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Article

Long-Term Survival Benefits of Porcine versus Pericardial Bioprostheses in Elderly Patients Undergoing Isolated Aortic Valve Replacement: A 32-Year Study

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Abstract

Background: The elderly population is growing at an unprecedented rate. Aortic valve disease increases with age. Bioprostheses are the valves of choice for older patients; however, the optimal tissue valve remains undetermined. The purpose of this investigation was to perform a life-of-patient survival comparison of the prototypical porcine and pericardial prostheses in elderly patients. **Methods**: The study population (N = 1480) consisted of patients 65 years of age and older who underwent isolated aortic valve replacement from 1990 through 2005 with a Carpentier-Edwards Porcine (n = 650) or Pericardial (n = 830) bioprosthesis. Propensity score-matched groups were created. **Results**: Valve selection was not associated with operative mortality. Survival estimates at 10 years were better for Pericardial (41.8%; 95% CI: 37.9 to 45.7) than Porcine (32.6%; 95% CI: 28.8 to 36.3); and 5.2% (95% CI: 3.2 to 7.1) versus 2.0%; (95% CI: 0.8 to 3.2) at 20 years ($p < 0.001$). E-value analysis found minimal influence of unknown study confounders. Factors associated with long-term mortality were porcine valve ($p < 0.001$), age ($p < 0.001$), diabetes mellitus ($p < 0.001$), preop renal insufficiency ($p < 0.001$), peripheral artery disease ($p = 0.011$), congestive heart failure ($p = 0.003$), New York Heart Association Class III or IV ($p = 0.004$), surgical history-reoperation ($p = 0.012$), transient ischemic attack ($p = 0.009$), prolonged ventilation ($p = 0.010$), postop renal insufficiency ($p < 0.001$), and atrial fibrillation ($p = 0.009$). The indexed Effective Orifice Area (EOAi) was assessed and did not influence observed long-term survival differences. **Conclusions**: This unusual lifetime study provided substantial evidence for the superiority of the pericardial over the porcine bioprosthesis in the aortic position in elderly patients. It demonstrated enhanced long-term survival benefits for elderly patients without any increase in perioperative mortality. It is intended to inform future investigation into aortic valve design.

Keywords

elderly; aortic valve disease; isolated aortic valve replacement; propensity score-matching

Introduction

The elderly represent the fastest growing segment of the population. Aortic valve (AV) disease increases with age and is the most common cause of death world-wide from valvular heart disease [1,2]. The treatment of choice is AV replacement (AVR)—surgical or transcatheter. Current guidelines [3,4] as well as surgical practice [5] favor the use of bioprostheses for elderly patients (age 65 and over). The question remains whether a porcine xenograft or a bovine pericardial valve furnishes enhanced long-term survival benefits for this cohort of patients.

Selecting the optimal bioprosthesis, either porcine or bovine pericardial, for elderly patients is not currently well defined in the medical literature. Several studies have attempted to compare the long-term performance of porcine and pericardial bioprostheses [6–12]. However, these studies have several limitations, including study design, lack of multivariable patient matching, inclusion of concomitant procedures, variable lengths of follow-up and multiple valve manufacturers. It is therefore not surprising that systematic meta-analyses [13–15] have revealed mixed results without a clear demonstration of long-term survival benefits of either valve tissue type.

The purpose of this 32-year study was to compare short- and long-term survival benefits in matched elderly patients undergoing isolated AVR with a porcine xenograft versus a bovine pericardial bioprosthesis using strict inclusion criteria and propensity score-matching of demographic/clinical variables. The goal was not to comment on currently available valve models, but rather to perform a unique analysis of the prototype porcine and pericardial

