 60-70 years) life expectancy, reoperation-free life expectancy, actual life-time reoperation risk, event-free life expectancy and actual life-time event risk were calculated. In addition, cumulative survival, reoperation-free survival and event-free survival were generated.

Validation of the model was attempted by comparing its outcome to long-term outcome of aortic valve replacement patients in a large dataset from Portland, Oregon, USA [19]. A Gompertz model [20] was constructed for late survival for aortic valve replacement patients operated since 1975 in this dataset. The Gompertz distribution is often used to model survival. It has a hazard of the form R*[exp(A*t)-1], where A is a shape parameter, R is a scale parameter, and t is time. In the regression, R is replaced by the log linear function R(**y**)

of the risk factors, and the Gompertz regression curve for patient survival is thus given by: $S(t|\mathbf{y}) = \exp[-R(\mathbf{y})\times(\exp(A\times t)-1)]$. The Gompertz distribution was obtained by modifying a previously reported Gompertz model for late survival after valve replacement [15]. Variables in the model were age, $(age)^2$, gender, CABG and valve type (tissue versus mechanical). The GLM-function in S-PLUS 2000 (Mathsoft, Seattle, WA, U.S.A.) was used to fit the Gompertz regression.

In addition, outcome as predicted with the microsimulation model was compared to outcome after autograft aortic root replacement according to a recently published study from a large center in Oklahoma, U.S.A. [21].

To investigate the effect of uncertainty in the parameter estimates on life-expectancy one-way sensitivity analyses were performed. This was done by ranging the estimates for valve-related events from half to double the baseline parameter values.

Results

Meta-analysis

Rotterdam experience. Pre-operative patient characteristics and outcome are displayed in Table I. Operative mortality was 3.5% (N=3, all non-valve-related). During follow-up no more patients died. Cumulative survival was 97% at 7 years (SE 2%). Replacement of the autograft was necessary in 3 patients.

One patient developed recurrent rheumatic fever requiring replacement of the autograft with a mechanical prosthesis 1.8 years after the initial operation. Two other patients developed progressive dilatation of the autograft root requiring replacement with respectively a cryopreserved aortic allograft and a mechanical prosthesis at 4.0 years and 6.5 years after the autograft procedure. Autograft reoperation-free survival was 86% (SE 7%) at 7 years. Stenosis of the pulmonary allograft required replacement in 1 patient and balloon dilatation in another patient, 2.1 and 0.7 years after operation respectively. No valvular thrombosis, thrombo-embolism or bleeding events were observed. One patient developed endocarditis of the pulmonary allograft and was treated by antibiotic therapy.

Table I. Overview of patient characteristics and outcome after autograft aortic valve replacement from the 4 studies selected for the meta-analysis.

	Rotterdam (N=85)	**Lille (N=70)**	**New York (N=145)**	**Nieuwegein (N=80)**
Year of publication	Unpublished	1998[3]	1998[6]	1999[5]
Study period	11/1988-2/2000	3/1992-4/1997	3/1987-4/1997	2/1991-4/1998
Follow-up	Mean: 4.2 years	Mean: 2.8 years	--	Median: 2 years
Patient years	358	185	345	189
Mean age (SD, range)	31 (9; 16-52)	31 (9; 16-49)	43 (--, 17-68)	34 (9.3; 16-56)
M/F ratio	52/33	52/18	118/27	54/26
Pre-op NYHA class III/IV	24%	26%	--	18%
Concomitant CABG	4%	4%	8%	1%
Early mortality (N)	3	0	7	0
Late mortality (N)	0	2	4	0
Valve thrombosis (N)	0	0	0	0
Thrombo-embolism (N)	0	0	3	0
Late bleeding (N)	0	0	0	0
Endocarditis (N)	0	1	2	0
Non-structural valve failure (N)	1	0	1	1
Structural valve failure (N)	2	0	2	1

-- = not able to obtain information

Literature search, data-extraction and pooling. The literature search yielded 42 papers of which only 3 satisfied our inclusion criteria [3,5,6]. Two authors were contacted for clarification and additional information, and one responded. An overview of the patient characteristics and outcome from these three studies is displayed in Table I. No heterogeneity was detected between the four studies. Pooled mean age was 37 years (range 16-68). Male/female ratio was 2.7. Pooled operative mortality was 2.6%. The pooled hazard for the different types of valve-related events is displayed in Table II.

Since none of the valve-related events in the meta analysis resulted in death, and this is probably an underestimation of the true lethality of valve-related events, an estimate of lethality was obtained by using estimates from recent literature on this subject [22,23]. These estimates are also displayed in Table II.

