Predicted Patient Outcome after Aortic Valve Replacement with Medtronic Stentless Freestyle Bioprostheses

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Background and aim of the study: **Knowledge on long-term patient outcome after implantation with the Medtronic Stentless Freestyle bioprosthesis is incomplete due to a limited follow up. In the present study, microsimulation was used to extrapolate the available primary data and to calculate the life expectancy and lifetime risks of valve-related events after aortic valve replacement (AVR) with the Freestyle bioprosthesis.**

Methods: **Eleven-year follow up data from 725 patients (mean age 72 ± 8 years; range: 36-92 years) who underwent AVR with a Medtronic Freestyle bioprosthesis were used to calculate the hazards of structural valvular deterioration (SVD) and of other valve-related events. Age-dependent Weibull distributions were used to model SVD. These results were incorporated into a mathematical microsimulation model, which then calculated the long-term outcomes for patients of any given age and gender.**

Results: **The annual hazards for thromboembolism and endocarditis were 2.9% and 0.45% per patient-year, respectively. For example, for a 72-year-old male patient the median time to SVD was 20.0 (17.8-22.4) years. The life expectancy, reoperation-free life expectancy and event-free life expectancy of this patient was 10.4, 9.7, and 7.2 years, respectively. The patient had a higher life expectancy compared to age and gender-matched persons in the general population. His lifetime risk of reoperation due to SVD was 15%.**

Conclusion: **The Medtronic Stentless Freestyle bioprosthesis performs well and offers a low lifetime risk of reoperation for elderly patients requiring AVR. The performance of the valve and the selective patient population might explain the higher life expectancy compared to age and gender-matched persons in the general population.**

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The Medtronic Freestyle aortic root bioprosthesis (Medtronic, Inc., Minneapolis, Minn. USA) is a stentless porcine aortic root, which was approved for initial implantation in human subjects in 1992. The stentless bioprosthesis is anticipated to be more durable than the conventional bioprosthesis because of a zero-pressure fixation process of the leaflets and alpha-amino oleic acid leaflet anticalcification treatment (1). The device is supplied as the intact porcine aortic root with ligated coronary arteries, which can be implanted using subcoronary, inclusion root, or freestanding root replacement techniques, respectively.

The Freestyle bioprosthesis has been associated with larger effective orifice areas (EOAs) and consequent low transvalvular gradients, superior hemodynamics, a greater reduction in left ventricular hypertrophy, and potential survival advantage (2-5). However, due to a lack of sufficient follow up, knowledge on the long-term outcome of patients after valve replacement and the lifetime risk of valve-related events remains incomplete. This information is necessary for comparison of the stentless valve with other types of bioprosthesis, and also in the choice of a valve for an individual patient.

In the present study, analyses of primary data from 725 patients were used to parameterize a mathematical microsimulation model, which then calculated and provided insight into the age-related life expectancy and lifetime risks of valve-related events after aortic valve replacement (AVR) with the Medtronic stentless Freestyle bioprosthesis.

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Clinical material and methods

Patients

A multicenter evaluation of the long-term outcome of the Medtronic stentless Freestyle bioprosthesis began in 1992 at 21 centers in North America and Europe. In 1997, a long-term study of the valve began at eight centers in the USA and Canada, which were selected for patient volume and protocol adherence. Between August 1992 and November 2001, a total of 725 patients (402 males, 323 females; mean age 72 ± 8 years; range: 36 to 92 years) underwent AVR with this bioprosthesis. The 30-day mortality was 5.2% (n = 38). The implant technique was subcoronary in 509 patients (70%), total root in 178 (25%), and root inclusion in 38 (5%).

Follow up

The patients were followed up prospectively and monitored for valve-related events, which were defined according to published guidelines (6). Both, clinical and echocardiographic data were obtained at specified intervals. The mean follow up of patients was 6.2 ± 3.2 years (range: 0 to 11.6 years). The total follow up was 4,491 patient-years (pt-yr).

Statistical analysis of primary data

Assuming a constant hazard over time, estimates of linearized annual occurrence rates were calculated for valve thrombosis, thromboembolism, hemorrhage, endocarditis and non-structural dysfunction, respectively. This was achieved by dividing the total number of a particular event by the number of observed patient-years. The mortality and reoperation rates directly resulting from each event was also calculated. Kaplan-Meier survival analysis was used to estimate patient survival and freedom from valve-related events.