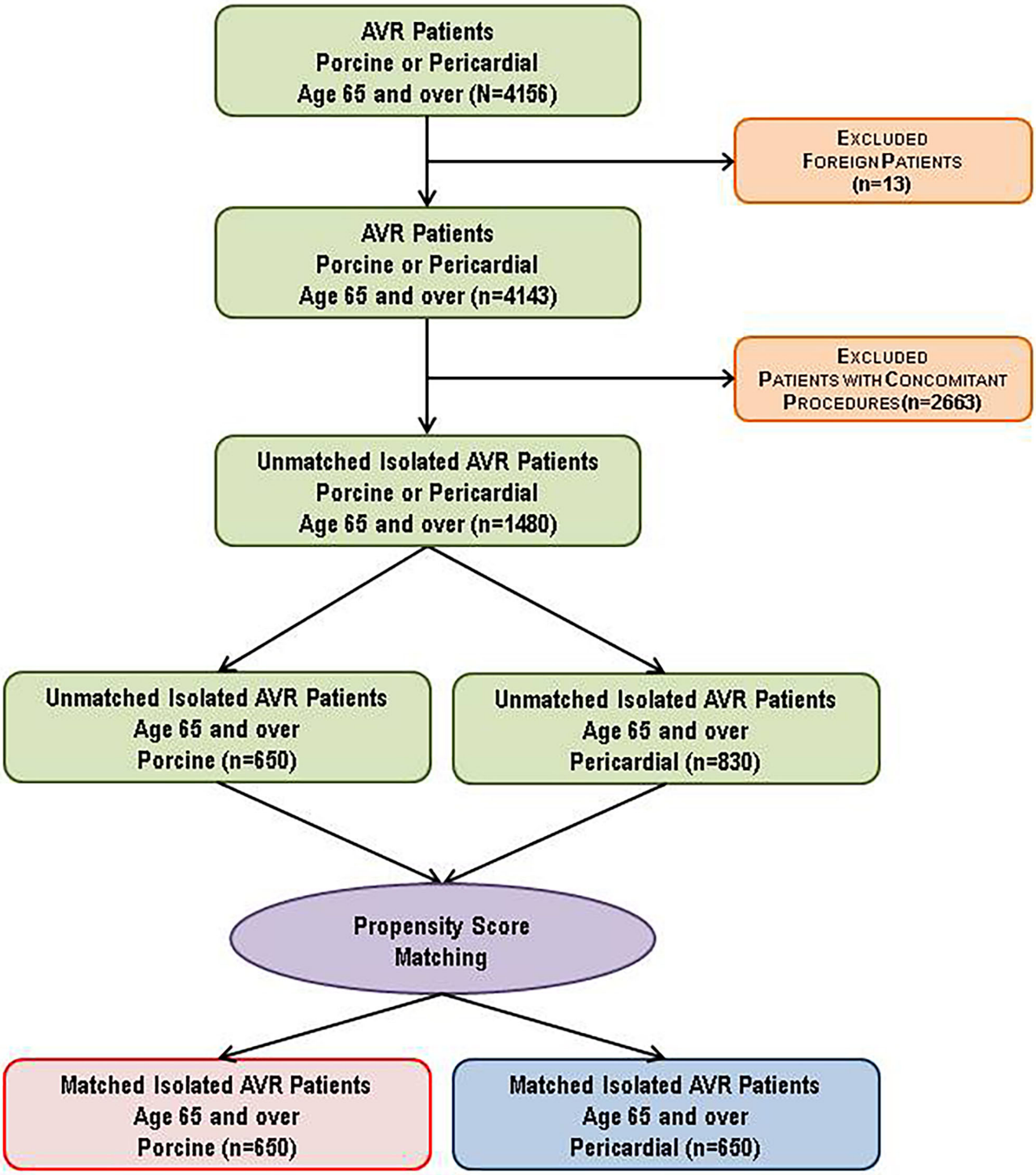

Fig. 1. Patient selection algorithm for the study. AVR, aortic valve replacement.

valves by a single manufacturer which spans the patient lifetime, in order to better inform current and future bioprosthetic valve design.

Materials and Methods

Patient Population

Data were retrospectively reviewed for 4156 consecutive patients who underwent aortic valve replacement (AVR) with a Carpentier-Edwards Porcine Model 2625 or a Pericardial Model 2700 (Edwards Lifesciences LLC, Irvine, CA, USA) between January 1990 and December 2005. Patients with concomitant procedures, e.g., coronary artery bypass grafting (CABG) were excluded from the study population. Foreign patients were also excluded due to the anticipated difficulty in achieving complete follow-up. This resulted in 650 Porcine and 860 Pericardial patients, which were subsequently used to conduct propensity score-matching (Fig. 1). Unmatched patients had markedly different demographic/clinical risk factor profiles. Following propensity score-matching, there was an appropriate balance in preoperative demographic/clinical risk factors, as well as year of operation (Fig. 2 and Table 1).