Table II. Pooled hazard of valve-related events and their lethality.

	Pooled hazard	**Estimate of lethality**
Valve thrombosis	0.0%/patient year	Not applicable
Thrombo-embolism	0.5%/patient year	10%
Bleeding	0.0%/patient year	Not applicable
Endocarditis	0.3%/patient year	25%
Non-structural valve failure	0.4%/patient year	Age-specific reoperation mortality
Structural valve failure	Weibull function (beta=2.47; sigma=29.1)	Age-specific reoperation mortality

Microsimulation

Average life expectancy, reoperation-free life expectancy, actual life-time reoperation risk, event-free life expectancy and actual life-time event risk for males and females in different age groups are displayed in Table III. This is illustrated for males in different age groups in Figure 2. For example, for a 37 year old male patient average life expectancy was 21.0 years, reoperation-free life expectancy 16.3 years, actual life-time reoperation risk 46%**,** event-free life expectancy 15.6 years and actual life-time event risk 52%. Corresponding cumulative survival was 57%, reoperation-free survival 35%, and event-free survival 32**%** at 20 years (Figure 3). In Figure 4 loss of life expectancy of a 37-year old male patient compared to a healthy 37-year old male is displayed.

Table III. Mean life expectancy, reoperation-free life expectancy, actual life-time reoperation risk (risk of at least 1 autograft-related reoperation), event-free life expectancy and actual valve-related life-time event risk (risk of at least 1 valve-related event) stratified by age and gender as calculated using the microsimulation model.

	Life expectancy (Mean (S.E.))	**Reoperation-free life expectancy** (Mean (S.E.))	**Actual life-time reoperation risk**	**Event-free life expectancy** (Mean (S.E.))	**Actual life-time event risk**
Age 25					
Male	28.2 years (0.12)	19.0 years (0.10)	64%	18.1 years (0.10)	70%
Female	34.3 years (0.14)	20.5 years (0.11)	75%	19.4 years (0.11)	80%
Age 35					
Male	22.6 years (0.10)	17.0 years (0.09)	50%	16.3 years (0.09)	56%
Female	27.4 years (0.12)	18.7 years (0.10)	62%	17.8 years (0.10)	67%
Age 45					
Male	18.4 years (0.09)	14.9 years (0.08)	38%	14.3 years (0.08)	44%
Female	22.3 years (0.11)	16.8 years (0.09)	50%	16.0 years (0.09)	56%
Age 55					
Male	17.1 years (0.09)	14.0 years (0.08)	35%	13.5 years (0.08)	40%
Female	17.9 years (0.09)	14.6 years (0.08)	37%	14.0 years (0.08)	43%
Age 65					
Male	12.5 years (0.08)	11.0 years (0.07)	22%	10.6 years (0.07)	27%
Female	12.5 years (0.08)	11.1 years (0.07)	22%	10.8 years (0.07)	27%

