

# CHAPTER IX

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## **PROGNOSIS AFTER AORTIC VALVE REPLACEMENT WITH DIFFERENT VALVE SUBSTITUTES: AGE- AND GENDER-SPECIFIC EVIDENCE BASED ESTIMATES USING MICROSIMULATION**

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Presented at the annual Computers in Cardiology conference, September 25 2001, Rotterdam, The Netherlands.

“Evidence-based Estimates of Outcome after Aortic Valve Replacement Using a Microsimulation Model”. JJM Takkenberg, EW Steyerberg, JPA Puvimanasinghe, MJC Eijkemans, LA van Herwerden, JDF Habbema, AJJC Bogers. *Computers in Cardiology Proceedings 2001, Volume 28:141-4*

## **Abstract**

*Prognosis after aortic valve replacement (AVR) is determined by multiple interrelated factors. Standard statistical methods do not allow detailed insight into the factors that affect outcome in the individual patient.*

*The application of a microsimulation model to predict age- and gender-specific outcome is illustrated using reported estimates on the occurrence of valve-related events and outcome after AVR with different aortic valve substitutes.*

*Compared to healthy age-matched individuals, life expectancy of patients after AVR is markedly reduced, especially in the younger age groups. This reduction is mainly due to excess mortality, while valve-related events play a minor role. Reoperation for structural valve deterioration is common in younger patients with tissue valves. Patients with mechanical valves have a high life-time risk of suffering thrombo-embolic and bleeding events. Life expectancy of old patients is near-normal, illustrating a healthy-patient effect.*

*Microsimulation allows detailed insight into the factors that affect survival after AVR. Microsimulation provides a useful and objective decision support tool*

## Introduction

Prognosis after aortic valve replacement (AVR) depends on multiple interrelated factors associated with the patient, the medical center, and the type of prosthesis used<sup>1</sup>. Currently 4 major types of aortic valve substitute can be distinguished, namely mechanical prostheses, bioprostheses, allografts and autografts. Their advantages and disadvantages are displayed in Table 1.

Given the number and complexity of factors that affect outcome after AVR, it can be difficult to make an objective selection of the preferred valve substitute in the individual patient. The application of a microsimulation model to predict age- and gender-specific outcome is illustrated using reported estimates on the occurrence of valve-related events and outcome after AVR with different aortic valve substitutes.

Table 1. Overview of the advantages and disadvantages of the 4 main types of aortic valve substitutes.

	<b>Mech</b>	<b>Bio</b>	<b>Allo</b>	<b>Auto</b>
<b>Durability</b>	Good	Limited	Limited	Limited
Age-dependent?	No	Yes	Yes	No/?
<b>Thrombogenicity</b>	Increased	Low	Low	Low
<b>Anticoagulation required?</b>	Yes	No	No	No
<b>Availability</b>	Good	Good	Limited	Limited
<b>Specific surgical expertise required</b>	No	No	Yes	Yes
<b>Endocarditis risk</b>	Increased	Increased	Low	Low

Mech = mechanical valve, Bio = bioprosthesis, Allo = allograft, Auto =autograft, ? = unknown.

## Methods

Figure 1 describes the microsimulation model that was developed to simulate the outcome of patients after AVR. 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 AVR, 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 of developing valve-related events<sup>2</sup> for the rest of his or her life. Eventually this patient will die of either valve-related or non-valve-related causes.

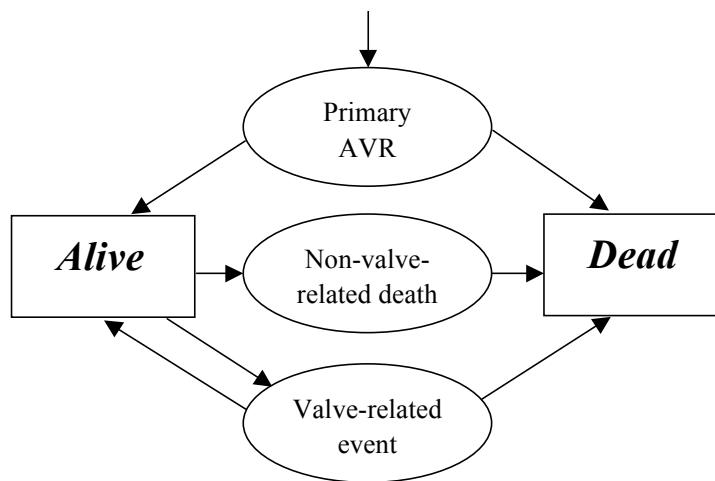


Figure 1. Schematic representation of different health states of a patient after AVR