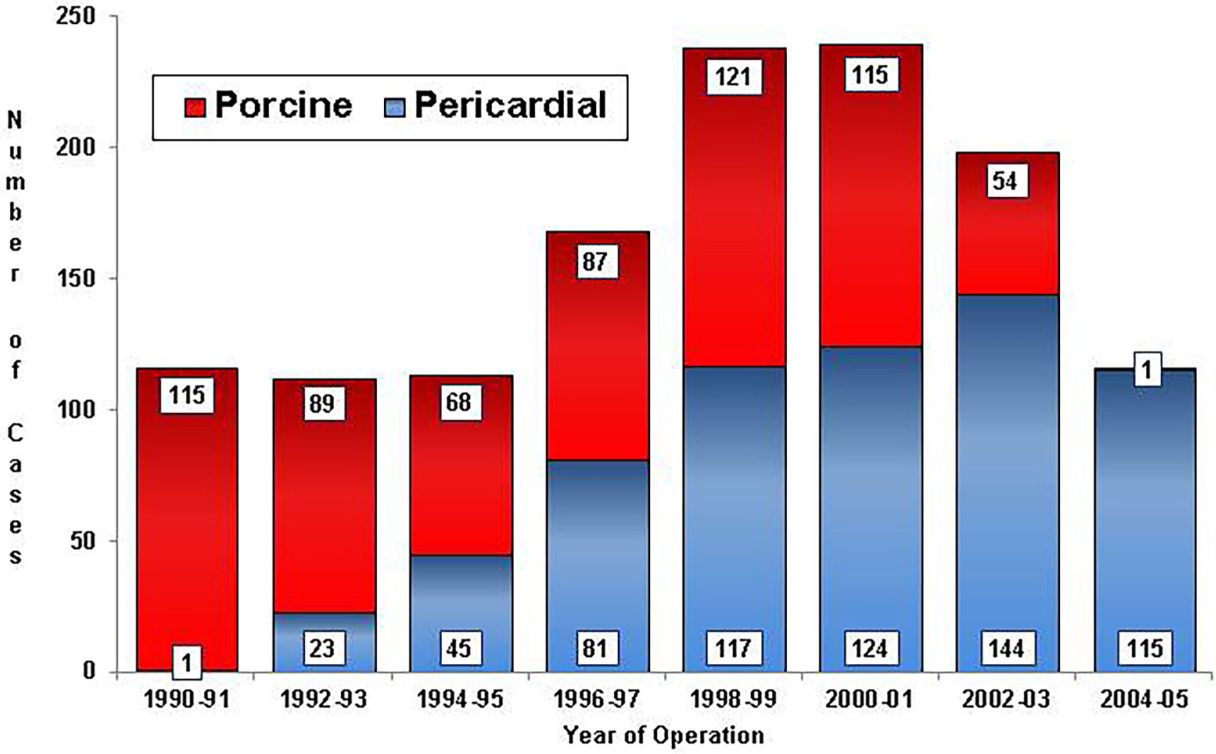

Fig. 2. Biannual distribution of cases by year of operation and valve type implanted in propensity score-matched patients.

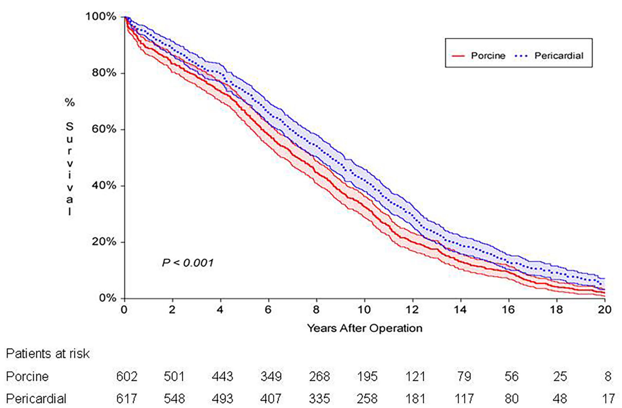

Fig. 3. Comparison of actuarial survival estimates of propensity score-matched patients with a Porcine versus a Pericardial bioprosthesis and discharged alive from the hospital.

Operative Technique

All operations were performed via median sternotomy using similar cardiopulmonary bypass and myocardial protection techniques (intermittent antegrade or combined antegrade/retrograde, cold sanguinous hyperkalemic cardioplegia). The selection of AV bioprosthesis was based on patient and surgeon preferences. Postoperative management of anticoagulation and medical therapy was determined by the referring cardiologist and not controlled in the present study.

Operative Data

The majority of Porcine (56.6%) and Pericardial patients (52.3%) experienced pure aortic stenosis ($p = 0.119$). There was a significant difference in AV dysfunction between groups in the degree of pure insufficiency ($p = 0.001$) and mixed (stenosis and insufficiency) disease ($p < 0.001$). Calcific was the most frequent valve pathology, 68.8% Porcine and 86.0% Pericardial ($p < 0.001$). Between-group differences in AV etiology were observed in the occurrence of bacterial endocarditis ($p = 0.015$), bicuspid ($p < 0.001$), and prosthetic valve dysfunction ($p = 0.012$) etiologies (Table 2).

The mean cardio-pulmonary bypass time for Porcine patients was 80.6 ± 36.3 minutes (range 11 to 335) and 95.4 ± 45.8 minutes (range 38 to 440) for Pericardial patients ($p < 0.001$). The mean duration of aortic cross-clamping for Porcine patients was 54.6 ± 28.1 minutes (range 11 to 161) and 60.4 ± 32.7 minutes (range 15 to 210) for Pericardial patients ($p = 0.001$).

Data Collection and Management

Perioperative data were obtained by prospective review of the patient's hospital record, applying a standardized methodology and definition of terms based on the guidelines of the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Records were subjected to multiple previous data checks and there were no missing data.

Table 1. Comparison of preoperative variables and risk factors for unmatched and propensity score-matched elderly patients undergoing isolated aortic valve replacement.

