Long-term follow-up after aortic valve replacement with Edwards Prima Plus stentless bioprostheses in patients younger than 60 years of age

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Objectives: The Edwards Prima Plus was one of the first stentless aortic valve bioprostheses, with larger orifice areas and improved hemodynamics compared to stented bioprostheses. The aim of the present single-center retrospective study was to assess the long-term results of the Edwards Prima Plus in patients 60 years old or younger.

Methods: From 1993 to 2001, 120 patients (99 men and 21 women) aged 60 years or younger underwent implantation of the Edwards Prima Plus. The indications were stenosis and/or insufficiency. Associated procedures were performed in 38 patients (31.7%). Of the patients, 39% had impaired left ventricular function. Follow-up data were acquired by telephone interview. Time-to event analyses were performed using the Kaplan-Meier method. Variables affecting survival and freedom from reoperation were evaluated using Cox regression analysis. The mean patient age at surgery was 53.1 ± 8.0 years. The follow-up data were 88.8% complete at a mean of 8.5 ± 4.5 years. The total follow-up was 1022.7 patient-years.

Results: At 10 and 15 years, the overall actuarial survival rate was $71.8\% \pm 4.4\%$ and $48.8\% \pm 9.6\%$, respectively. Survival was significantly lower for patients with older age, aortic insufficiency as the surgical indication, and small prosthesis size (≤ 25 mm vs ≥ 27 mm). Reoperation was performed in 20 patients (16.7%), with a hospital mortality of 5%. At 10 and 14 years, the overall freedom from reoperation rate was $85.6\% \pm 3.7\%$ and $65.2\% \pm 8.6\%$, respectively. Freedom from reoperation was significantly lower in patients with a small prosthesis size (≤ 25 mm) and insufficiency as the indication for surgery.

Conclusions: In patients aged 60 years or younger, an Edwards Prima Plus can provide reliable long-term results with acceptable freedom-from-reoperation rates. (*J Thorac Cardiovasc Surg* 2014;147:264-9)

The Edwards Prima Plus (EPP) was introduced in the early 1990s. It is one of the first stentless aortic valves (SAVs). The SAVs have larger orifice areas and lower transvalvular pressure gradients than the stented aortic valve replacements (AVRs) owing to improved hemodynamics.¹ Reduced calcification in the murine model could be shown for the preservation method used for the EPP.² Furthermore, the clinical midterm results also revealed excellent freedom from structural valve deterioration.³

The actual guidelines recommend mechanical AVR in patients aged 60 years or younger and bioprosthetic AVR in patients older than 60 years.⁴ This is because of the greater durability of mechanical AVR, which circumvents the need for later reoperations. However, no significant difference exists in survival between mechanical and bioprosthetic AVR.⁵ EPP could have better longevity and therefore also be used in younger patients, because it has

demonstrated advanced hemodynamics and a reduced potential for calcification. The aim of the present single-center retrospective study was to assess the long-term results after implantation of an EPP in patients aged 60 years or younger to determine whether the age recommendation in guidelines can be lowered for implantation of EPPs.

METHODS

From 1993 to 2001, 120 consecutive patients aged 60 years or younger underwent implantation of an EPP. Either the patient's explicit desire for a bioprosthetic AVR or a contraindication to oral anticoagulation resulted in the choice of an EPP. During the study period, 321 patients aged 60 years or younger underwent implantation of a mechanical prosthesis in the aortic position. The indications were stenosis and/or regurgitation. Patients with endocarditis and dissections of the ascending aorta were excluded.

Follow-up data were acquired through telephone interviews and/or clinical examination and follow-up was closed on October 21, 2010. The follow-up data were 88.8% complete at a mean of 8.5 ± 4.5 years. The total follow-up period was 1022.7 patient-years, with a maximum of 17.0 years.

Data collection and statistical analyses were done according to the current guidelines for reporting mortality and morbidity after cardiac valve interventions.⁶ The local ethics committee approved the study.

