Porcine vs Bovine Bioprosthetic Aortic Valves: Long-Term Clinical Results

ADULT CARDIAC

Michael Persson, MD, Natalie Glaser, MD, PhD, Anders Franco-Cereceda, MD, PhD, Johan Nilsson, MD, PhD, Martin J. Holzmann, MD, PhD, and Ulrik Sartipy, MD, PhD

Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; Department of Cardiothoracic Surgery, Karolinska University Hospital, Stockholm, Sweden; Department of Cardiology, Stockholm South General Hospital, Stockholm, Sweden; Division of Cardiothoracic Surgery, Department for Clinical Sciences Lund, Lund University and Skåne University Hospital, Lund, Sweden; Functional Area of Emergency Medicine, Karolinska University Hospital, Huddinge, Stockholm, Sweden; and Department of Internal Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

Background. **Previous studies have reported superior hemodynamic performance with bovine bioprosthetic aortic valves compared with porcine valves. However, conflicting results mean the long-term effect on survival is not well known. The aim of this study was to examine long-term survival, rate of aortic valve reoperations, and heart failure hospitalizations after surgical aortic valve replacement (AVR) with porcine vs bovine bioprosthetic valves.**

Methods. **This was a population-based cohort study including all patients who had undergone AVR in Sweden from 1995 to 2012, with or without concomitant coronary artery bypass grafting. Patients were identified through the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry. Baseline and outcome data were gathered from national registries. Propensity scores and inverse probability of treatment weighting were used to control for intergroup differences. Analyses accounted for competing risk of death when appropriate.**

Results. **A total of 12,845 patients underwent AVR with porcine (n = 4198) or bovine (n = 8647) prostheses. We found a small but significant difference in mortality favoring porcine prostheses: 78% vs 76%, 47% vs 43%, and 17% vs 15% at 5, 10, and 15 years, respectively (hazard ratio, 0.90; 95% confidence interval, 0.85-0.96). Porcine prostheses were associated with an increased risk of reoperation (hazard ratio, 1.48; 95% confidence interval, 1.11-1.98), but no difference in the risk of heart failure hospitalization. Results were similar in patients who underwent isolated AVR.**

Conclusions. **Consistent with previous reports, we found that patients receiving porcine prostheses had a higher rate of reoperation compared with bovine prostheses. However, porcine prostheses were associated with improved long-term survival compared with bovine prostheses.**

(Ann Thorac Surg 2021;111:529-36)

According to current guidelines, surgical aortic valve replacement (AVR) is the recommended treatment for severe aortic stenosis and regurgitation. For patients with an increased surgical risk, transcatheter aortic valve implantation is an alternative.[1] The prognosis after surgical AVR is excellent, particularly in older patients.[2] The most commonly used valve types today are bioprosthetic valves made from porcine or bovine tissue. Their popularity is likely because of the reduced need for anticoagulant therapy compared with mechanical prostheses.[3,4] Previous studies have reported superior hemodynamic performance, lower frequency of prosthesis-patient mismatch, and improved left ventricular mass regression using bovine compared with porcine valves.[5-8]

It has been assumed that this translates into impaired long-term clinical outcomes with porcine valves and has likely contributed to a shift in preference among surgeons toward bovine pericardial prostheses.[9] However, it is not known if porcine valves have inferior long-term clinical results compared with bovine prostheses.[10]

There is limited evidence, mostly from small studies that show conflicting results.[5,6,9,11] In a recent systematic literature review performed by our research group,[12] 5 of the 7 included articles had only 1 valve model in either one or both study groups. This approach compares the performance of different valve models with each other, but it will not examine differences in the xenograft

Dr Holzmann discloses a financial relationship with Actelion and Pfizer.

The Supplemental Material can be viewed in the online version of this article [https://doi.org/10.1016/j.athoracsur.2020.05.126] on http://www.annalsthoracicsurgery.org.

Accepted for publication May 11, 2020.

Address correspondence to Dr Persson, Department of Cardiothoracic Surgery, Karolinska University Hospital, SE-171 76 Stockholm, Sweden; email: michael.persson@ki.se.