Variables	Unmatched Patients			Propensity Score-matched Patients		
	Porcine	Pericardial	SMD	Porcine	Pericardial	SMD
No. of patients	650 (100.0)	830 (100.0)		650 (100.0)	650 (100.0)	
Gender			0.099			0.003
Male	363 (55.8)	504 (60.7)		363 (55.8)	362 (55.7)	
Female	287 (44.2)	326 (39.3)		287 (44.2)	288 (44.3)	
Age at operation (years)	76.8 SD: 5.2	76.1 SD: 5.4	0.132	76.8 SD: 5.2	76.7 SD: 5.3	0.019
Family history of CAD	84 (12.9)	170 (20.5)	0.204	84 (12.9)	91 (14.0)	0.032
Hypertension	384 (59.1)	471 (56.7)	0.047	384 (59.1)	383 (58.9)	0.003
Smoking history	87 (13.4)	96 (11.6)	0.055	87 (13.4)	80 (12.3)	0.032
Dyslipidemia	191 (29.4)	192 (23.1)	0.142	191 (29.4)	164 (25.2)	0.093
Diabetes	114 (17.5)	165 (19.9)	0.060	114 (17.5)	120 (18.5)	0.024
Renal insufficiency	45 (6.9)	33 (4.0)	0.130	45 (6.9)	32 (4.9)	0.085
Peripheral artery disease	63 (9.7)	97 (11.7)	0.065	63 (9.7)	63 (9.7)	0.000
Congestive heart failure	318 (48.9)	448 (54.0)	0.101	318 (48.9)	326 (50.2)	0.025
Bacterial endocarditis	19 (2.9)	10 (1.2)	0.121	19 (2.9)	10 (1.5)	0.094
Arrhythmia	184 (28.3)	201 (24.2)	0.093	184 (28.3)	179 (27.5)	0.017
Prior myocardial infarction	95 (14.6)	127 (15.3)	0.019	95 (14.6)	95 (14.6)	0.000
Angina symptoms	335 (51.5)	460 (55.4)	0.078	335 (51.5)	346 (53.2)	0.034
Prior stroke	20 (3.1)	44 (5.3)	0.111	20 (3.1)	23 (3.5)	0.026
NYHA Class III/IV	556 (85.5)	720 (86.7)	0.035	556 (85.5)	558 (85.9)	0.009
Impaired EF (<0.50)	288 (44.3)	357 (43.0)	0.026	288 (44.3)	284 (43.7)	0.012
Reoperation	156 (24.0)	156 (18.8)	0.127	156 (24.0)	132 (20.3)	0.089

Numbers in parentheses are percentages. Abbreviations: SMD, standardized mean difference; SD, standard deviation; CAD, coronary artery disease; NYHA, New York Heart Association; EF, ejection fraction.

A cross-sectional follow-up was conducted between January 2020 and July 2022. Information from government and genealogical internet sites, as well as publicly available obituaries and death notices were used to determine patient survival status. A 99.4% follow-up was obtained with four Porcine patients lost-to-follow-up and 99.8% in the Pericardial group with one patient lost-to-follow-up.

Statistical Analysis

An a priori power analysis was conducted to identify the appropriate sample size for the study. The optimal sample size utilized a moderate effect size (0.30) with beta (β) = 0.80 and alpha (α) = 0.05. The sample size generated was sufficient to support adequate power and the precision of reported confidence intervals (CI). Patient demographic/clinical data are presented as frequency distributions and simple percentages. Values of continuous variables are expressed as mean $\pm$ standard deviation. Univariate analyses of selected preoperative and postoperative discrete variables were accomplished using χ^2 with the appropriate degrees of freedom or Fisher's exact test to assess the equality of proportions. Two-sample t-tests were used for normally distributed continuous variables and Mann Whitney U test for non-normally distributed continuous variables.

To control for measured potential confounders in the dataset, a propensity score was generated for each patient from a multivariable logistic regression model based on selected demographic/preoperative clinical covariates as independent variables, and valve type as the dependent variable. Porcine patients were then matched to Pericardial patients in a 1:1 ratio using a Rosenbaum optimal matching algorithm [16]. The quality of the match between groups was determined by standardized mean differences with a value of $<$0.1 considered indicative of adequate balance.

To identify variables associated with operative mortality, a multivariable logistic regression model was developed using 24 demographic, preoperative and intraoperative clinical characteristics as independent variables and hospital mortality as the dependent variable (**Supplementary Table 1**). Regression coefficients and odds ratios with 95% confidence limits were calculated. A Cox proportional hazards regression model was used to determine the influence of multiple demographic/clinical variables (**Supplementary Table 2**) on long-term survival in patients discharged alive from the hospital. Regression coefficients and hazard ratios, with 95% confidence limits were calculated to determine the relative influence of each covariate on the survivor function. Coefficients were computed by the method of maximum likelihood.

Table 2. Comparison of aortic valve dysfunction and etiology in propensity score-matched elderly patients undergoing isolated valve replacement.

Valve pathology	Porcine	Pericardial	p value
No. of patients	650 (100.0)	650 (100.0)	
Aortic valve dysfunction			
Pure stenosis	368 (56.6)	340 (52.3)	0.119
Pure insufficiency	128 (19.7)	85 (13.1)	0.001
Mixed disease (stenosis and insufficiency)	154 (23.7)	225 (34.6)	<0.001
Aortic valve etiology			
Rheumatic	43 (6.6)	28 (4.3)	0.067
Congenital	17 (2.6)	21 (3.2)	0.510
Calcific	447 (68.8)	559 (86.0)	<0.001
Bacterial endocarditis	21 (3.2)	8 (1.2)	0.015
Bicuspid	75 (11.5)	11 (1.7)	<0.001
Prosthetic valve dysfunction	36 (5.5)	18 (2.8)	0.012
Other etiology	11 (1.7)	5 (0.8)	0.131

Numbers in parentheses are percentages.

Table 3. Comparison of hospital morbidities for propensity score-matched elderly patients undergoing isolated aortic valve replacement.

