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# Assessing the benefit of biological valve prostheses: cumulative incidence (actual) vs. Kaplan–Meier (actuarial) analysis<sup>☆</sup>

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## Abstract

**Objective:** The standard method of analysing structural valve degeneration (SVD) of biological prostheses is the Kaplan–Meier method. In order to assess SVD with regard to competing risks (e.g. death particularly in elderly patients) cumulative incidence (actual analysis) was compared to Kaplan–Meier (actuarial analysis). **Methods:** We retrospectively analysed 257 patients older than 60 years, who underwent mitral valve replacement with different biological prostheses between 1974 and 2000. Reoperation-free survival was determined, both according to Kaplan–Meier and cumulative incidence analysis. **Results:** For the total group of patients older than 60 years, the 10- and 15-year freedom from reoperation was  $79 \pm 5$  and  $55 \pm 8\%$ , respectively, according to Kaplan–Meier and  $90 \pm 2$  and  $83 \pm 3\%$  according to cumulative incidence analysis. For patients older than 65 years of age ( $n = 170$ ), Kaplan–Meier analysis revealed  $85 \pm 7\%$  freedom from reoperation at 10 years vs.  $94 \pm 3\%$  according to cumulative incidence analysis. For those between 60 and 65 years of age ( $n = 87$ ), Kaplan–Meier freedom from reoperation was  $76 \pm 7\%$  at 10 years and  $48 \pm 9\%$  at 15 years vs.  $86 \pm 4$  and  $75 \pm 5\%$  according to cumulative incidence analysis. **Conclusions:** Kaplan–Meier analysis overestimates the 10- and 15-year risk of SVD compared to cumulative incidence analysis, thus underestimating the benefit of biological valve replacement. Cumulative incidence analysis may lead to a more complete evaluation of risk and benefit and thus better patient management.

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**Keywords:** Actual analysis; Cumulative incidence; Competing risks; Valve replacement; Freedom from reoperation

## 1. Introduction

The standard method of analysing structural valve degeneration (SVD) of biological prostheses and, in a more general sense, survival without reoperation (the so-called disease-free survival) is Kaplan–Meier analysis. Originally designed to describe freedom from death, Kaplan–Meier estimation was also extended to nonfatal complications like reoperation. The probability of a patient's reoperation, however, is based on the assumption of immortality. Additionally relevant in terms of patient prognosis is whether the patient will experience the failure of his biological valve or whether he will die before the

implanted valve fails. Kaplan–Meier analysis projects the risk outward from the followed subjects to those lost by death, and therefore would overestimate the risk of reoperation of deceased in describing what the risk would have been if their death had not occurred. By considering competing risks, cumulative incidence may provide a means of estimating reoperation-free survival in elderly patients who have a higher, age-related risk of death. Recently, a comparison between actuarial and actual analysis has been described among a population of cardiac patients in the United States observing an overestimated risk of reoperation [7] and actual analysis was added to the guidelines for reporting morbidity and mortality after cardiac valvular operations [10].

In order to assess a potential overestimation of Kaplan–Meier analysis compared to cumulative incidence analysis in a European population, we analysed data of our patients

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who underwent biological mitral valve replacement (MVR) at the German Heart Center in Munich.

## 2. Methods

### 2.1. Study population and data sources

A total of 257 patients older than 60 years of age underwent MVR with a biological prosthesis between 1974 and 2000 at our institution. The study population was divided into two different age classes, i.e. 60–65 years and older than 65 years, in order to assess age-related differences in outcome. Information on date of birth, date and type of the intervention, sex, year of implantation, type of biological valve and reason for reoperation were obtained from the respective medical files retrospectively and listed in Table 1. In our study, freedom from reoperation rather than freedom from SVD was chosen to characterize patient outcome, because on the one hand the exact beginning of SVD is difficult to define and echocardiographic findings were not completely available especially in the early study period and on the other hand the event of reoperation seemed to be more patient-relevant.