Statistical Analysis

All data were analyzed with PASW Statistics, version 18.0.0 (SPSS, Chicago, Ill). Descriptive statistics are reported as the mean $\pm$ standard deviation for continuous variables and as frequencies and percentages

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Abbreviations and Acronyms

AVR = aortic valve replacement
EPP = Edwards Prima Plus
SAV = stentless aortic valve

for categorical variables, unless otherwise noted. Survival and time-to-event analyses were performed using Kaplan-Meier actuarial methods. Age-stratified curve comparisons were performed using the log-rank test. All *P* values were 2-sided. In addition, proportional hazard models were used to investigate the following variables as risk factors for survival and freedom from reoperation: gender, age, left ventricular function, aortic valve lesion, associated procedures, and EPP diameter. The preoperative characteristics often associated with mortality (eg, renal function, diabetes, chronic obstructive lung disease, peripheral arterial disease, pulmonary hypertension) were not adequately captured during the earlier portion of the study. In the later portion of the study, these characteristics were not often present (probably because of the low age of the study cohort). Thus, these characteristics were not entered as covariates in the analyses.

Age- and gender-matched survival estimates from the German general population were obtained from the Human Life Table Database.⁷ Age- and gender-specific conditional probabilities of surviving a 1-year age interval were used to create an age- and gender-matched patient sample. The survival line depicted in Figure 1 represents these averaged conditional probabilities of survival.

RESULTS

The baseline preoperative characteristics and operative data are presented in Table 1.

Overall, the hospital mortality was 3.3% (*n* = 4). At 10 and 15 years, the overall actuarial survival rate was 71.8% ± 4.4% and 48.8% ± 9.6%, respectively

(Figure 1). For isolated implantation of an EPP, the actuarial survival at 10 and 15 years was 69.5% ± 5.5% and 62.5% ± 8.2%. The linearized mortality rate was 3.3%/y overall and 3.0%/y for isolated implantation of an EPP. On univariate risk stratification, older age, isolated insufficiency as the surgical indication, and small prosthesis size (EPP ≤25 mm vs ≥27 mm) significantly lowered survival. Multivariate risk stratification supported these risk factors (Table 2).

Overall, reoperation was performed in 20 patients: in 17 because of structural valve deterioration and in 3 because of endocarditis. At 10 and 14 years, the overall freedom from reoperation rate was 85.6% ± 3.7% and 65.2% ± 8.6%, respectively (Figure 2). Only 1 patient was at risk at 15 years for determining the freedom from reoperation rate and 3 patients were for determining the 14-year freedom from reoperation rate. Therefore, the later reoperation rates should be considered with caution, and additional follow-up is needed. Univariate and multivariate risk stratification revealed small prosthesis size (EPP ≤25 mm vs ≥27 mm) and isolated insufficiency as the surgical indication as predictors of inferior freedom-from-reoperation rates (Table 2).

The hospital mortality of patients after reoperation was 5% (*n* = 1) and, in consideration of the low number of cases, comparable to the overall hospital mortality.

DISCUSSION

The use of biologic AVR in younger patients is still controversial. The major disadvantage of biologic AVR is structural

FIGURE 1. Survival of study population compared with general population and patients with normal left ventricular function, isolated aortic valve procedure, and stenotic valve lesion. EPP, Edwards Prima Plus.

TABLE 1. Baseline characteristics and operative data

Characteristic	Value
Patients	120
Mean age (y)	53.1 ± 8.0
Gender	
Male	99 (82.5)
Female	21 (17.5)
Aortic valve lesion	
Stenosis	38 (31.7)
Insufficiency	51 (42.5)
Mixed lesion	31 (25.8)
Left ventricular function	
Normal (LVEF > 50%)	73 (61)
Moderately impaired (LVEF < 50% but > 30%)	33 (27)
Profoundly impaired (LVEF < 30%)	14 (12)
Isolated EPP implantation	82 (68.3)
Combined procedure	38 (31.7)
Implanted valve size (mm)	
23	1 (0.8)
25	22 (18.3)
27	50 (41.7)
29	47 (29.2)

Data in parentheses are percentages. EPP, Edwards Prima Plus; LVEF, left ventricular ejection fraction.

valve deterioration and the need for reoperation. In 1998 and 2006, the American Heart Association and the American College of Cardiology recommended the use of bioprosthetic AVR in patients older than 65 years.^{8,9} An update in 2010 lowered the age to 60 years⁴ because of improved valve durability and lowered risk of reoperation, even with the increasing life expectancy. The EPP, as a representative of SAVs, shows better hemodynamic performance than a stented AVR.¹ In patients with left ventricular impairment, implantation of SAVs results in greater improvement of left ventricular function¹⁰ and a reduction of late mortality is shown.¹¹ Additionally, there could be an effect on long-term durability, owing to less stress on the bioprosthetic cusps caused by a more physiologic flow pattern.