Variables	Porcine		Pericardial		p value
No. of patients	650	(100.0)	650	(100.0)	
Any postoperative morbidity	291	(44.8)	303	(46.6)	0.504
Any postoperative major morbidity	192	(29.5)	139	(21.4)	<0.001
Reoperation cardiac related	39	(6.0)	44	(6.8)	0.571
Permanent stroke	4	(0.6)	11	(1.7)	0.069
Prolonged ventilation (>24 hours)	167	(25.7)	101	(15.5)	<0.001
Renal insufficiency	49	(7.5)	61	(9.4)	0.232
Deep sternal wound infection	5	(0.8)	2	(0.3)	0.256
Any other postoperative morbidity					
Transient ischemic attack	21	(3.2)	10	(1.5)	0.046
Gastrointestinal disorder	21	(3.2)	40	(6.2)	0.013
Atrial fibrillation	135	(20.8)	126	(19.4)	0.533
Renal dialysis	21	(3.2)	14	(2.2)	0.230
Cardiac arrest	39	(6.0)	24	(3.7)	0.053
Multisystem failure	9	(1.4)	4	(0.6)	0.163

Numbers in parentheses are percentages.

Patient survival was expressed according to the method of Kaplan and Meier with 95% CI using time zero as the date of operation and late death as the endpoint in matched patients. The equality of survival distribution was tested using the log-rank algorithm. Sensitivity analysis was conducted to discern if preoperative unmeasured confounders may have influenced the outcomes. The approach by VanderWeele and Ding [17] was used, which generated an "E-value" with the 95% CI. Two measures were calculated-one for the effect size estimate and the other for the lower bound of the 95% CI. All probability values reported in the analyses were two-sided and not adjusted for multiple testing with a value of ≤0.05 indicating significant differences between measurements. All analyses were performed using NCSS statistical software (Version 2019, NCSS, LLC, Kaysville, UT, USA).

Results

Hospital morbidities and mortality were documented in accordance with the guidelines of the Society of Thoracic Surgeons Adult Cardiac Surgery Database [18]. Postoperative morbidity during the indexed hospitalization was similar for the two groups (p = 0.504), (Table 3). Specific complication rates were comparable, with the exception of gastrointestinal disorder (p = 0.013), transient ischemic attack (p = 0.046), and prolonged ventilation ($p < 0.001$).

The operative mortality rate was 6.2% (81 of 1300), 7.4% (48 of 650) for Porcine and 5.1% (33 of 650) for Pericardial patients (p = 0.085). Logistic regression identified five independent correlates of operative mortality including age at operation (p = 0.013), female gender (p = 0.013), re-

Table 4. Variables influencing late mortality as evidenced by Cox regression analysis in combined propensity score-matched elderly patients undergoing isolated aortic valve replacement.

Predictor variables	Regression Coefficient	Standard Error	Hazard Ratio	95% CI Lower	95% CI Upper	p value[a]
Preoperative						
Age at operation	0.053	0.006	1.05	1.04	1.07	<0.001
Diabetes mellitus	0.291	0.079	1.34	1.15	1.56	<0.001
Renal insufficiency	0.525	0.143	1.69	1.28	2.24	<0.001
Peripheral artery disease	0.271	0.103	1.31	1.07	1.60	0.011
Congestive heart failure	0.192	0.064	1.21	1.07	1.37	0.003
NYHA class III or IV	0.257	0.091	1.29	1.08	1.54	0.004
Surgical history-reoperation	0.204	0.080	1.23	1.05	1.43	0.012
Intraoperative						
Valve type (Porcine)	0.270	0.061	1.31	1.16	1.48	<0.001
Postoperative						
Transient ischemic attack	0.572	0.203	1.77	1.19	2.64	0.009
Prolonged ventilation	0.208	0.079	1.23	1.05	1.44	0.010
Renal insufficiency	0.676	0.129	1.97	1.53	2.53	<0.001
Atrial fibrillation	0.197	0.074	1.22	1.05	1.41	0.009

[a] Only significant variables ($p < 0.050$) are listed. Abbreviations: CI, confidence interval; NYHA, New York Heart Association.

Table 5. Comparison of patient valve size implanted, body surface area, eoa, and eoai cm^2/m^2 for propensity score-matched elderly patients undergoing isolated aortic valve replacement.

Valve size	Porcine n	Porcine BSA Mean (SD)	Porcine EOA Mean (SD)	Porcine EOAi Mean (SD)	Pericardial n	Pericardial BSA Mean (SD)	Pericardial EOA Mean (SD)	Pericardial EOAi Mean (SD)
19 mm	57	1.70 (0.18)	0.90 (1.01)	0.54 (0.06)	99	1.73 (0.18)	1.10 (0.00)	0.64 (0.07)
21 mm	225	1.75 (0.17)	1.50 (0.00)	0.86 (0.08)	236	1.83 (0.21)	1.30 (1.00)	0.72 (0.08)
23 mm	256	1.90 (0.16)	1.70 (1.00)	0.90 (0.08)	189	1.97 (0.19)	1.50 (0.00)	0.77 (0.08)
25 mm	77	1.94 (0.17)	1.90 (0.00)	0.99 (0.09)	102	2.05 (0.18)	1.80 (0.00)	0.89 (0.08)
27 mm	27	1.90 (0.15)	2.30 (0.00)	1.22 (0.10)	22	2.08 (0.18)	2.10 (0.00)	1.02 (0.09)
29 mm	8	1.96 (0.04)	2.80 (0.00)	1.43 (0.03)	2	2.09 (0.15)	2.20 (0.00)	1.06 (0.08)
Overall	650	1.83 (0.19)	1.62 (0.31)	0.89 (0.16)	650	1.90 (0.22)	1.44 (0.25)	0.76 (0.12)

Abbreviations: BSA, body surface area; EOA, effective orifice area; EOAi, effective orifice area index; SD, standard deviation.

nal insufficiency ($p < 0.001$), arrhythmia ($p = 0.002$), and prior stroke ($p = 0.017$). Neither valve type (Porcine or Pericardial, $p = 0.077$) nor valve etiology was associated with operative mortality.