From microsimulation or Monte Carlo-type simulation conclusions can be drawn for a specific patient profile (for example 40-year old male) by performing calculations of random individual life histories of patients. 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 the outcome. An attractive feature of microsimulation is that it has a memory, for example it can adjust operative mortality, taking into account whether the individual patient has had previous AVRs.

The information on outcome after AVR with the 4 different valve substitutes were obtained from previously performed meta-analyses<sup>3-6</sup> and entered into the microsimulation model. Details on the input of the model can be found in these papers. 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 be solely attributed to valve-related events<sup>7,8</sup>, we multiplied the age and gender specific mortality hazard of the general population with an age and gender-related hazard for excess mortality, based on previous work<sup>3, 4, 9, 10</sup>.

For male patients at 6 different ages (25, 35, 45, 55, 65 and 75 years) life expectancy, event-free life expectancy and actual lifetime risks of the various valve-related events and reoperation were calculated.

### Results

Figure 2 displays total life expectancy after AVR for males at different ages, depending on the type of aortic valve substitute implanted. For example, for a 45-year-old male patient total life expectancy is 18.9 years with an autograft, 17.7 years with a mechanical valve, 17.5 years with an allograft, and 15.9 years with a bioprosthesis. Total life expectancy decreases with older age from 23.4-27.6 years in a 25-year-old patient down to 7.2-7.6 years in a 75-year-old patient, depending on the type of valve substitute used.

Figure 2. Life expectancy (LE) after aortic valve replacement with different aortic valve substitutes