The risk of structural valvular deterioration (SVD) in a bioprosthesis depends on the age of the patient at valve implantation, and on the time elapsed since the operation. The risk decreases with implantation age, but increases with time since implantation. Age-dependent Weibull distributions have been shown to describe this relationship well. The Weibull models were constructed on Egret windows version 2.0.1 (Cytel Software Corp.). In this data set, SVD was diagnosed at reoperation.

The microsimulation model

The microsimulation model is a computer application that simulates the life of a patient after AVR with a given valve type, and takes into account the morbidity and mortality that the patient may experience. The mortality of a patient after valve replacement is composed of the mortality experience of the general population and an excess mortality. This excess mortality is due to valve-related events and to mortality associated with underlying valve pathology, left ventricular function and valve replacement procedure, respectively. The model calculates patient outcome by superimposing the morbidity and mortality estimates of valve-related events on the other components of patient mortality. A detailed account of the microsimulation structure and methodology has been provided previously.

The mortality experience of the general population was incorporated into the model by means of the life-table of the relevant population (American males in the present analysis). Mortality due to valve-related

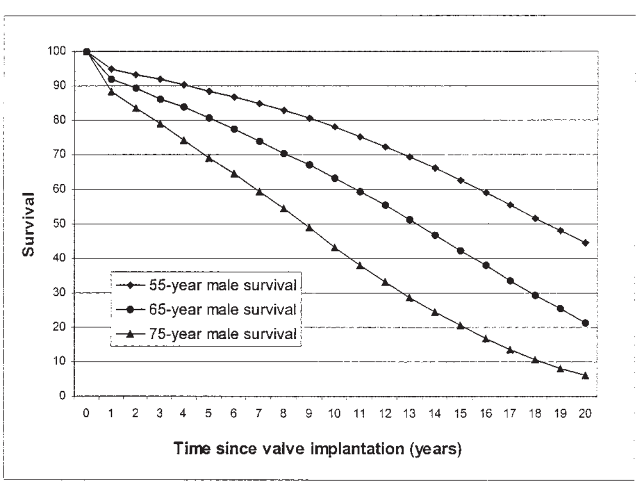

Figure 1: Microsimulation estimates of actuarial survival of male patients after aortic valve replacement with the Medtronic Freestyle valve.

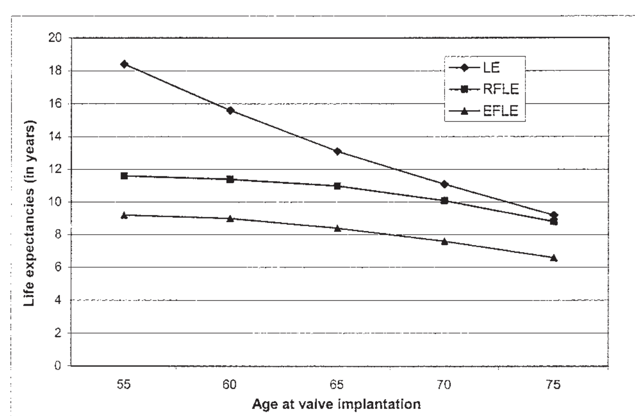

Figure 2: Life expectancy (LE), reoperation-free life expectancy (RFLE) and event-free life expectancy (EFLE) of male patients after aortic valve replacement with the Medtronic Freestyle valve.

events was incorporated using the results of analyses of the primary data. The excess mortality, not accounted for by the valve-related events, was represented by age- and gender-specific hazard ratios. These hazard ratios were estimated by calibrating the model outputs with age-specific survival curves obtained from the Kaplan-Meier analyses of the Freestyle primary data. The hazard ratios were 0.85, 0.8, and 0.6 for male patients aged 55, 65, and 75 years, respectively.

Sensitivity analysis

The effect of uncertainty in the parameter estimates of the model was investigated by means of a one-way sensitivity analysis. Variation of the estimates by their 95% confidence intervals yielded only very small changes in the long-term outcomes. Hence, for this analysis, the larger rangers were defined by increasing and decreasing the baseline estimates by 25%.

Results

Analyses of primary data

The incidence of valve-related events and their outcomes are listed in Table I. As depicted in the table, thromboembolism occurred with an annual incidence of 2.9% per pt-yr, while the incidence of hemorrhage was 0.95% per pt-yr. The Weibull formula for the freedom from SVD was used: $S(t) = e^{-(t / \sigma)^{\wedge}\beta}$, where σ and β denote the scale and shape parameters of the model. The value of the scale (σ) parameter of the Weibull model depends on age: $\sigma = e^{1.7 + 0.0191 * age}$. The shape parameter (β) reflects the changing risk of SVD over time, and was estimated at 4.545. With these parameters, and by extrapolation of the available primary data, the median time to reoperation due to SVD with the Freestyle valve is estimated at 14.4 (13.5-15.4) years, 17.5 (16.0-19.1) years, and 21.2 (18.7-24.0) years, respectively, for 55-, 65-, and 75-year-old male patients.