Follow-up was collected for 1219 propensity score-matched patients discharged from the hospital alive: 602 Porcine and 617 Pericardial. The median survival time for Porcine patients was 7.2 years: interquartile range (IQR) 3.7–11.0, ranging from 5 weeks to 24.1 years. In Pericardial patients, the median survival time was 8.6 years: IQR 4.7–12.6, ranging from 6 weeks to 26.9 years ($p < 0.001$). Since survival was better for Pericardial patients, the length of follow-up was necessarily longer.

A Cox proportional hazards regression model of propensity score-matched patients, identified 14 covariates associated with late mortality (Table 4). Valve type, but not etiology, was associated with late mortality with hazard ratio for Porcine patients versus Pericardial patients of 1.29 (95% CI: 1.15 to 1.44; $p < 0.001$). The E-value for the effect size estimate was 1.67 and for the CI 1.44 suggesting it was unlikely that unmeasured or unknown confounders would have had a substantially greater effect on the measured outcome.

Survival estimates for patients discharged from the hospital alive are shown in Fig. 3. At 10 years, survival estimates for Pericardial were better (41.8%; 95% CI: 37.9 to 45.7) than Porcine (32.6%; 95% CI: 28.8 to 36.3); and 5.2% (95% CI: 3.2 to 7.1) versus 2.0%; (95% CI: 0.8 to 3.2) at 20 years ($p < 0.001$). Pericardial patients demonstrated enhanced long-term survival over Porcine patients (HR = 1.29, 95% CI: 1.15 to 1.44, $p < 0.001$) in the present study. The time-related risk hazard for mortality demon-

Table 6. Comparison of indexed EOA for propensity score-matched elderly patients undergoing isolated aortic valve replacement.

Indexed EOA	Porcine		Pericardial		p value
No. of patients	650	(100.0)	650	(100.0)	
Severe PPM (<0.65 cm^2/m^2)	55	(8.5)	114	(17.5)	<0.001
Moderate PPM (0.65 to 0.85 cm^2/m^2)	143	(22.0)	401	(61.7)	<0.001
Mild/Insignificant PPM (>0.85 cm^2/m^2)	452	(69.5)	135	(20.8)	<0.001

Numbers in parentheses are percentages. Abbreviation: PPM, prosthesis-patient mismatch.

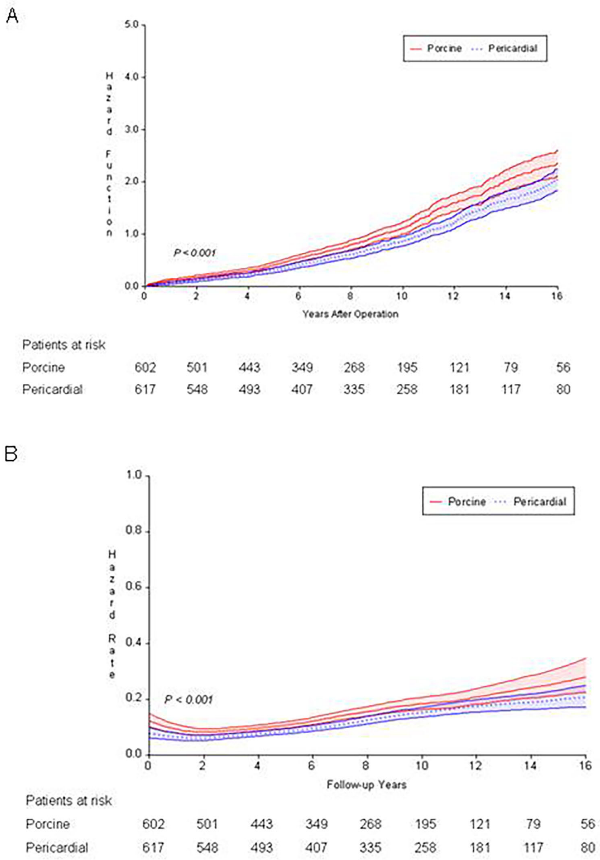

Fig. 4. All-cause mortality in propensity score-matched patients with a Porcine versus a Pericardial bioprosthesis discharged alive from the hospital. (A) Cumulative hazard function curves with 95% confidence limits. (B) Hazard rates curves with 95% confidence limits.