0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2020.05.126

material used. Of the 7 paper included in the systematic literature review and meta-analysis,[12] only 1 study had a study population of more than 3000 patients.[9]

Therefore, we have conducted a nationwide population-based study including all valve models used during the study period to compare porcine vs bovine bioprostheses. The aim of this study was to examine the difference in long-term survival, rate of aortic valve reoperations, and heart failure hospitalizations after surgical AVR with porcine vs bovine bioprosthetic valves.

Patients and Methods

The study was approved by the regional Human Research Ethics Committee, Stockholm, Sweden (Dnr: 2017/886-32). The need for informed consent was waived by the Ethics Committee.

Study Design

This was an observational, population-based, nationwide cohort study of all patients who underwent surgical bioprosthetic AVR with or without concomitant coronary artery bypass grafting (CABG) or ascending aortic surgery in Sweden from January 1, 1995, to December 31, 2012. Study reporting followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and RECORD (Reporting of Studies Conducted Using Observational Routinely-Collected Health Data) guidelines for observational studies using routinely collected data.[13,14] The SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry was used to identify the cohort.[15] The SWEDEHEART register is a nationwide register that collects preoperative and postoperative data on all patients that undergo cardiac surgery in Sweden.[16] The National Patient Register maintained by the National Board of Welfare and the LISA (Longitudinal Integration Database for Health Insurance and Labor Market Studies) register maintained by Statistics Sweden were used to obtain additional baseline characteristics.[17] The National Patient Register collects data regarding all in-patient visits in Sweden, including date of admission, date of discharge, and diagnosis codes according to the International Classification of Diseases.[18] The LISA register contains information regarding family status, household income, education level, and other socioeconomic baseline characteristics. Survival status and date of death were obtained from the Cause of Death register maintained by the National Board of Health and Welfare.[19] The Swedish personal identity number enabled individual cross-linking between the different registries.[20] The valve model was obtained from the SWEDEHEART register. An algorithm was written to define the valve model as either porcine or bovine according to manufacturer information, thereby creating the 2 study groups.

Outcomes

The primary outcome was all-cause mortality. Date of death was obtained from the Cause of Death registry. The secondary outcomes were aortic valve reoperation (including valve-in-valve transcatheter aortic valve implantation) and hospitalization for heart failure. Data regarding these outcomes were obtained from the SWEDEHEART register and the National Patient Register, respectively. The secondary outcomes were chosen as suitable surrogates to represent clinically relevant bioprosthetic failure.

Statistical Analysis

Baseline characteristics were described as means and standard deviations for continuous variables. Categorical variables were described as frequencies and percentages. Time to event was calculated as time in days from the date of surgery until the date of the respective event or end of follow-up (December 31, 2013 for aortic valve reoperation and death, and December 31, 2012 for heart failure hospitalization). At the time of data delivery from the National Patient Register, it only contained information until the end of 2012, which is why the end of follow-up for hospitalization for heart failure differs from the end of follow-up for death and reoperation. The Kaplan-Meier method was used to estimate cumulative survival. We also estimated the difference in restricted mean survival time at 15 years. The restricted mean survival time is a robust measure that represents the mean event-free survival time in a prespecified period.[21,22] The association between valve type and survival was assessed using a weighted Cox regression model in which the weights were derived from propensity scores estimated using generalized boosted regression modeling.[23,24] All variables reported in Table 1 were used in the estimation of propensity scores. We decided that trimming was not necessary because we found no patients with extreme weights. Balance between the groups was assessed by standardized mean differences. An absolute standardized difference of less than 0.1 was considered an ideal balance.[25] Flexible parametric survival models were used to estimate the cumulative incidence of aortic valve reoperation and heart failure, accounting for the competing risk of death.[26] Analyses were repeated in a subset of patients who only underwent isolated AVR. Data management and statistical analyses were performed using Stata version 15.1 (Stata Corp LP, College Station, TX) and R programming language version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Missing Data