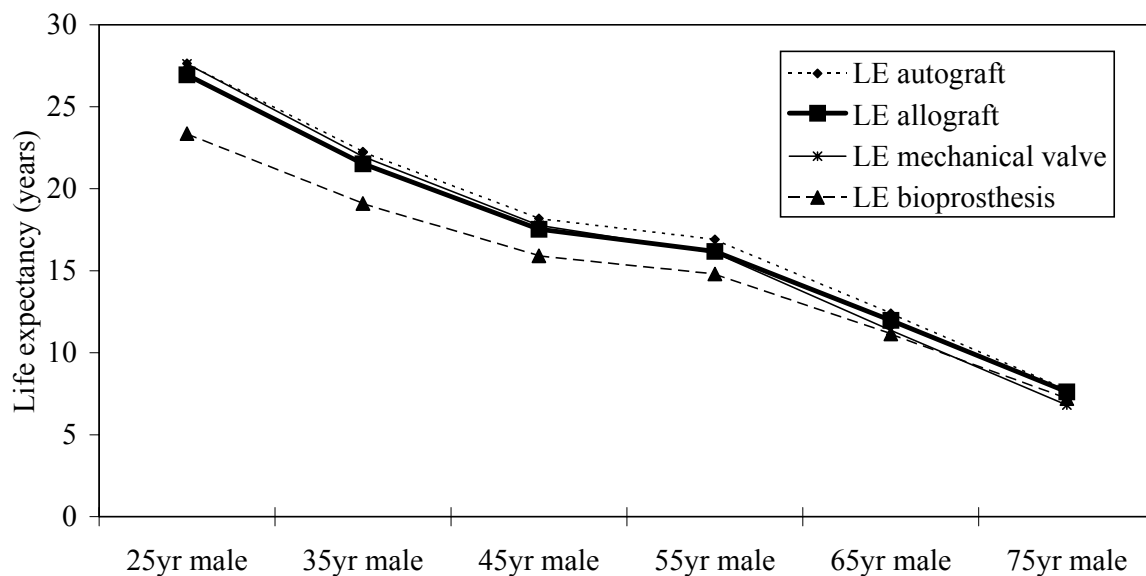
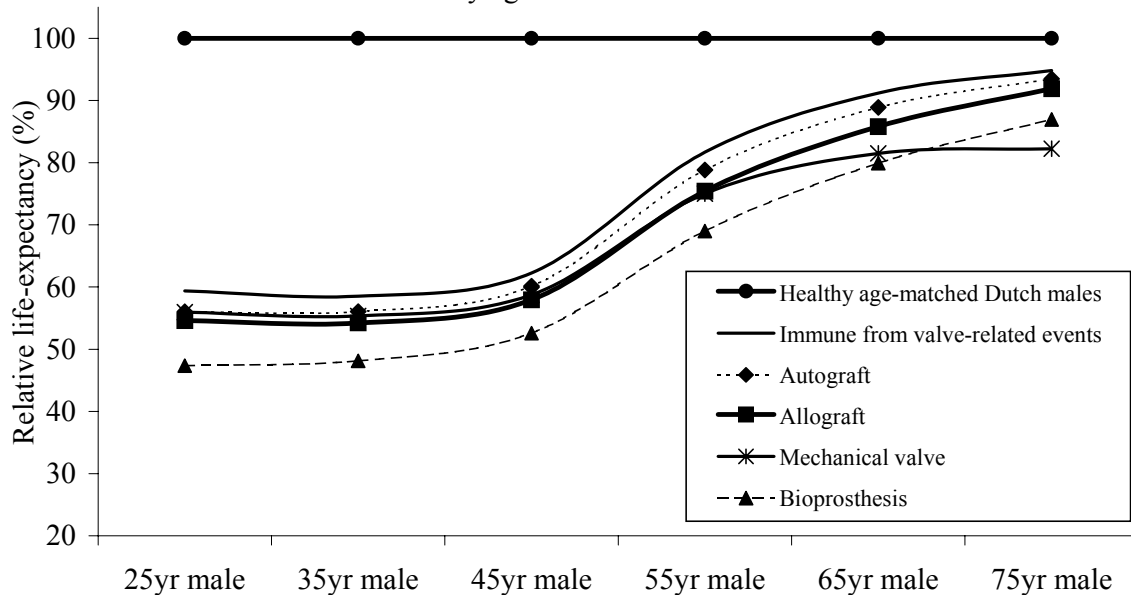


Figure 3. Relative life expectancy after aortic valve replacement compared to healthy age-matched Dutch males



Compared to healthy age- and gender-matched individuals, life expectancy of patients after AVR is markedly reduced. As illustrated in Figure 3, this reduction is most pronounced in younger patients and decreases with older age. For example, a 45-year-old patient with a bioprosthesis has a relative life expectancy of 53% (47% reduction in life expectancy compared to a healthy individual), while a 75-year-old patient with a bioprosthesis has a life expectancy of 87% (13% reduction in life expectancy).

Valve-related events play only a minor role in the reduction of life expectancy. This is illustrated in Figure 3. For example, the relative life expectancy of a 45-year-old male with a mechanical valve is 59% while in the hypothetical case of absence of valve-related events his relative life expectancy would be 62%, still a 38% reduction compared to the general Dutch male population.

On the other hand valve-related events do play a major role in the life of patients after AVR, as is evidenced by Figure 4. While in a 45-year-old total life expectancy is approximately 16-19 years (Figure 2), event-free life expectancy (EFLE; Figure 4) varies from 14 years with an autograft down to 9 years with a bioprosthesis. Especially in the younger age groups there are considerable differences in event-free life expectancy between the different valve substitutes.