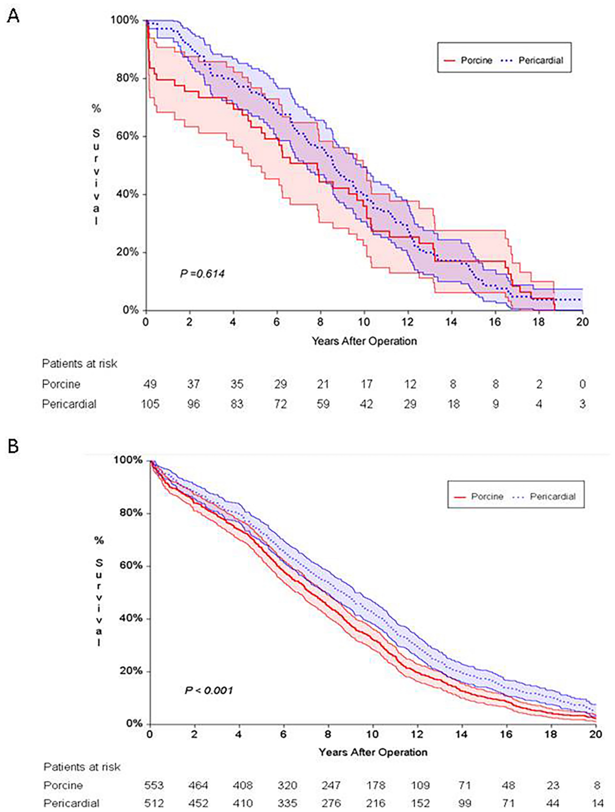

Fig. 5. Actuarial survival estimates with 95% confidence limits of propensity score-matched patients with a Porcine versus a Pericardial bioprosthesis discharged alive from the hospital. (A) patients with severe PPM (EOAi <0.65 cm^2/m^2). (B) Patients without severe PPM (EOAi $\geq$0.65 cm^2/m^2).

strated that survival differences developed relatively late in the course of the follow-up, beginning at approximately 10 years, and continuing to diverge thereafter (Fig. 4A,B).

To evaluate the potential impact of prosthesis-patient mismatch (PPM), implanted valve sizes (Table 5) were matched to the corresponding published Effective Orifice Area (EOA) cm^2 for each of the two bioprostheses [19,20]. EOA was then divided by patient body surface area to generate an indexed EOA (EOAi) cm^2/m^2 for each patient in the groups.

To further assess the influence of PPM [21] on long-term survival, a comparison of EOAi cm^2/m^2 was conducted for propensity score-matched groups. The overall mean EOAi of the Porcine group (0.89 cm^2/m^2, SD: 0.16) was significantly higher ($p < 0.001$) than in the Pericardial group (0.76 cm^2/m^2, SD: 0.12). A greater proportion of patients with a moderate PPM was noted in the Pericardial group (61.7% *vs*. 22.0%; $p < 0.001$). Severe PPM was also greater among Pericardial patients (17.5% *vs*. 8.5%; $p <$ 0.001; Table 6).

Among patients with severe PPM, there was also no long-term survival difference (HR = 1.09, 95% CI: 0.77 to1.55, $p = 0.614$) between the two valve groups (Fig. 5A).

However, among patients without severe EOAi (Fig. 5B), Pericardial patients had improved long-term survival (HR = 1.31, 95% CI: 1.16 to 1.48; $p < 0.001$). Therefore, valve hemodynamic characteristics as manifested by EOAi do not appear to account for the survival difference observed in the present study.

Discussion

Since the introduction of transcutaneous surgical techniques, there has been a 60% increase in AVR procedures in the Medicare population [22]. However, surgical AVR remains an effective therapeutic intervention and represents a definitive treatment for select patients based upon careful diagnostic evaluation of specific risks and benefits.

Bioprostheses have become the valve of choice for elderly patients by guideline recommendations and by clinical practice [3–5]. Bioprostheses fall into two broad categories—porcine xenograft or bovine pericardium tissue. Numerous studies have explored the key issue of long-term patient survival with porcine versus pericardial bioprostheses with conflicting results [6–15]. Although surgical center-specific effects cannot be ignored, virtually all studies to date have somewhat limited follow-up and are confounded by including multiple different valve manufacturers and models, as well as the presence of concomitant CABG surgery. Removal of CABG surgery during the index operation from the results of a recent large national experience actually changed the primary survival outcome [23].

This investigation sought to compare two distinct bioprostheses models from the same manufacturer, in isolated AVR operations performed during the same time period. In the present study, valve choice was surgeon-driven in a group of generally high-performing cardiac surgeons with similar techniques and comparable operative outcomes. This propensity score-matched comparison highlights the specific contribution of valve type on long-term patient survival in elderly patients. Within this context, it was determined that Pericardial valves were associated with enhanced long-term survival compared to the Porcine bioprosthesis ($p < 0.001$).

To fully evaluate bioprosthetic valve function and its impact on short- and long-term survival, it is necessary to follow patients for 20 years or longer [24]. Few studies in the literature have attempted this type of lengthy follow-up. To the best of our knowledge, this report represents the longest follow-up of Porcine versus Pericardial bioprostheses in elderly patients undergoing isolated AVR surgery. The conundrum of such extensive follow-up is that by the time the necessary long-term information is available, the prostheses (and perhaps surgical techniques and processes of care management) have changed. Even within the same manufacturer, there may be changes in valve design and tissue processing methods that may influence long-term results. It must be emphasized, however, that the purpose of this study was not to compare the currently marketed valve types, but rather to use the prototypes of porcine and pericardial bioprosthetic valves in order to perform a unique patient life-time analysis that may secondarily influence current and future valve design.

