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Abstract: OBJECTIVES: Outcome of aortic valve replacement may be influenced by the choice of bioprosthesis. Pericardial heart valves are described to have a favourable haemodynamic profile compared with porcine valves, although the clinical notability of this finding is still controversially debated. Herein, we compared the long-term results of two commonly implanted bioprosthesis at a single centre. METHODS: All consecutive patients undergoing isolated aortic valve replacement with either a Carpentier-Edwards Magna pericardial prosthesis or a Medtronic Mosaic porcine prosthesis between 2002 and 2008 were analysed regarding preoperative characteristics, short- and long-term survival, valve-related complications and echocardiographic findings. RESULTS: The Medtronic Mosaic was implanted in 163 patients and the Carpentier-Edwards Magna in 295 patients. The sizes of implanted valves were 22.4 ± 1.5 mm for the Mosaic and 21.8 ± 1.8 mm for the Magna (P = 0.001). The long-term survival rate was 76 and 56% after 5 and 10 years for the Medtronic Mosaic, which was comparable with the Carpentier-Edwards Magna (77 and 57%; P = 0.92). Overall long-term survival was comparable with an age- and sex-matched Austrian general population for both groups. Valve-related adverse events were similar between groups. The post-operative mean transvalvular gradient was significantly increased in the Mosaic group (24 ± 9 mmHg vs 17 ± 7 mmHg; P < 0.001). CONCLUSIONS: Both types of aortic bioprostheses offer excellent results after isolated aortic valve replacement. Despite relevant differences in gradients, long-term survival was comparable with the expected normal survival for both bioprostheses. Patients with a porcine heart valve had a higher postoperative transvalvular gradient.

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Comparable long-term results for porcine and pericardial prostheses after isolated aortic valve replacement

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Abstract

Objectives
Outcome of aortic valve replacement may be influenced by the choice of bioprosthetic valve. Pericardial heart valves are described to have a favorable hemodynamic profile compared to porcine valves, although the clinical notability of this finding is still controversially debated. Herein we compared the long-term results of two commonly implanted bioprostheses at a single center.

Methods
All consecutive patients undergoing isolated aortic valve replacement with either a Carpentier-Edwards Magna or a Medtronic Mosaic porcine prosthesis between 1997 and 2008 were analyzed regarding preoperative characteristics, short- and long-term survival, valve related complications and echocardiographic findings.

Results
The Medtronic Mosaic was implanted in 290 patients and the Carpentier-Edwards Magna in 295 patients. The sizes of implanted valves were 22.5±1.6 mm for the Mosaic and 21.8±1.8 mm for the Magna (p<0.001). Long term survival rate was 73% and 55% after 5 and 10 years for the Medtronic Mosaic, which was comparable to the Carpentier-Edwards Magna (76% and 59%; p=0.688). Further, overall survival was comparable to an age and sex matched Austrian general population for both groups. The postoperative mean transvalvular gradient was significantly increased in the Mosaic group (23±8 mmHg versus 16±6 mmHg; p<0.001). Severe prosthesis patient mismatch was present in five Mosaic patients.
Conclusion

Both types of aortic bioprostheses offer excellent results. Despite relevant differences in gradients, survival was comparable to the expected normal survival for both bioprostheses. Patients with a porcine heart valve had a higher prevalence of prosthesis patient mismatch.

Keywords

Aortic valve replacement, biologic heart valves, bioprosthesis, Survival analysis
Introduction

Aortic valve replacement is among the most commonly performed procedures in cardiac surgery. The optimal prosthesis for aortic valve replacement has not yet been developed. Bioprostheses do not require a lifelong anticoagulation as opposed to mechanical prostheses and offer a satisfactory hemodynamic profile. However, the risk of structural valve degeneration has to be considered.

The number of biologic heart valve implantations significantly increased over the last decades. This is not only due to an increasingly older patient cohort, where biologic prostheses are favoured[1, 2]. The higher durability enabled by improved anticalcification treatment and other optimizations of valve design led to a higher implantation rate in a younger patient population. The two most commonly implanted biologic prostheses are either stent-mounted native porcine aortic heart valves or bovine pericardial valves[3]. Both prostheses have proven clinical outcome over time[4, 5]. They have undergone modifications in design during the past decades to optimize hemodynamic performance and prolong durability.

Pericardial prostheses are credited to have a favorable hemodynamic profile compared to porcine valves[6, 7]. However, the impact of improved postoperative transvalvular gradients on outcome is still a matter of debate. Furthermore, high transvalvular gradients in porcine heart valves seems to be at least partly caused by an echocardiographic phenomenon[8].