Although data were complete for many variables, including exposure and outcome, there were some missing data. The variables with most missing data were left ventricular ejection fraction and estimated glomerular filtration rate, with 27% and 11% missing data, respectively. For all variables with missing data, the weights were constructed to also balance rates of missingness in both groups.[23,24]

Results

We identified 12,845 patients who underwent isolated AVR or AVR with concomitant CABG with porcine (n = 4198, 32%) or bovine (n = 8647, 68%) prostheses from the

Table 1. Baseline Characteristics in 12,845 Patients Who Underwent Aortic Valve Replacement in Sweden Between 1995 and 2013 Before and After IPTW

		Unweighted			IPTW		
Variable	Missing (%)	Bovine (n = 8647)	Porcine (n = 4198)	SMD	Bovine (n = 12,506.2)[a]	Porcine (n = 12,072.0)[a]	SMD
Age, y	0	73.61 ± 8.59	76.16 ± 6.88	0.328	74.36 ± 8.10	74.71 ± 7.52	0.055
Female	0	3581 (41.4)	1811 (43.1)	0.035	5269.6 (42.1)	5076.1 (42.1)	0.002
Not married	11.6	2791 (36.1)	1389 (38.4)	0.048	4039.6 (36.5)	3977.5 (37.4)	0.017
Non-Nordic birth region	11.3	413 (5.3)	179 (4.9)	0.017	569.7 (5.1)	534.4 (5.0)	0.006
Educational level	20.1			0.103			0.026
<10 y		3400 (47.7)	1645 (52.4)		4917.4 (49.1)	4817.3 (50.1)	
10-12 y		2513 (35.2)	1045 (33.3)		3467.6 (34.6)	3314.9 (34.5)	
>12 y		1217 (17.1)	448 (14.3)		1630.6 (16.3)	1483.1 (15.4)	
Household income	11.6			0.210			0.023
Quartile 1 (lowest)		1780 (23.0)	1060 (29.3)		2763.1 (25.0)	2753.5 (25.9)	
Quartile 2		1846 (23.9)	992 (27.4)		2751.0 (24.9)	2661.1 (25.0)	
Quartile 3		2008 (25.9)	831 (23.0)		2786.1 (25.2)	2609.9 (24.5)	
Quartile 4 (highest)		2104 (27.2)	735 (20.3)		2753.6 (24.9)	2622.3 (24.6)	
Body mass index, kg/m^2	14.0	26.71 ± 4.41	26.20 ± 4.31	0.117	26.57 ± 4.35	26.50 ± 4.30	0.016
Diabetes	0	1638 (18.9)	709 (16.9)	0.054	2317.2 (18.5)	2207.9 (18.3)	0.006
Atrial fibrillation	0	1336 (15.5)	691 (16.5)	0.028	1952.5 (15.6)	1905.5 (15.8)	0.005
Hypertension	0	2715 (31.4)	1077 (25.7)	0.127	3731.3 (29.8)	3472.5 (28.8)	0.023
Hyperlipidemia	0	953 (11.0)	344 (8.2)	0.096	1277.7 (10.2)	1181.0 (9.8)	0.014
Prior stroke	0	962 (11.1)	473 (11.3)	0.005	1383.5 (11.1)	1411.6 (11.7)	0.020
Peripheral vascular disease	0	719 (8.3)	390 (9.3)	0.034	1057.6 (8.5)	1057.4 (8.8)	0.011
Pulmonary disease	0	765 (8.8)	379 (9.0)	0.006	1100.7 (8.8)	1090.3 (9.0)	0.008
Prior myocardial infarction	0	1377 (15.9)	781 (18.6)	0.071	2074.0 (16.6)	2079.0 (17.2)	0.017
Prior PCI	0	711 (8.2)	205 (4.9)	0.135	916.3 (7.3)	812.6 (6.7)	0.023
Prior major bleeding event	0	514 (5.9)	321 (7.6)	0.068	791.4 (6.3)	802.9 (6.7)	0.013
Prior venous thromboembolism	0	230 (2.7)	95 (2.3)	0.026	326.3 (2.6)	310.4 (2.6)	0.002
Alcohol dependency	0	183 (2.1)	58 (1.4)	0.056	236.4 (1.9)	187.5 (1.6)	0.026
Liver disease	0	84 (1.0)	45 (1.1)	0.010	119.3 (1.0)	123.9 (1.0)	0.007
History of cancer	0	795 (9.2)	409 (9.7)	0.019	1151.7 (9.2)	1146.3 (9.5)	0.010
eGFR	11.4			0.098			0.022
>60 mL•min•1.73 m^2		4920 (64.3)	2246 (60.2)		6990.3 (63.0)	6823.6 (63.3)	
45-60 mL•min•1.73 m^2		1779 (23.3)	962 (25.8)		2690.4 (24.2)	2565.5 (23.8)	
30-45 mL•min•1.73 m^2		743 (9.7)	385 (10.3)		1098.1 (9.9)	1046.7 (9.7)	
15-30 mL•min•1.73 m^2		125 (1.6)	93 (2.5)		208.2 (1.9)	226.7 (2.1)	
<15 mL•min•1.73 m^2[b]		79 (1.0)	45 (1.2)		113.9 (1.0)	120.4 (1.1)	
Prior heart failure	0	1718 (19.9)	955 (22.7)	0.070	2562.5 (20.5)	2517.8 (20.9)	0.009
Left ventricular ejection fraction	26.8			0.069			0.033