Table 1  
Patient characteristics

Characteristics		Distribution
Patients	Total, age > 60	257
	60 < age ≤ 65	87
	Age > 65	170
Age (years)	Mean	70.7
	Range	60–87.9
Sex	Male	93
	Female	164
Year of implantation	1974–1979	26
	1980–1989	102
	1990–2000	129
Valve model	Carpentier–Edwards	19
	Hancock	72
	Xenomedica	21
	Ionescu–Shiley	1
	Liotta	2
	Biocor	23
	Mosaic	40
	Intact	78
	St. Jude Bio	1
Follow-up (years)	Mean	5.6
	Total	1440
	Maximum	24.3
Re-operation	Total	27
	For SVD	23
	For NSVD	3
	For endocarditis	1

### 2.2. Statistical analyses

Reoperation-free survival was estimated by two different methods. The Kaplan–Meier (KM) estimation, as the widely used standard method, does not differentiate between censored events. To consider censored events like death as competing risk, cumulative incidence analysis was performed [2–8]. To illustrate the differences between Kaplan–Meier and cumulative incidence analysis, survival curves were added to the figures, although actual curves lack comparability with other populations. All estimates were calculated for all patients 60 years of age and above as well as for the subgroups 60–65 years of age and for those older than 65 years. Cumulative incidence analyses were performed using an SAS macro [1] (Anderson WN, Edwards Lifesciences, Irvine, CA). All calculations were carried out with the software package SAS version 6.12 (SAS Institute Inc., Cary, NC).

## 3. Results

Eighty-seven patients (34%) lived at the end of the study. A total of 21 patients (8%) died of valve-related complications. Of the remaining 149 deaths, 47% were of cardiac and 18% of non-cardiac origin. Unexplained deaths (33%) were mostly due to varying requirements as to how long communities have to keep their death certificates. Death within 30 days after mitral valve surgery was observed in 27 patients (11%). Combined valve and bypass surgery was performed in 77 patients, whereas 180 received isolated MVR. Twenty-seven patients underwent a reoperation (11%), 23 of them for SVD, three for non-structural dysfunction and one for endocarditis. Follow-up was 99% complete with a cumulative total of 1439.6 patient-years of follow-up and with a maximum of 24 years.

For the total group of patients older than 60 years, the 10- and 15-year freedom from reoperation was  $79 \pm 5$  and  $55 \pm 8\%$ , respectively, according to Kaplan–Meier analysis. Cumulative incidence yielded considerably higher percentages of patients without a reoperation:  $90 \pm 2\%$  after 10 and  $83 \pm 3\%$  after 15 years (Fig. 1). Similar differences were observed for patients between 60 and 65 years of age ( $n = 87$ ): Kaplan–Meier figures were  $76 \pm 7\%$  freedom from reoperation at 10 years vs.  $86 \pm 4\%$  according to cumulative incidence analysis and  $48 \pm 9$  vs.  $75 \pm 5\%$  after 15 years, respectively (Fig. 2). For those older than 65 years of age ( $n = 170$ ), Kaplan–Meier freedom from reoperation was  $85 \pm 7\%$  at 10 and  $73 \pm 13\%$  at 15 years vs.  $94 \pm 3$  and  $92 \pm 3\%$  according to cumulative incidence analysis (Fig. 3).

## 4. Discussion

The respective advantages and disadvantages of both

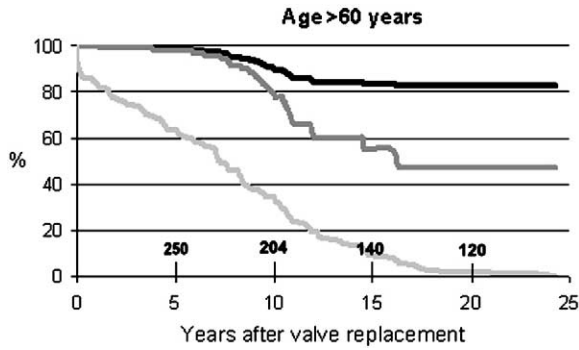


Fig. 1. Overall survival (S) compared to cumulative incidence (CI) freedom from reoperation. The numbers denote the patients remaining at risk for Kaplan–Meier analysis.