The data presented herein are intended to be hypothesis generating rather than definitive. Perhaps the reason for the discrepancies reported in the literature relate to the complexity of the research question. Aside from species and tissue differences—porcine valve versus bovine pericardium—processing methods vary and have evolved over time. Moreover, valve design and construction and resultant orifice areas differ, both between and within tissue types over subsequent models. Controversy is likely to persist into the transcatheter AV replacement era, as one major manufacturer used bovine pericardium and the other porcine tissue. However, here again, valve design is so markedly different that the impact of species differences may prove indeterminable.

As with any historical study, results need to be viewed within the context of the surgical practices of the time. Although current operative mortality for surgical AVR hovers around 2.0% [25], operative mortality observed in this study is consistent with that generally reported during the surgical time period [26,27]. Similarly, the difference in ventilation times likely reflected the slightly earlier years of the porcine experience and may have also accounted for the longer length of hospital stay.

Although the strict inclusion criteria in this study sought to limit the comparison to two distinct valve models from the same manufacturer within the context of a single group of surgeons, the data available do not allow speculation regarding the relative influence of valve design, tissue components (pericardial versus porcine), species of origin, or tissue processing methodology. Nonetheless, the comparison should be viewed as one of bioprostheses as they were produced for clinical practice, rather specifically reflective of biologic mechanisms of the observed differences. Although PPM has been associated with late mortality in AVR patients [28], as indeed it was in this patient population, this phenomenon cannot account for the mortality differences observed herein, as Porcine patients actually had a lower prevalence of PPM and a greater calculated EOAi cm^2/m^2 than Pericardial patients.

Study Limitations

As an observational, nonrandomized investigation conducted by a retrospective review, there are several study limitations that must be acknowledged. Notwithstanding the application of sophisticated multivariable statistical techniques, propensity score-matching corrected for group differences included in the dataset but may have overlooked important but unrecognized clinical characteristics that could have influenced the outcomes. E-value sensitivity analysis was used to assess the potential impact of unmeasured variables. However, this analysis cannot be substituted for the covariate balance of a prospective randomized control trial.

Risk profiles and surgical outcomes of AVR may have changed dramatically during the course of the study, characterized by increasing patient risk and decreasing operative mortality. Therefore, it is uncertain that these results would be reproduced by similar follow-up of present day surgical AVR in elderly patients with currently-produced bioprostheses. Moreover, since this study focuses on a single porcine and a single pericardial valve, it cannot be certain that similar results would be obtained with comparison of all models of porcine and pericardial valves. However, what may be compromised in terms of generalizeability is hopefully gained by elimination of heterogeneity. Based on available data, it is impossible to define the subtlety of clinical judgment used by surgeons in determining which patients received a Porcine or a Pericardial bioprosthesis.

Despite the fact that the late mortality data were remarkably complete over the period of follow-up, we do not have information regarding reoperations or the occurrence of other inter-current events such as hospital readmissions for heart failure or prosthetic valve endocarditis. Although different mechanisms for valve deterioration have been well-described in the literature for these two types of bioprosthesis [8,29], there has been no difference reported in the incidence of reoperation in multiple studies [7,8]. Therefore, although it would be instructive to know the incidence of reoperation and its potential impact on long-term patient survival, this remains unknown. Moreover, any future analysis of reoperation and its attendant risks must incorporate the emergence of valve-in-valve procedures, which may significantly impact clinical outcomes related to valve degeneration. Differences in medical therapy during the long follow-up period can have a major impact on patient survival [30], although there is no a priori reason to believe that these varied between valve types in the present study.

Conclusions

These long-term, comparative findings demonstrate that, within a single manurfacturer, the Pericardial bioprosthesis in the aortic position provided enhanced long-term survival benefits over the Porcine valve without any increase in operative mortality in elderly patients. The results of this long-term study provide an important benchmark for future comparative evaluation of the optimal tissue choice in the construction of AV bioprostheses.

Abbreviations

AV, aortic valve; AVR, aortic valve replacement; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; EF, ejection fraction; EOA, effective orifice area; EOAi, effective orifice area index; HR, hazard ratio; IQR, inter-quartile range; NYHA, New York Heart Association; OR, odds ratio; PPM, prosthesis-patient mismatch; SD, standard deviation; SMD, standardized mean difference.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

GE, EAT and PAK conceptualized the research study and its methodology, as well as reviewed and edited the manuscript. GE conducted the data curation, project administration, and provided software and statistical resources. GE and PAK provided supervision of the study, performed data validation, formal analyses of the data, and wrote the original draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was reviewed by the Institutional Review Board with waiver of the requirement for informed patient consent. The Northcentral University Institutional Review Board approved the study with a Review Level: Exempt-Category 2 (Submission ID 1370667). Please note that the IRB study closure form was successfully submitted on May 28, 2020, in accordance with the University's requirements. Please note that this is a retrospective study in which patient consent was not appropriate as all the patients had expired and the IRB concurred.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.6917.

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