The aim of the current study was to compare two commonly implanted bioprostheses at a single center in a real-world setting. The Medtronic Mosaic porcine biologic aortic heart valve and the Carpentier-Edwards Magna pericardial aortic bioprosthesis were analysed regarding survival, reoperation rate, valve related complications and echocardiographic data.
Materials and Methods

Study Population

Data of all consecutive patients undergoing isolated aortic valve replacement with either a Carpentier-Edwards Magna (Edwards Lifesciences, Irvine, CA, USA) or a Medtronic Mosaic porcine prosthesis (Medtronic, St Paul, MN, USA) between 1997 and 2008 at a university hospital were prospectively collected and analyzed. The surgeon made the decision regarding the type of valve prosthesis independent of this analysis. The Medtronic Mosaic was implanted since 1997 and the Carpentier-Edwards Magna was implanted since 2002. All patients with concomitant surgical procedures except of root and/or annular enlargement were excluded from this analysis. All patients without contraindications received phenprocoumon for three months after surgery. Patients were followed by general practitioners and cardiologists without a stringent study protocol.

Data management

The internal review board approved this project (EK 955/2011). Informed patient consent was waived. Patients’ characteristics and risk factors were documented prospectively in the electronic documentation system of our institution. Risk scores (linear and logistic EuroSCORE) were calculated and stored. Follow up was performed in accordance with the current guidelines for reporting mortality and morbidity after cardiac valve interventions[9]. All postoperative hospitalizations and outpatient visits in public hospitals of the same city were assessed. In addition, every patient was contacted by telephone to complete follow – up. Our databank was closed with March 2013.
Mortality. Early mortality was defined as all cause mortality during the first 30 days. In addition to our follow-up, overall mortality was yearly crosschecked with the countrywide database maintained by the national statistical institute (Statistics Austria, Vienna, Austria). All deaths in Austria are registered in the database with the full name, the date of birth and the date of death. Every Austrian citizen who was operated at our department and died thereafter in Austria could be identified. Therefore, follow-up for survival is considered as complete except of foreign patients or patients who left the country.

Morbidity. Nine percent of patients were lost to follow-up for valve related complications after the early postoperative period, 10% in the Edwards Magna group and 8% in the Medtronic Mosaic group with no significant difference between valve types (p=0.346).

Echocardiography. At least one echocardiographic follow up in the echo lab of our institution could be performed in 41% of this population. We calculated the projected effective orifice area index (EOAI) according to the implanted valve size using previously published effective orifice area (EOA) measures and the actual body surface area[7].

Statistical Analysis
Descriptive statistical methods were applied to depict the study population regarding preoperative risk factors. A $\chi^2$ test was performed to analyze the frequencies of binary outcomes between treatment groups. Continuous variables were presented as mean and standard deviations and compared by the T-test. Further, analysis of variance was
used to assess differences in outcome parameters between valve types. The Kaplan-Meier method with a Log-Rank test was performed to compare survival and the number of valve-related events between groups. Further, we calculated the average annual event rates by dividing the observed number of events by the number of follow-up years. Cumulative survival of an age and sex-matched Austrian standard population was computed by the life table method, based on age-sex-specific mortality data of the year 2005 published online by the Austrian Federal Statistical Agency (‘Statistics Austria’). Cumulative survival and 95% confidence intervals for the study population were computed using the product-limit (Kaplan-Meier) method and compared to the standard population. For further survival analysis, a Cox regression was performed for the variables ‘logistic EuroSCORE’ and ‘calculated PPM’. The two-sided significance level was set to 5%. The R package (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics 20 (IBM, Armonk, New York, USA) were used for statistical analysis.
Results

The Medtronic Mosaic was implanted in 290 patients (49.6%) and the Carpentier-Edwards Magna in 295 patients (50.4%). Basic demographic data and risk scores were comparable between groups except for a minor difference in body weight (Table 1). Subjects receiving the Carpentier-Edwards Magna showed a trend towards a lower mean transvalvular gradient prior to implantation (64±24 mmHg versus 59±24 mmHg; p=0.094). The mean implanted valve size was 22.5±1.6 mm for the Medtronic Mosaic, which was significantly larger than the Carpentier-Edwards Magna size (21.8±1.8 mm; p<0.001, Figure 1A). Procedural characteristics including cross clamp time and intraoperative risk factors were comparable (Table 1).

Early mortality between 1997 and 2008 was significantly higher in the Mosaic group (7.6% versus 2.7%; p=0.008). However, analysis of the subgroup of patients receiving the Medtronic Mosaic valve in the same time period as the Carpentier-Edwards Magna was implanted (2003 to 2008), overall early mortality was 2.9% and did not differ between groups (Table 1). Long term survival rate was 73% and 55% after 5 and 10 years for the Medtronic Mosaic, which was comparable to the Carpentier-Edwards Magna (76% and 59%; p=0.688). The overall survival (including perioperative mortality) was comparable to the age and sex matched survival of the Austrian population for both groups (Figure 2).