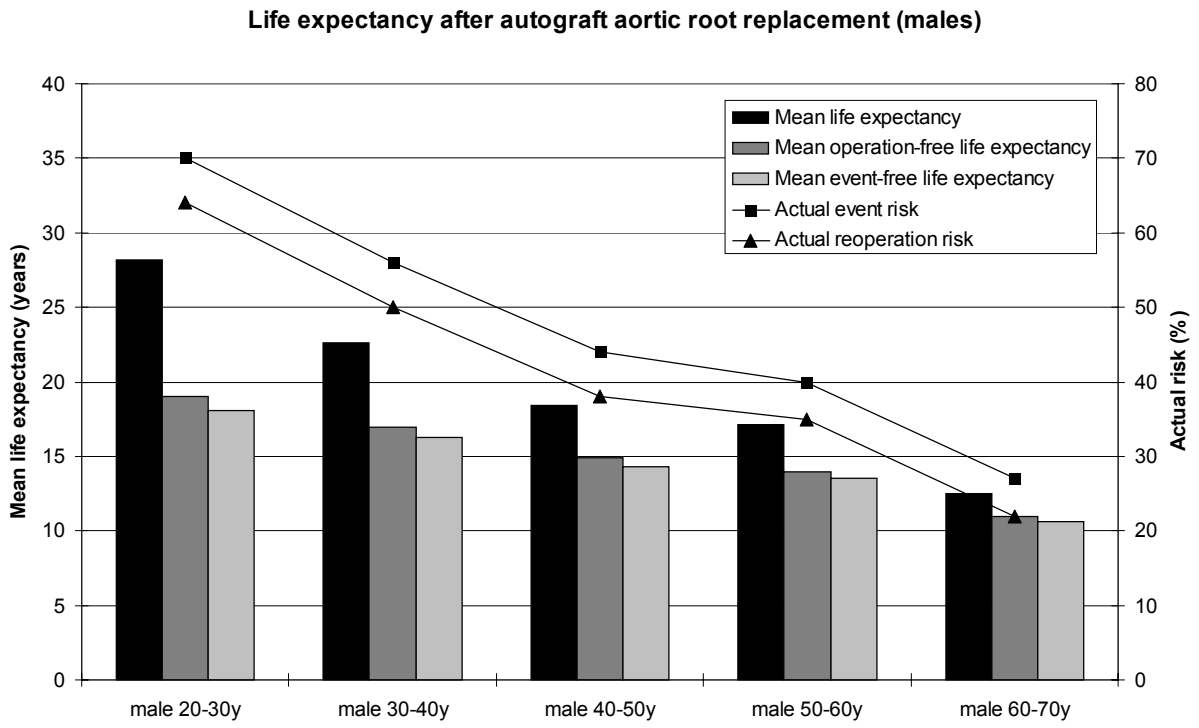

Figure 2. Average life expectancy, reoperation-free life expectancy, event-free life expectancy (left Y-axis), actual life-time reoperation risk and actual life-time event risk (right Y-axis) for males in different age groups.

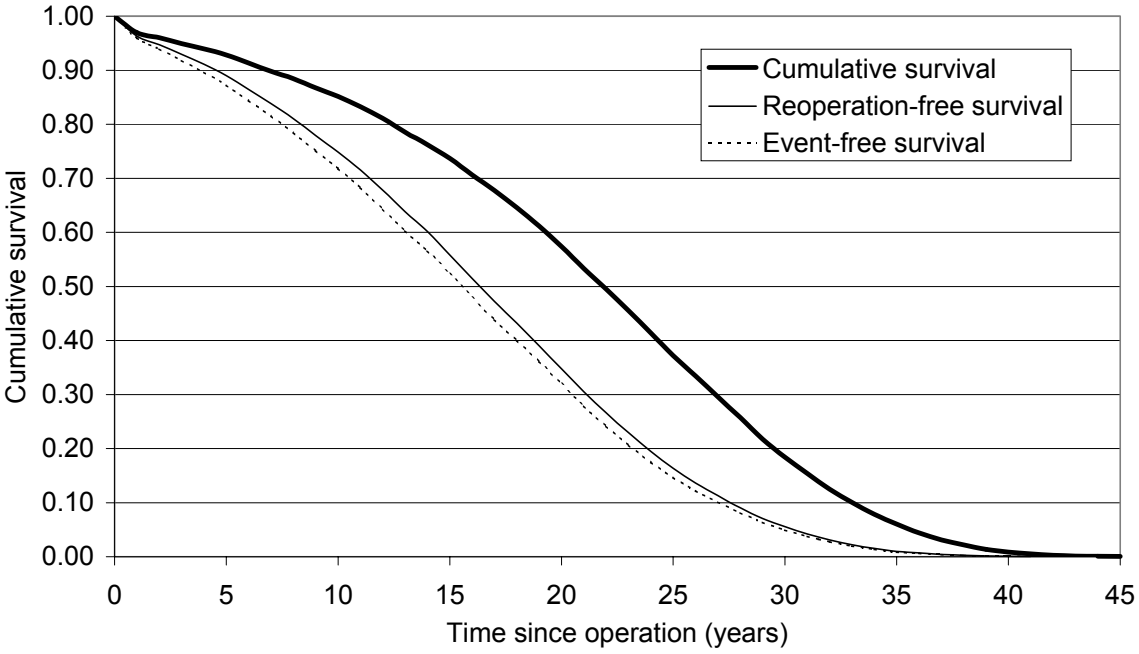

Figure 3. Cumulative survival, reoperation-free survival and event-free survival of a 37-year-old male after autograft aortic root replacement, as calculated using the microsimulation model.