Microsimulation model calculations

The microsimulation model calculated actuarial patient survival of male patients at different ages of valve implantation (Fig. 1).

The model was also used to calculate total life expectancy (LE), reoperation-free life expectancy (RFLE), and event-free life expectancy (EFLE) following AVR with the Freestyle bioprostheses for male patients of different ages. The valve-related events and their outcomes are listed in Table I. For a 65-year-old man, for example, LE was 13.1 years, RFLE 11.2 years, and EFLE 8.4 years. The LE, RFLE, and EFLE for men at different ages of valve implantation are illustrated in Figure 2.

The LE of male valve recipients was also compared with that of age- and gender-matched controls in the general population. The relative LE increased with the age of valve replacement and, at an implantation age over 67 years, was more than that of the general population controls (Fig. 3). The microsimulation model also calculated the 'actual' or lifetime risks of thromboembolism and SVD after valve implantation according to the different age at implantation (Fig. 4). The lifetime risk of SVD reduced with advancing age of implantation, and was 20% and 8%, respectively, for 70- and 75-year-old males.

Sensitivity analysis

The LE and EFLE of a 65-year-old male patient, for extreme values of valve-related events, is provided in Table II. Changes in the SVD risk were seen to have the greatest influence on both parameters.

Discussion

The Medtronic freestyle stentless bioprosthesis is anticipated to be more durable than the conventional stented bioprosthesis because its leaflets are fixed with glutaraldehyde
at zero pressure and treated with alpha-amino-oleic acid to mitigate calcification. Stentless valves in general have very good hemodynamic characteristics, with low transvalvular gradients and large EOAs, which

Table I: Valve-related events and their outcomes after aortic valve replacement with the Medtronic Stentless Freestyle bioprosthesis.

Valve-related event	No. of events	LOR (%/pt-yr)	Reoperation rate	Mortality rate
Thromboembolism	130	2.9	0	0.06
Valve thrombosis	2	0.04	0	0.5
SVD	11	0.24	100	0
Endocarditis	20	0.45	0.5	0.3
Hemorrhage	43	0.95	0	0.07
NSD	13	0.28	0.77	0

LOR: Linearized occurrence rate; NSD: Non-structural dysfunction; SVD: Structural valvular deterioration.

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Table II: Summary of sensitivity analysis for a 65-year-old male patient after aortic valve replacement with the Medtronic Freestyle bioprosthesis.

Valve-related event	Baseline estimate	Plausible range*		LE (years)		EFLE (years)	
		Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable
Valve thrombosis	0.04	0.03	0.05	13.1	13.1	8.4	8.4
Thromboembolism	2.9	2.18	3.63	13.1	13.0	8.8	8.0
Hemorrhage	0.95	0.71	1.19	13.1	13.0	8.6	8.2
Endocarditis	0.45	0.34	0.56	13.1	13.0	8.4	8.3
NSD	0.28	0.21	0.35	13.1	13.1	8.4	8.4
Time to SVD (years)+	17.5	21.9	13.1	13.3	12.7	8.9	7.5

*Baseline estimates were increased and decreased by 25% to estimate the plausible range.
+Median time to SVD.
EFLE: Event-free life expectancy; LE: Life expectancy; NSD: Non-structural dysfunction; SVD: Structural valvular deterioration.

may result in a longer survival after surgery. Recent data (4) have confirmed low gradients and large EOAs associated with the Freestyle stentless aortic bioprosthesis which are maintained for at least six years after implantation. Other reports have also shown an excellent five-year freedom from thromboembolism, hemorrhage, prosthetic endocarditis, SVD and reoperation of 97, 99, 99, 98, and 96%, respectively, after the implantation of different stentless valves (7). For the Freestyle valve, similar five-year results were reported, with freedom from thromboembolism of 97%, from SVD of 100%, from endocarditis of 99%, and from reoperation of 99% (8). The present findings shows that the Freestyle valve remains durable at longer follow up, and that freedom from structural valve failure and reoperation and event-free life expectancy are high.