The observed valve related complications were similar in both groups except of a borderline significantly increased annualized rate of peripheral emboli in the Carpentier-Edwards Magna group (0.7% versus 0.3%; p=0.051; Table 2).
The postoperative mean transvalvular gradient (4±3 months after surgery) was significantly higher in the Mosaic group (23±8 mmHg versus 16±6 mmHg; p<0.001; Figure 1B). The calculated percentage of moderate (EOAI <= 0.85cm²/m² and > 0.65cm²/m²) and severe prosthesis patient mismatch (EOAI <= 0.65cm²/m²) was significantly worse for the Medtronic Mosaic prosthesis (moderate: 49% versus 19%; severe 2% versus 0%; p<0.001). Severe patient-prostheses mismatch showed a trend towards decreased survival in a Cox-regression analysis including the preoperative logistic EuroSCORE (p=0.062).
Discussion

Herein we present a single-center, direct, non-randomized comparison of two bioprostheses currently implanted in the majority of surgical aortic valve replacements in an elderly patient cohort[3]. In contrast to other recent publications, we evaluated a very distinct patient group, which was limited to isolated aortic valve replacements[10]. Thereby, we avoided possible confounding factors such as concomitant coronary artery bypass grafting or other surgical procedures. This resulted in a higher survival rate compared to the publication by Said et al[10]. However, overall survival was equal in both groups of our study. Moreover, it was also comparable to the age and sex matched Austrian population (Figure 2).

The valve related complication rate was low and did only show a minor trend for increased peripheral emboli in the Carpentier-Edwards Magna group. Our data are comparable with previous publications reporting favorable survival with these valves in an elderly population[4, 5, 11]. Differences in early mortality between the two cohorts are probably related to the fact that the Medtronic Mosaic valve was introduced five years earlier at our department. This is confirmed by the sub-analysis of patients who were operated in the same time period (2003 to 2008), which showed similar early mortality in both valve types.

The central question, which is always addressed in the literature regarding porcine heart valves, is the presence, cause and effect of high transvalvular gradients[7]. As expected, transvalvular gradients were also increased in our postoperative echocardiographic follow up of the Medtronic Mosaic valve. However, long-term survival was not affected by gradients and did not differ between groups. A potential explanation may be that the observed differences in gradients as such do not affect
long-term outcome in this elderly patient cohort. Otherwise, the observed higher gradients measured in the Mosaic valve could also be caused by an echocardiographic phenomenon[8]. The concept of this phenomenon, called pressure recovery, was previously published and advocates that the majority of the observed gradient in the Medtronic Mosaic group is again transferred to aortic pressure after the aortic prosthesis due to the laminar flow pattern[12].

Another aspect has to be addressed in the discussion regarding postoperative transvalvular gradients. Previous publications highlighted the variable labeling of valve sizes and also reported a difference in the inner diameter of size-matched prostheses up to 2 mm[13, 14]. Therefore, studies comparing different aortic valve prosthesis according to the labeled implanted valve size have to be interpreted with caution. Our department introduced the Medtronic Mosaic early and previously published a randomized analysis comparing implanted valve sizes in relation to the real annular diameter measured with a hegar dilator[15]. The implanted Carpentier-Edwards Magna labeled sizes were smaller compared to the Medtronic Mosaic valve for a standardized annular measurement. This was observed again in the current analysis. Not one 19mm Medtronic Mosaic valve was implanted in this patient population and the average diameter according to the labeled size was 0.7 mm higher in the Medtronic Mosaic group (Figure 1A).

The size of the implanted prosthesis is major determinant for prosthesis patient mismatch[16]. A severe mismatch below 0.65cm²/m² has been identified as a potential risk factor for long-term mortality[17]. Severe prosthesis patient mismatch may induce turbulent flow in the ascending aorta, which would theoretically diminish the pressure recovery effect. Our data are in line with the current perception regarding the impact of severe prosthesis patient mismatch on long-term survival. Five patients
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with severe prosthesis patient mismatch were observed during the study period, all in the Medtronic Mosaic group. These five patients did present with a trend towards increased mortality. However, no difference could be detected in the moderate prostheses patient mismatch group as previously described[17].

Limitations

The current study is retrospective in nature. Although follow-up for survival was complete due to the crosscheck with the statistical institute, follow-up for valve related adverse events was based solely on a database research and telephone follow-up. Restoration of normal life expectancy in elderly patients should not be extrapolated to younger age groups, as death from competing causes obscure valve related mortality. Furthermore, elderly patients accepted for cardiac surgery at a given age may be in a better general health condition compared to the general population. Only routine echocardiographic studies without a distinct time schedule were available. Therefore, the projected rather than the measured effective orifice area index was used for prosthesis patient mismatch grading. Due to the later introduction of the Carpentier-Edwards Magna, follow-up time periods differ between the two groups.