Figure 4. Event-free life expectancy after aortic valve replacement with different aortic valve substitutes

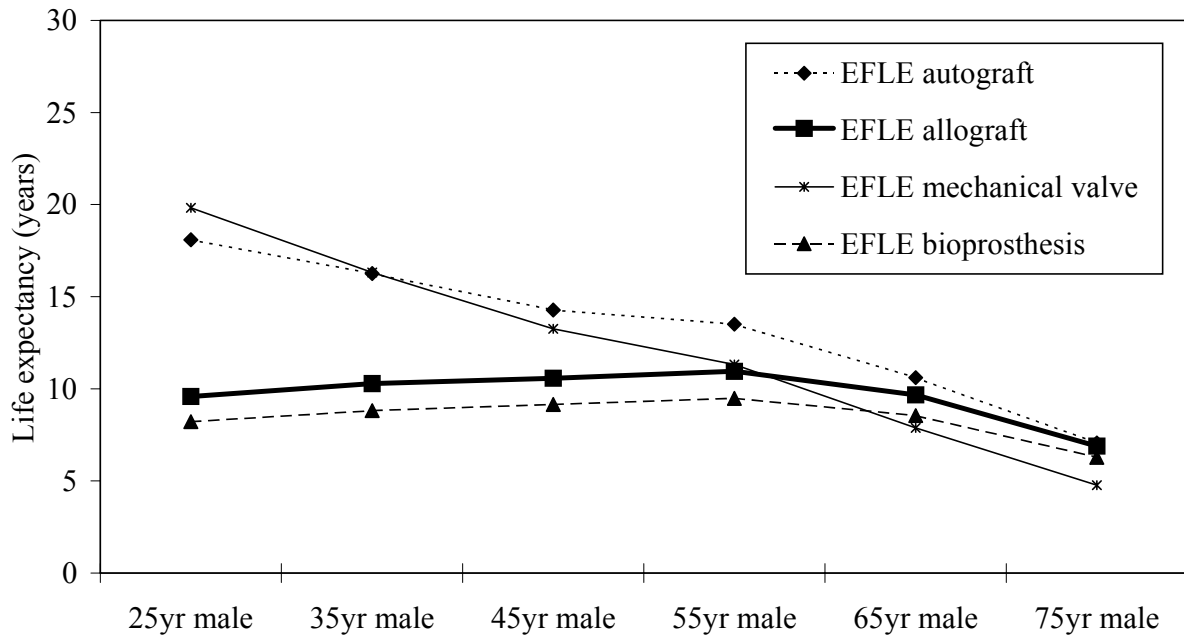
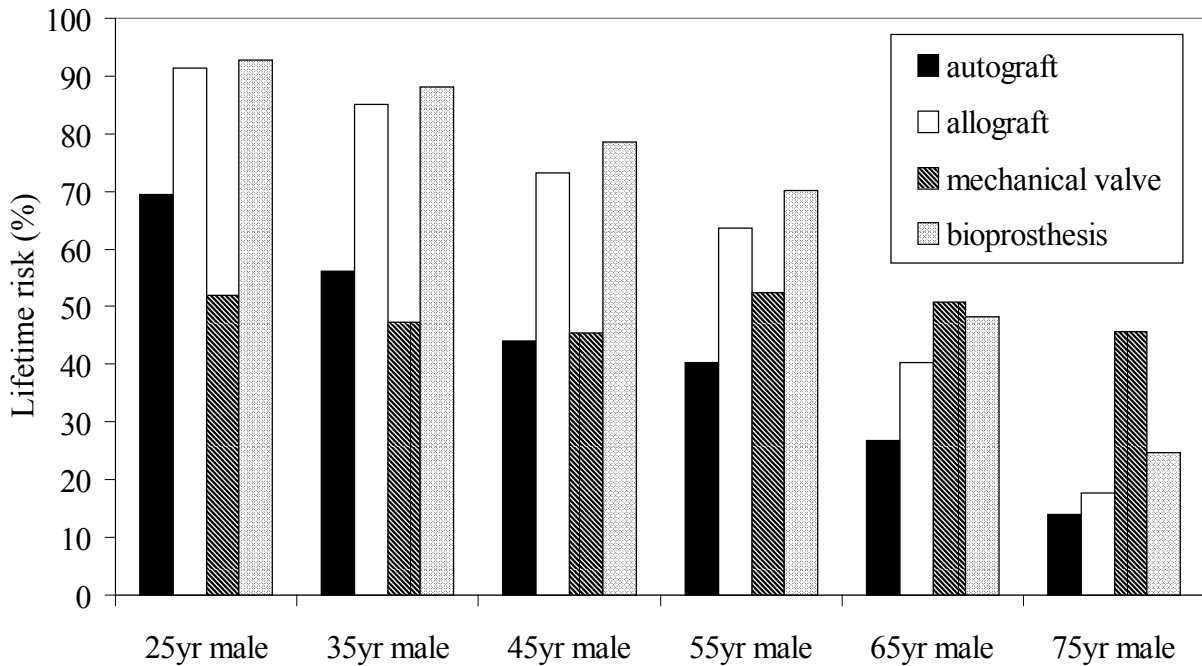