The two types of simulation model that have been used to identify patient outcome after AVR are the Markov state-transition model and the microsimulation model (9,10). In the present study, the microsimulation model (designed at the Erasmus MC, Rotterdam) was used to provide insight into the age- and gender-related life expectancy and lifetime risks of valve-related events after AVR with the Freestyle valve. The microsimulation model allows simulation of the life histories of individual patients; by modeling complex outcome paths that may result from many of the competing risks, this provides a useful adjunct to standard statistical methods in calculating patient outcome after AVR.

The LE, RFLE, and EFLE for males of different ages, as estimated by the microsimulation model, are depicted graphically in Figure 2. The valve-related events (see Table II) indicate a relatively high rate of thromboembolism which may in part be explained by the rel-

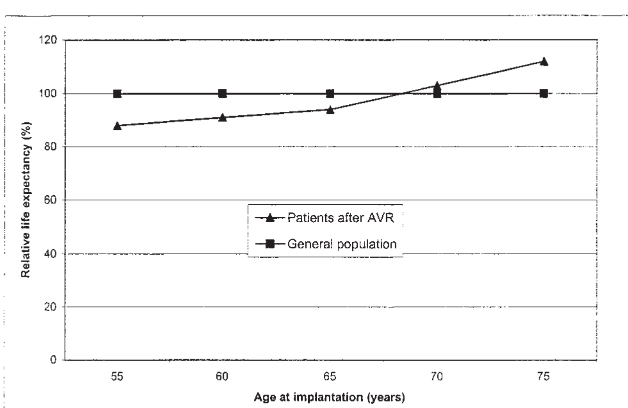

Figure 3: Life expectancy of men after aortic valve replacement (AVR) relative to that of men in the general population.

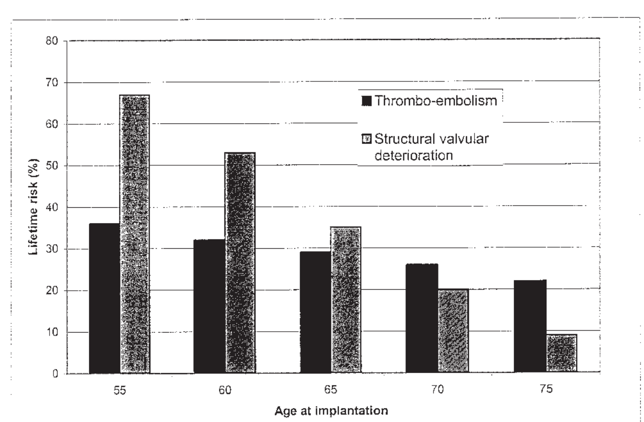

Figure 4: Lifetime risks of thromboembolism and reoperation for structural valvular deterioration after aortic valve replacement with the Medtronic Freestyle bioprosthesis.

atively high mean age of the patient population. For example, the LE of a 65-year-old patient was estimated at 13.1 years, which is only slightly lower than that of a male in the relevant general population (this translates to a 98% relative LE for the patient) (Fig. 3). The relative LE of a hypothetical patient who is immune from valve-related events and from operative mortality is lower than that of the general population. This means that there is an excess mortality of the patient which may be related to the underlying valve pathology, to left ventricular residual hypertrophy and functional abnormality and the valve replacement procedure, respectively (11,12). This excess mortality was calculated by calibrating the model output with the survival curves of the primary Medtronic Freestyle dataset. However, even if this excess mortality is taken into account, the LE of those patients who received a Freestyle valve at an age of >68 years is still better than that of the general population. Clearly, a combination of the Freestyle bioprosthesis and a selected patient population results in excellent survival.

Kvidal and colleagues, who investigated excess mortality after heart valve replacement, described an increasing excess hazard during follow up and a decreasing excess hazard with advancing age of implantation (13). These findings support a 'multiplicative' excess mortality, which was a structural assumption in the present model. The use of an 'additive' model may increase LE estimates, especially in patients aged <70 years. In the present study, a sensitivity analysis was used to underscore the importance of the excess mortality on the outcomes of patients after AVR. The effect on LE and EFLE of a 65-year-old male, due to an increase and decrease of the hazard ratio, is provided in Table II.