Various studies have reported on the mortality and durability after AVR, but only few were primarily concerned

TABLE 2. Risk factors for survival and freedom from reoperation in multivariate analysis

Characteristic	Survival			Freedom from reoperation		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.07	1.01-1.14	.04	0.96	0.97-0.92	.22
Gender	1.68	0.56-5.04	.35	4.05	0.94-17.5	.06
Aortic valve lesion	5.17	1.38-15.64	.01	0.25	0.09-0.71	.01
Left ventricular function	0.46	0.17-1.21	.11	1.68	0.6-4.7	.33
Associated procedures	1.44	0.68-3.04	.34	1.68	0.57-4.95	.34
Diameter of EPP (≤25 mm)	3.06	1.49-6.3	.00	6.36	2.26-17.87	.00

OR, Odds ratio; CI, confidence interval; EPP, Edwards Prima Plus.

with the long-term results in younger patients. For example, Weber and colleagues¹² recently published a comparison of stented pericardial tissue valves and mechanical prostheses for AVR in patients younger than 60 years old. They reported a reduced midterm survival after implantation of stented pericardial tissue valves; however, they had a mean follow-up of just 33 months. In particular, for SAVs, owing to their introduction only about 20 years ago, only few long-term results have been published for larger cohorts of patients aged 60 years old. For example, Bach and colleagues¹³ reported excellent clinical outcomes and durability for the Medtronic Freestyle prosthesis (Medtronic, Minneapolis, Minn), although they reported on only about 57 patients with a mean follow-up of just 6.8 years. For the EPP, no long-term results for patients aged 60 years or younger have been published. The longest published follow-up has been for patients with a mean age of 72.2 years.¹⁴

Data for comparison of our study population was found in the younger subgroups of larger studies. In general, one should always consider the differences between the study cohorts, because of their influence on the outcome. Survival will be lowered by various comorbidities, the use of combined procedures, and an impaired left ventricular function. Furthermore, isolated insufficiency as cause of AVR is associated with inferior early- and long-term survival, especially in younger age patients.¹⁵ The age of the study cohort is of particular importance, because it influences the survival of the study cohort and the durability of the prostheses and because freedom from reoperation decreases with the younger age of patients.⁵ These facts must be considered, because our study cohort had a high fraction of patients with impaired left ventricular function (39%) and isolated insufficiency as the surgical indication (42.5%), and in 31.7% of the cases, additional procedures were done.

A review of selected studies is presented in Table 3, which clarifies the comparable survival throughout the different valve types, if one remembers the differences in the study cohorts (especially the difference in the mean age). For the comparison of bioprosthetic AVR and mechanical AVR, comparable survival was also approved by several randomized trials.^{5,16} However, Ruel and colleagues¹⁶ showed a survival advantage of about 13% at 20 years of follow-up for bioprostheses compared with mechanical AVR. Freedom from death, attributable to ischemic or hemorrhagic stroke after 20 years, was 14% greater for those with tissue AVR than those with mechanical AVR.¹⁶ Additionally, the requirement for lifelong anticoagulation treatment¹⁷ results in an elevated risk of bleeding¹⁸ and thromboembolic complications.¹⁵

The comparison with the age- and gender-matched general German population was done by creating a comparable cohort inside our study population. To obtain such a cohort,

FIGURE 2. Freedom from reoperation of total study population and stratified by diameter of Edwards Prima Plus (EPP).

we included the patients with isolated implantation of an EPP and normal left ventricular function. The patients with isolated aortic valve regurgitation as the surgical

indication were excluded because of the previously mentioned impaired survival.¹⁵ Figure 1 shows the slightly lower survival of this selected cohort than that of the general