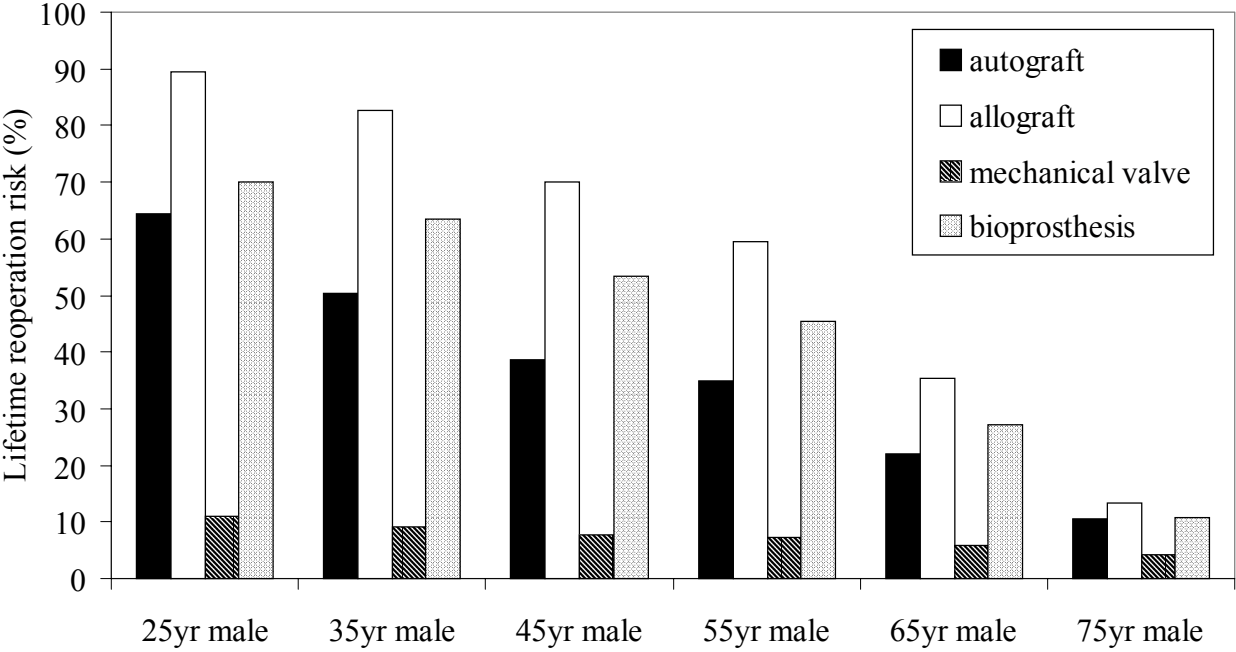
Figure 5. Lifetime risk by valve substitute of at least 1 valve-related event for male patients at different ages



In Figure 5 the lifetime risk of experiencing at least one valve related event is displayed for men at different ages and with the 4 different types of valve substitute. In younger patients the autograft and the mechanical valve have considerably lower lifetime risks of valve-related events compared to allografts and bioprostheses. With older age this difference diminishes, and in patients 65 years and older bioprostheses are associated with lower lifetime risks compared to mechanical valves. This is caused by increased bleeding risk and risk of death due to bleeding in older patients with mechanical valves, while on the other hand in patients 65 years and older life expectancy is relatively short and the chance of reoperation for structural valve deterioration of a tissue valve (autograft, allograft or bioprosthesis) diminishes.

Figure 6 displays the lifetime risk of at least one reoperation for males at different ages and with different valve substitutes. Lifetime reoperation risk for mechanical valves is low in all age groups. However, patients with tissue valves have high lifetime risks of reoperation especially in the younger age groups.