Although the Kaplan-Meier and actuarial methods are commonly used to estimate the survival of patients after AVR, these methods have now been extended to summarize valve-related events such as SVD that are not necessarily fatal. In the latter instance, the methods estimate freedom from SVD by also censoring patients who had died and would therefore never experience the event. Thus, it describes the risk of SVD for the patient based on the assumption of immortality, and this results in an over-estimation of the actual risk of SVD. This error is magnified with advancing age of valve implantation, and may serve to under-estimate the benefits of biological valve implantation. An alternative to the method of summarizing complications that are not necessarily fatal (such as SVD) is the cumulative incidence or 'actual' analysis, which takes into consideration the competing risk of death and calculates the percentage of patients who will experience an event before they die. Hence, this answers the more pertinent question, 'what is the lifetime risk of the event?' (14-17). The microsimulation model calculates the lifetime risk of SVD and of other valve-related events. In the case of the 65-year-old patient, for example, the lifetime risk of reoperation due to SVD was 30% after AVR with the Freestyle valve, whereas with the microsimulation model a 15% lifetime risk of reoperation was calculated for the Carpentier-Edwards supra-annular valve. The higher chance of reoperation for a 65-year-old male with a Freestyle valve is mainly due to the fact that the patients in the sample population have a long life expectancy which, at some ages, is even higher than that of the general population

Study limitations

The main study limitations included structural assumptions in the microsimulation model and the uncertainty associated with the input parameters. For example, although a constant hazard was assumed for the valve-related events other than SVD, these hazards may vary with increasing age and age at implantation. Many other patient- and surgery-related factors have been shown to influence overall survival after AVR (18,19). However at present, the model calculates outcome for an average risk profile only. The moderate numbers of events for some valve-related events and patient selection provide a degree of uncertainty to the input parameters of the model.

In conclusion, a microsimulation process was used to provide detailed insight into patient outcome after AVR with the Medtronic Freestyle valve. In the present patient population, outcome in terms of life expectancy and event-free life expectancy was excellent. This information should prove very useful for patient counseling and in selecting the optimal valve prosthesis for any given patient.

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Meeting discussion

DR. STEVEN F. BOLLING (Michigan, USA): In your microsimulation model was there a difference between survival and event-free survival, of survival from reoperation, and of the type of implantation such as subcoronary implant and full root? Did you break the data down and examine the details separately?

DR. PIETER KAPPETEIN (Rotterdam, Netherlands): In these patients there was no difference in survival, but it would be very interesting to see if the root inclusion technique led to less structural valve deterioration, as only a minority of patients were in that group. Actually, a larger group is needed to answer that question with this model.

DR. BOLLING: One limitation of your study was that the mean patient age at implantation was 72 years, which is very old. At that age there is very little difference in life expectancy between the three groups, unlike the situation for 20-year-old patients where the difference is huge. Mathematically, does that limit your ability to discriminate among the groups? I find it hard to believe that life expectancy in the implanted patients is higher than for the general population. I cannot see how this operation is protective for the patients.

DR. KAPPETEIN: Yes, it is true that at the end of the curve the groups are very close together. It would be especially interesting to see if, in the younger patient population, we can provide a better life expectancy with another valve. But yes, the present patient population was quite old.

DR. DENNIS MODRY (Edmonton, Canada): I would like to add some information to this situation. The 5% early mortality rate was surely due to the learning curve - the later, more important issue later will be mortality pertaining to valve function. During the past five years at the University of Alberta we have placed about 600 Freestyle valves, with only four deaths. We follow all patients prospectively with echocardiography. Half of the patients are aged under 50, but the age range is 20 to 96 years. In time, we should be able to add information about the younger age group with regards to early mortality, but I am not sure why it would be different. We no longer find placing these valves to be very complex or difficult - it is just routine. The other point to make is that in about one-fourth of the patients given the Freestyle valve the placement was as a full root - the remainder were subcoronary implants. So the technique used is irrelevant in terms of mortality outcome. Reoperations or multiple procedures have also been irrelevant in terms of outcome. When you achieve a 'comfort level' in placing stentless valves you get very good outcomes. The notion has been introduced that the technology associated with the Freestyle valve may promise long-term durability but, as Sir Magdi Yacoub said earlier, it would be very good to have a prospective study in younger people comparing the Ross procedure and stentless valves - particularly the Freestyle. We have a fairly large series of Ross procedures, but they have not been evaluated prospectively against the Freestyle.

DR. BOLLING: We have been implanting Freestyle valves for 13 years, during which time the percentage of subcoronary implants has gone down, and the percentage of full roots has gone up. Was that also the case in your overall series?

DR. KAPPETEIN: Yes, it was. For the elderly population it is important to use a valve which provides a good quality of life, as the type of prosthesis used has much less influence on life expectancy in older patients. But it is much more important in a younger patient population, as we have shown.