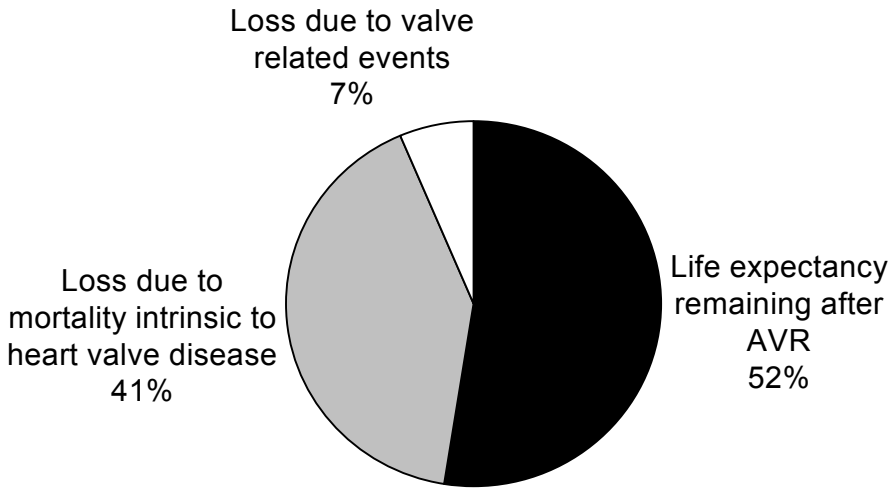

Figure 4. Loss of life expectancy of a 37-year old male after autograft aortic root replacement compared to a 37-year old healthy male.

We observed an adequate similarity between the survival as calculated with the microsimulation method or with the Gompertz model (Figure 5). Also, a good agreement at mid-term follow up was seen by comparing outcome produced by the microsimulation model to recently reported results from Oklahoma, U.S.A. [21].

One-way sensitivity analyses showed that varying the individual parameters had very little effect on the mean life expectancy in all age groups. The most pronounced effect was seen in the youngest age group. By ranging the estimates of valve-related events from half to double the baseline parameter values, for structural valve failure maximum change in life expectancy was 0.6 year, for thrombo-embolism 0.4 year, for endocarditis 0.4 year, and for non-structural valve failure 0.1 year.

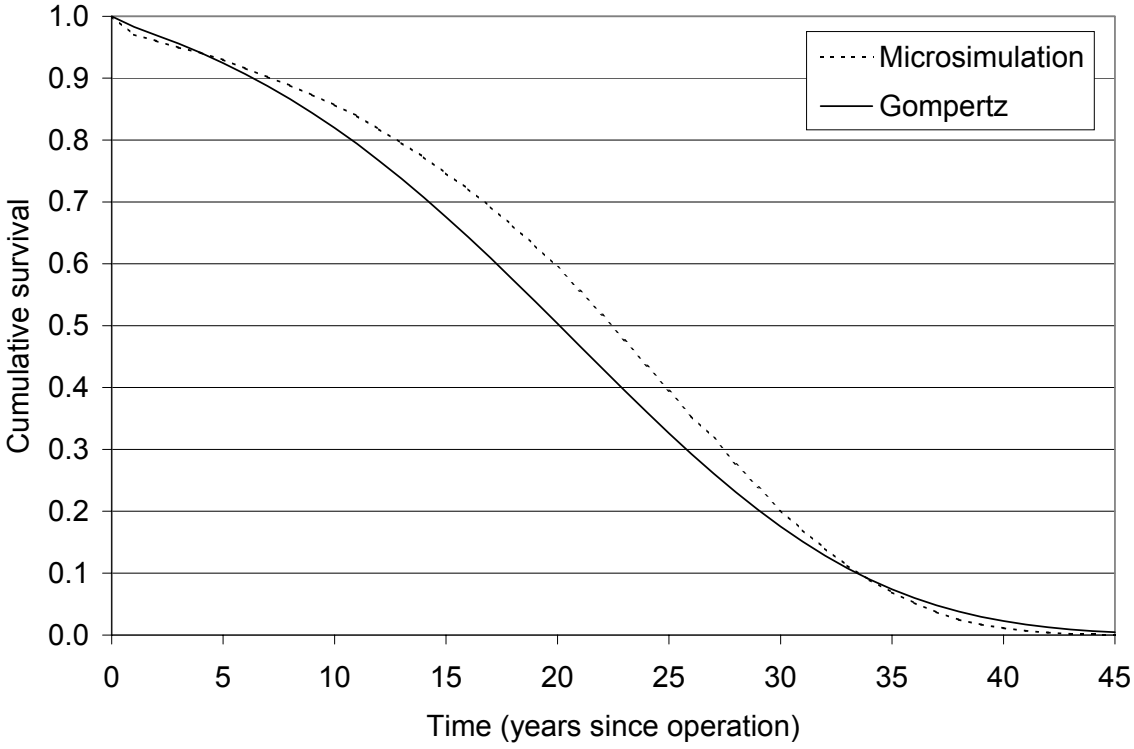

Figure 5. Comparison of survival of 35-year old males after autograft aortic root replacement as calculated using the microsimulation model with survival of 35-year old males after aortic valve replacement derived from the Portland dataset using the Gompertz model.