	At 10 years	At 15 years
CI	90 ± 2%	83 ± 3%
KM	79 ± 5%	55 ± 8%
$\Delta_{(CI-KM)}$	11%	29%
S	34 ± 4%	9 ± 2%

tissue and mechanical valves are well known. However, to advise a patient correctly of what the probability of ever experiencing a reoperation because of valve failure before dying is, remains difficult, because of competing, non-valve-related risks.

The aim of this study was to predict patient outcome as accurately as possible on the basis of data accumulated at

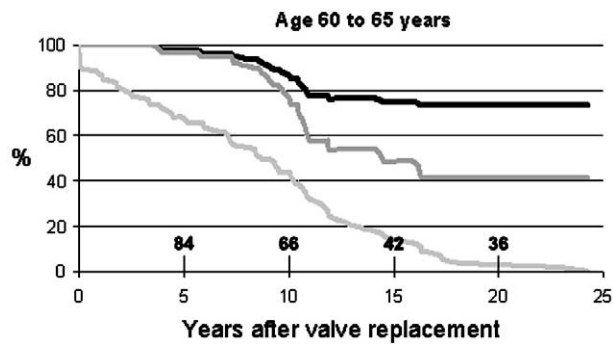


Fig. 2. Overall survival (S) compared to cumulative incidence (CI) freedom from reoperation. The numbers denote the patients remaining at risk for Kaplan–Meier analysis.

	At 10 years	At 15 years
CI	86 ± 4%	75 ± 5%
KM	76 ± 7%	48 ± 9%
$\Delta_{(CI-KM)}$	10%	26%
S	44 ± 6%	14 ± 4%

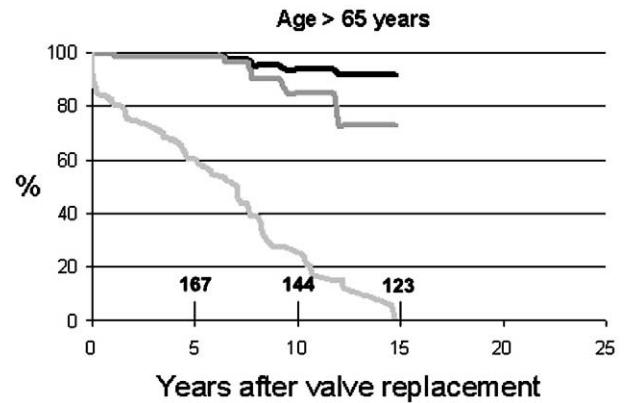


Fig. 3. Overall survival (S) compared to cumulative incidence (CI) freedom from reoperation. The numbers denote the patients remaining at risk for Kaplan–Meier analysis.

	At 10 years	At 15 years
CI	94 ± 3%	92 ± 3%
KM	85 ± 7%	73 ± 13%
$\Delta_{(CI-KM)}$	9%	19%
S	26 ± 5%	6 ± 3%

the German Heart Center in over 25 years using a method that has already been empirically validated: cumulative incidence (actual analysis) [9].

When compared to standard Kaplan–Meier figures, freedom from reoperation according to cumulative incidence analysis yielded more favourable results for the long-term fate of biological prostheses (cf. Figs. 1–3). For the age-group 60 years and older, we observed a higher rate of freedom from reoperation by 11 and 29% after 10 and 15 years, respectively, when comparing Kaplan–Meier to cumulative incidence (Table 2). This difference was not primarily due – as previously thought – to age of the patients: In the group 65 years and older, the analyses differed by 9 and 19% after 10 and 15 years, respectively. In the younger age group (age 60–65 years), however, the difference between the two methods amounted to 10% at 10 years and 26% at 15 years, respectively. The observed difference is the result of taking the risk, which death always poses, into account. Actuarial freedom from reoperation

Table 2  
Freedom from reoperation, Kaplan–Meier vs. cumulative incidence analysis

Age (years)	Freedom from reoperation, Kaplan–Meier vs. cumulative incidence analysis	
	At 10 years (%)	At 15 years (%)
>60	79:90	55:83
60–65	76:86	48:75
>65	85:94	73:92

estimates the conditional risk of a patient to get a reoperation under the condition that he survives this period. From the point of view of a 70-year-old patient, however, it might be more important to know: “What is the chance my valve will fail before I die?”