(*Continued*)

Table 1. Continued

		Unweighted			IPTW		
Variable	Missing (%)	Bovine (n = 8647)	Porcine (n = 4198)	SMD	Bovine (n = 12,506.2)[a]	Porcine (n = 12,072.0)[a]	SMD
>50%		4797 (73.0)	1987 (70.2)		6570.2 (72.3)	6306.8 (71.6)	
30%-50%		1395 (21.2)	683 (24.1)		2001.2 (22.0)	2043.1 (23.2)	
<30%		377 (5.7)	161 (5.7)		522.3 (5.7)	463.8 (5.3)	
Pacemaker/ICD	0	268 (3.1)	103 (2.5)	0.039	366.5 (2.9)	327.3 (2.7)	0.013
Active endocarditis	0	275 (3.2)	96 (2.3)	0.055	370.1 (3.0)	333.3 (2.8)	0.012
Emergent operation	0	114 (1.3)	65 (1.5)	0.019	164.7 (1.3)	165.9 (1.4)	0.005
Concomitant CABG	0	3422 (39.6)	2139 (51.0)	0.230	5376.3 (43.0)	5375.9 (44.5)	0.031
Period of surgery	0			0.440			0.055
1995-2002		2046 (23.7)	1566 (37.3)		3364.6 (26.9)	3456.9 (28.6)	
2003-2007		3103 (35.9)	1730 (41.2)		4763.5 (38.1)	4686.8 (38.8)	
2008-2013		3498 (40.5)	902 (21.5)		4378.2 (35.0)	3926.8 (32.5)	

[a]The overall numbers of patients in each group are not necessarily integers, owing to inverse probability of treatment weighting; [b]This category includes patients on dialysis.

Values are mean ± SD or n (%).

CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; IPTW, inverse probability of treatment weighting; PCI, percutaneous coronary intervention; SMD, standardized mean difference.

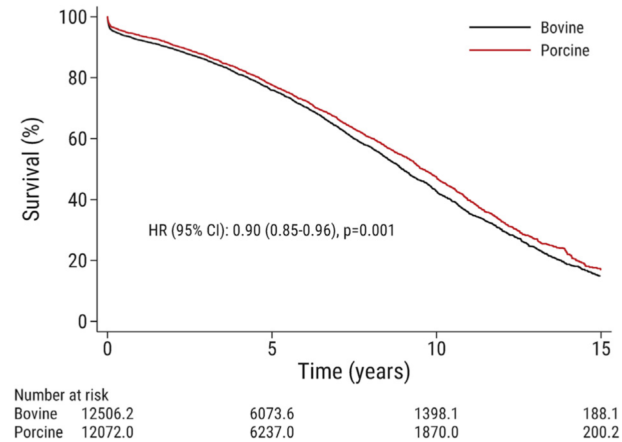

Figure 1. The Kaplan-Meier estimated survival is plotted against time after surgery and stratified according to type of bioprosthesis (bovine or porcine). Bovine bioprostheses are the reference group. The numbers of patients at risk are not necessarily integers, owing to inverse probability of treatment weighting. (CI, confidence interval; HR, hazard ratio.)