Discussion

We demonstrated that the combined use of meta-analysis and microsimulation allows one to estimate long-term outcome after autograft aortic root replacement based on current mid-term results. Comparison with published data indicates that the microsimulation model is capable of producing a reliable estimate of long-term prognosis after autograft aortic root replacement [19,21].

In the meta-analysis only studies on autografts implanted with the root replacement technique were included. Although the subcoronary and inclusion root implantation techniques are still used in some centers, 77% of Ross procedures are done using the root replacement technique [24]. Since surgical technique may influence outcome we chose to include only autograft roots [25].

Microsimulation allows detailed insight into the occurrence of events that affect patient survival. This can not be achieved with standard statistical methods. According to the model life expectancy after autograft aortic root replacement is much shorter compared to the

healthy age-matched population. For instance, life expectancy of a healthy 37-year-old male is 40 years, while after autograft root replacement this is only 21 years, a loss of 19 years. Of these 19 years, 16.4 years can be explained by excess mortality as a consequence of the heart valve disease of the patient (for instance sudden unexpected unexplained death and cardiac death) and only 2.6 years by the occurrence of autograft valve related events. Autograft valve related events therefore seem to have little impact on survival. However, they do have a major impact on reoperation free survival and event free survival, evidenced by a actual life-time reoperation risk of 46% and a actual life-time event risk of 52%.

The choice for a particular aortic valve prosthesis for the individual patient is a complex one, influenced by patient factors (for example age, gender, etiology of valve disease, coronary artery disease, heart rhythm, patient preference), physician factors (personal experience, preference), and the center's surgical experience with different types of aortic valve replacement or repair. With the increasing number of valve replacement or reconstruction options, it becomes even more difficult to make a rational choice. For the younger patient who has a relatively long life expectancy on the one hand one would like to choose a durable valve (mechanical prosthesis) that will last a life time, but on the other hand one would like to avoid lifelong anticoagulation (increased risk of thrombo-embolism and bleeding) and choose a human tissue valve. The durability of mechanical prostheses is well recognized, since long-term follow-up data are available. However, long-term data on durability of autograft roots are not available yet. In this respect, the microsimulation model is an important tool to accurately predict (reoperation-free) life expectancy for individual patients by taking into account patient age and gender (and concomitant life expectancy). Of course the choice of an aortic valve prosthesis is a complex one that cannot be solved by solely taking into account age and gender. The model should be expanded by adding other valve type options (mechanical valves, bioprostheses, and cryopreserved allograft roots) and factors that may influence the choice of a prosthesis (for instance the need for coronary artery bypass grafting). Eventually, the model could be used as an objective decision support system to help the physician and the patient in making an adequate choice.

The current version of the microsimulation model still has several other limitations. It is based on pooled mid-term clinical results. Although no clear heterogeneity was detected between the studies, mean patient age, operative mortality, and the occurrence of thrombo-embolic events was somewhat higher in the New York center compared to the other 3 centers. Furthermore, we assumed that the pooled hazard of valve-related events for thrombo-embolism, endocarditis and non-structural valve failure is linear. We did not adjust the hazard

for thrombo-embolism to the age of the patient because this relationship probably only becomes important at ages over 55 [26]. Since the autograft is mainly used in younger patients it seems irrelevant to add age-adjusted hazards for thrombo-embolism. Also, we constructed the Weibull model for the occurrence of structural valve failure requiring reoperation based on a small number of events. In addition, reoperation for structural valvular failure of the pulmonary allograft was not included. However, since outcome as calculated using microsimulation is very similar to recently reported long-term clinical results we are confident that it represents an accurate estimate of long-term outcome in patients after autograft aortic root replacement. A final limitation is the fact that the excess mortality in the microsimulation model due to heart valve disease is based on data from mechanical and bioprosthetic valve studies, and therefore a 'worst case scenario'.

The clinical application of a model such as we describe is only feasible if the input of the model is regularly being fed with new information that arises from the growing worldwide clinical experience with implantation of aortic valve substitutes. This requires a continuous effort to ascertain precision and validity of the predictions made by the model. Also, new surgical strategies like aortic valve repair, and new types of prostheses like the stentless bioprosthesis, should be considered in the future.

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