To date, 10% of all patients have had a reoperation, and a few more would be expected in the 87 patients who remained alive. When the whole series is completed (every valve either explanted or the patient dead), the cumulative incidence value of 17% at 15 years (Fig. 1) may be about the percentage of all patients who will in fact have had a reoperation. In fact, if 16 of those 87 patients should undergo a reoperation, the cumulative incidence value at 15 years would be achieved. On the other hand, the Kaplan–Meier at 15 years is 45% (Fig. 1); even if every single one of the remaining 87 patients (34%) had an explant, it would not equal the Kaplan–Meier estimate (10% + 34% = 44%). The Kaplan–Meier estimate of reoperation will never be ‘actually’ achieved, as long as patients continue to die.

One important limitation of a competing risks analysis is the mathematical assumption of independent events. This assumption may not be true. Death prevents subsequent re-interventions, but re-interventions may alter subsequent risks of death [3]. Therefore, projecting risk outward from the followed subjects to those lost to death might over- (or under-) estimate what the reoperation risk of the latter subjects would have been if their death had been prevented. The lack of population comparability in cumulative incidence analysis is a further argument for providing both curves – Kaplan–Meier and cumulative incidence.

Another limitation of our study is to be seen in its retrospective design. In the 26-year study period, many changes and improvements in echocardiographic evaluation of valve function could be observed and a comparable set of data was therefore not available. Precise histological findings were made available after reoperation, though, making freedom from reoperation a more reliable measure of valve function than freedom from SVD and, in our point of view, also a more patient-relevant one.

## 5. Conclusion

The difference between the respective freedom from reoperation was evident for all patient outcomes we analysed. In the subgroup of patients 60–65 years of age with an earlier progression of mitral valve disease, this difference was more evident which might be due to the presence of severe risk factors for death. Bioprostheses are usually recommended for patients 70 years and older. Our data also suggest a benefit in a younger age group. Cumulative incidence curves enabled us to determine lower age bounds for the use of biological valves, depending on the eventual risk of replacement one wishes to tolerate.

Our study confirms the observations of Grunkemeier and associates in a German population and helps to underline the importance of cumulative incidence in evaluating patient outcome in view of the fact that this method is not usually applied. We request that reporting cumulative incidence figures should become standard.

## Acknowledgements

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## Appendix A. Conference discussion

**Dr J. Revuelta (Santander, Spain):** I fully agree with your aim. However, you have mixed the terms “structural valve deterioration” with “freedom from reoperation.” As you well know, not all patients with SVD are reoperated and not all reoperated patients have SVD. Your study only demonstrates that actuarial analysis overestimates the freedom from reoperation compared to actual analysis of biological prostheses in the mitral position. Do you have any comment on that?

**Dr Guenther:** We also calculated actuarial and actual freedom from structural valve degeneration, however, we chose freedom from reoperation, because here we had a fixed date to use. Sometimes it is difficult to determine the beginning of structural valve degeneration.

**Dr D. Wheatley (Glasgow, Scotland):** It is always difficult when you present a paper and then somebody asks you why you didn’t do it differently, but I will ask you that. Most of us I would think would use

biological valves in the aortic position, certainly in Western Europe and North America. Did you do a similar sort of study with a population of aortic valve replacements?

**Dr Guenther:** Until now we only studied our patients with mitral valve replacement. We don't have data on aortic valve replacement, but we plan to analyze this patient group.

**Dr Wheatley:** What is the message that you would give to the audience

now about your experience on bioprostheses in the mitral position? Do you have a recommendation as a result of this?

**Dr Guenther:** Well, taking into account these results and the fact that we have to deal with an increasing number of older patients with significant co-morbidity, and considering the fact that with newer technologies in management of atrial fibrillation, we think that bioprostheses may have a renaissance.