TABLE 3. Long-term outcome of several comparable studies

Investigator	Prosthesis type	Patient age (y)	Survival (%)	Freedom from reoperation (%)
Present study	EPP	53.1	10 y: 71.8% 15 y: 48.8%	10 y: 85.6% 14 y: 65.2% Median: 14.5 y
Welke et al, ¹⁹ 2011	Stented bioprosthesis (Carpentier-Edwards)	50-64 (mean NR)	10 y: ~72% 15 y: ~57%	10 y: 68% 15 y: ~41%
McClure et al, ²² 2010	Stented bioprosthesis (Carpentier-Edwards)	≤65 y (mean NR)	10 y: 71.5% 15 y: 43.7%	NR for age ≤65 y
Valfre et al, ²³ 2010	Hancock II stented bioprosthesis	≤60 y (mean NR)	10 y: 69.4% 15 y: 60.0%	10 y: 87.4% 15 y: 62.6%
Ruel et al, ¹⁶ 2007	Stented bioprosthesis	47.6 y	10 y: ~80.0% 15 y: ~75.0% 20 y: 65.5%	20 y: 11.4% Median: 10.2 y
	Mechanical prosthesis	47.6 y	10 y: ~80.0% 15 y: ~70.0% 20 y: 52.3%	20 y: 73.0% Median: >35 y
Rizzoli et al, ²⁴ 2006	Hancock II stented bioprosthesis	≤60 y (mean NR)	NR for age ≤60 y	15 y: 55.8%
Oxenham et al, ¹⁸ 2003	Mechanical prosthesis (Bjork-Shiley)	53.9 y	10 y: 64.0% 20 y: 28.4%	10 y: 95.8% 20 y: 92.6%
	Stented bioprosthesis	53.9 y	10 y: 65.7% 20 y: 31.1%	10 y: 88.7% 20 y: 43.8%
Hammermeister et al, ^{5,25} 2000, 1993	Mechanical prosthesis	59 y	11 y: 47% 15 y: 34%	11 y: 93% 15 y: 90%
	Stented bioprosthesis	59 y	11 y: 41% 15 y: 21%	11 y: 84% 15 y: 71%
Chambers et al, ²⁰ 1997	Pulmonary autograft procedure (Ross procedure)	32 y	20 y: 61%	20 y: autograft, 75% 20 y: homograft, 80%

EPP, Edwards Prima Plus; NR, not reported.

population. If one remembers that the reported mortality rates for younger patients after AVR have been greater than those in the general population, but that older patients reach the same survival rate as the general population,¹⁹ these are satisfactory results.

In terms of the durability of bioprosthetic AVR, the freedom from reoperation rates in the different studies were comparable (Table 3). In summary, EPP showed better freedom from reoperation rates than did various other studied valves, especially remembering the low mean age of our study cohort with its effect on lowering durability.⁵ In the present study, age did not lower the freedom from reoperation (Table 2), another indication of the superior durability of EPP. Mechanical AVR showed superior durability; however, the low reoperation rates for mechanical AVR must be weighed against the disadvantages. The pulmonary autograft procedure shows high freedom from autograft or pulmonary position homograft replacement²⁰ but is still controversial regarding late autograft competence and the consequences of creating pulmonary valve disease. Additionally, it was primarily used for patients far younger than those in our cohort and lacks comparable long-term results.²⁰

In particular, patients with impaired left ventricular function should be considered. The improved hemodynamic behavior of SAVs has been reported to lead to an improvement in left ventricular function¹⁰ and a resulting survival benefit.²¹ In general, patients with impaired left ventricular function tend to have a worse outcome. This results in a reduction of patients in need of reoperation. Because of the high freedom from reoperation observed in the present study, the implantation of EPP can be especially recommended for these patients.

Study Limitations

The major limitation was the retrospective nature of our study, which could have led to an underestimation of the complication rates owing to patient misinterpretation or recall bias. Despite this limitation, we must remember that a controlled randomized trial of young patients involving stentless, stented, and mechanical AVR is not possible or, at least, would be very difficult to perform.

CONCLUSIONS

After AVR with EPP in younger patients (which, to our knowledge, has not yet been studied in larger cohorts), we found long-term results in survival, comparable to those for stented biologic AVR and mechanical AVR. Freedom from reoperation after implantation of EPP was at least comparable to that after stented AVR but was worse than that after mechanical prostheses.

We have concluded that AVR with EPP is also an acceptable option for the treatment of aortic valve disease in younger patients.

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