In conclusion, both types of aortic bioprostheses offer excellent long-term results as documented by comparison with the Austrian standard population. Differences in transvalvular gradients had no impact on long-term survival, as long as severe prosthesis patient mismatch was avoided.
# Tables

Table 1: Preoperative patient characteristics, procedural specifications and follow up.

| Factor                              | Porcine | Pericardial | P-value |
|-------------------------------------|---------|-------------|---------|
| Age (years)                         | 74±8    | 73±9        | 0.261   |
| Sex (f/m)                           | 55%/45% | 54%/46%     | 0.756   |
| Height (cm)                         | 167±9   | 166±12      | 0.241   |
| Weight (kg)                         | 75±14   | 78±18       | 0.037   |
| Body surface area (m²)              | 1.88±0.21 | 1.91±0.23  | 0.182   |
| NYHA II                             | 34%     | 31%         | 0.813   |
| NYHA III-IV                         | 61%     | 63%         | 0.813   |
| Linear EuroSCORE                    | 8±3     | 7±3         | 0.111   |
| Logistic EuroSCORE                  | 11±11   | 10±10       | 0.302   |
| EF > 50% (%)                        | 72%     | 75%         | 0.686   |
| Heart rate (bpm)                    | 73±15   | 72±13       | 0.375   |
| Systolic blood pressure (mmHg)      | 131±24  | 131±22      | 0.963   |
| Diastolic blood pressure (mmHg)     | 73±35   | 71±16       | 0.440   |
| FVC (l)                             | 2.7±0.9 | 2.7±0.8     | 0.815   |
| FEVI (%)                            | 88.6±21.8 | 87.7±23.6 | 0.709   |
| Hemoglobin (g/dl)                   | 12.8±1.6 | 13.0±1.8   | 0.209   |
| Platelets (G/l)                     | 223±72  | 227±69      | 0.494   |
| Creatinine (mg/dl)                  | 1.2±0.7 | 1.2±0.7     | 0.692   |
| Mean preoperative gradient (mmHg)   | 64±24   | 59±24       | 0.094   |
| Duration of anesthesia (min)        | 277±66  | 275±64      | 0.693   |
| Cross clamp time (min)              | 59±20   | 57±14       | 0.164   |
|                          | Porcine | Pericardial | P value |
|--------------------------|---------|-------------|---------|
| Red blood cell units (packs) | 2.7±1.7 | 2.8±2.2     | 0.598   |
| Valve Size (mm)          | 22.5±1.6| 21.8±1.8    | <0.001  |
| Revision for bleeding    | 6.2%    | 7.1%        | 0.658   |
| Early mortality (1997 – 2008) % | 7.6    | 2.7         | 0.008   |
| Early mortality (2003 – 2008) % | 3.1    | 2.7         | 0.832   |
| Follow Up (months)       | 73±44   | 61±27       | <0.001  |

Caption: Porcine: Medtronic Mosaic; Pericardial: Carpentier-Edwards Magna;

Continuous data are presented as the mean ± standard deviation; categorial data as percentage; bpm: beats per minute.
Table 2: Valve related long-term outcome regarding adverse events (%/year).

| Factor                                      | Porcine | Pericardial | P-value |
|---------------------------------------------|---------|-------------|---------|
| Structural valve deterioration (reoperation)| 0.3%    | 0.1%        | 0.996   |
| Nonstructural dysfunction (reoperation)     | 0.3%    | 0.3%        | 0.829   |
| Embolism                                    |         |             |         |
| Stroke                                      | 1.8%    | 2.2%        | 0.682   |
| TIA                                         | 0.6%    | 0.7%        | 0.779   |
| Emboli                                      | 0.3%    | 0.7%        | 0.051   |
| Myocardial infarction                       | 0.3%    | 0.2%        | 0.845   |
| Valve thrombosis                            | 0.2%    | 0.2%        | 0.775   |
| Bleeding event                              | 0%      | 0.1%        | 0.315   |
| Endocarditis                                | 0.5%    | 1.0%        | 0.309   |
| Endocarditis (reoperation)                  | 0.1%    | 0.3%        | 0.987   |

Caption: Porcine: Medtronic Mosaic; Pericardial: Carpentier-Edwards Magna;

Continuous data are presented as the mean ± standard deviation; categorical data as percentage; valve related complications are presented as annualized rates, p-values are retrieved from the Kaplan-Meier Log-Rank analyses.
Figure legends

Figure 1: Implanted valve sizes and postoperative transvalvular gradients
Caption: A) Valve sizes according to manufacturers labeling (p<0.001); B) An interpolation line for each group was drawn with a LOESS function.

Figure 2: Cumulative survival compared the age and sex matched population
Caption: The age and sex matched standard population represents the expected overall Austrian survival for the year 2005.
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