Figure 6. Lifetime risk by valve substitute of at least 1 reoperation for male patients at different ages





## **Discussion and conclusions**

Many interrelated factors play a role in the prognosis of patients after AVR and it may therefore be hard to select the preferred aortic valve substitute in the individual patient. Microsimulation offers an objective and reliable tool to support the decision for a particular aortic valve substitute in the individual patient.

In addition, from a scientific point of view microsimulation is useful for obtaining improved knowledge on the outcome after AVR. Using microsimulation it is possible to determine the factors that cause the reduced life expectancy in patients after AVR compared to the general population. Knowledge of these factors can be used to optimize treatment strategies and eventually improve outcome.

Limitations of the microsimulation model necessitated certain structural assumptions. For example, a constant hazard was assumed for several valve-related events, although these hazards may in fact be dependent on time and age. Another issue concerns the excess mortality that was built in the model. These age- and gender-related multiplicative hazard ratios were obtained from previous work on survival after implantation with mechanical monoleaflet prostheses and stented bioprostheses<sup>3,9</sup>. We validated our excess mortality estimates using the Portland dataset and found good agreement<sup>4,10</sup>. Therefore we are confident that it is a good reflection of reality. Finally, survival after AVR not only depends on age and gender, but also on many risk factors, including pre-operative NYHA class and the presence of a coronary heart disease<sup>8, 11</sup>. These factors were not taken into account in the microsimulation model. In this study we only considered male patients for the purpose of illustration. However, the model is also capable of calculating life expectancy for female patients.

We are currently expanding the microsimulation model to cover other valve types and alternative surgical strategies like aortic valve repair, in order to provide an objective evidence-based clinical decision support system with easy access for clinicians. This requires continuous refinement and regular updates on the input of the model as more experience is gained with the different types of aortic valve substitutes to provide valid estimates of prognosis for future patients.

## **Acknowledgements**

This study was in part supported by grant 99141 from the Board of Health Care Insurance (College voor Zorgverzekering), The Netherlands.

## References

1. Grunkemeier GL, London MR. Reliability of comparative data from different sources. In: Butchart EG, Bodnar E, eds. *Thrombosis, embolism, and bleeding*. London: ICR Publishers, 1992.
2. Edmunds LH, Jr., Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. *J Thorac Cardiovasc Surg* 1996; 112:708-11.
3. Puvimanasinghe JP, Steyerberg EW, Takkenberg JJ, et al. Prognosis after aortic valve replacement with a bioprosthesis : predictions based on meta-analysis and microsimulation. *Circulation* 2001; 103:1535-41.
4. Takkenberg JJ, Eijkemans MJ, van Herwerden LA, et al. Estimated event-free life expectancy after autograft aortic root replacement in adults. *Ann Thorac Surg* 2001; 7:S344-8.
5. Takkenberg JJ, Eijkemans MJ, van Herwerden LA, et al. Prognosis after aortic root replacement with cryopreserved allografts in adults. (submitted).
6. Takkenberg JJM, Puvimanasinghe JPA, van Herwerden LA, et al. Prognosis after aortic valve replacement with SJM bileaflet prostheses: Impact on outcome of varying thrombo-embolic hazard. *Eur Heart J Supplements* 2001;3 (Suppl Q):Q27-32.
7. Blackstone EH. The choice of a prosthetic heart valve: how shall patient-specific recommendations be made? *J Heart Valve Dis* 1998; 7:1-3.
8. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol* 2000; 35:747-56.
9. Steyerberg EW, Kallewaard M, van der Graaf Y, van Herwerden LA, Habbema JD. Decision analyses for prophylactic replacement of the Bjork-Shiley convexo-concave heart valve: an evaluation of assumptions and estimates. *Med Decis Making* 2000; 20:20-32.
10. Grunkemeier GL, Li HH, Starr A. Heart valve replacement: a statistical review of 35 years' results. *J Heart Valve Dis* 1999; 8:466-70.
11. Stahle E, Kvidal P, Nystrom SO, Bergstrom R. Long-term relative survival after primary heart valve replacement. *Eur J Cardiothorac Surg* 1997; 11:81-91.