SWEDEHEART register. A total of 1417 patients were excluded because of an unknown valve model. The most common valve type in the porcine group was the Biocor valve (St Jude Medical, St Paul, MN) (24%), followed by the Mosaic valve (Medtronic, Minneapolis, MN) (16%). In the bovine group, the most common valve was the Perimount (Carpentier-Edwards, Irvine, CA), which made up 75%, followed by the Mitroflow valve (Sorin Group, Arvada, CO), which made up 12%. In the unweighted cohort, there were differences in baseline characteristics between the groups, with patients who received porcine valves being older, and more frequently having had prior percutaneous coronary intervention and concomitant CABG. After inverse probability of treatment weighting, no standardized mean differences were greater than 5.5% (Supplemental Figure 1). Baseline characteristics are described in Table 1. The number of operations per year and the use of bovine prostheses increased during the study period. However, the absolute number of operations with porcine prostheses remained similar across the study period. The proportion of porcine and bovine valve use is presented in Supplemental Figure 2. Similar balance was achieved in the isolated AVR group (Supplemental Figure 3). Kaplan-Meier estimated survival and the cumulative incidence function for aortic valve reoperation and heart failure hospitalization is shown in Supplemental Figures 4 and 5. Baseline characteristics in the isolated AVR subgroup is presented in Supplemental Table 1.

Survival

During a median follow-up time of 4.9 years (total follow-up time of 70,773 patient-years), the Kaplan-Meier estimated survival at 5, 10, and 15 years in the weighted cohort was 78% vs 76%, 47% vs 43%, and 17% vs 15%, respectively, in patients with porcine and bovine bioprostheses (Figure 1). The difference in restricted mean

Table 2. Incidence Rates of Death, Aortic Valve Reoperation, and Heart Failure in Patients With Bovine or Porcine Aortic Valve Bioprostheses

	All Patients[a]		Isolated AVR	
Variable	Bovine (n = 12,506.2)	Porcine (n = 12,072.0)	Bovine (n = 6519.3)	Porcine (n = 6061.8)
Death, events/PY	4960.4/66,349.5	5008.7/70,186.5	2312.1/34,609.4	2266.3/34,805.1
Incidence rate per 100 PY (95% CI)[b]	7.5 (7.2-7.7)	7.1 (6.8-7.4)	6.7 (6.4-7.0)	6.5 (6.1-7.0)
Aortic valve reoperation, events/PY	184.2/65758.4	289.9/68,920.8	119.7/34,248.6	156.9/34,123.3
Incidence rate per 100 PY (95% CI)[b]	0.3 (0.2-0.3)	0.4 (0.3-0.5)	0.3 (0.3-0.4)	0.5 (0.3-0.6)
Heart failure, events/PY	1485.1/55,255.0	1632.1/58,339.4	716.4/28,688	747.2/28,935
Incidence rate per 100 PY (95% CI)[b]	2.7 (2.5-2.9)	2.8 (2.6-3.0)	2.5 (2.3-2.7)	2.6 (2.3-2.9)

[a]The numbers of patients and events are not necessarily integers, owing to inverse probability of treatment weighting; [b]Incidence rate was calculated using a Poisson model in the weighted sample.

AVR, aortic valve replacement; CI, confidence interval; PY, person-years.

survival time at 15 years was 0.4 (95% confidence interval [CI], 0.2-0.6) years. The incidence rate of death per 100 patient years was 7.1 (95% CI, 6.8-7.4) and 7.5 (95% CI, 7.2-7.7) in the porcine and bovine groups, respectively (Table 2). Patients in the porcine group had a significantly lower risk of all-cause mortality compared with patients in the bovine group (hazard ratio [HR], 0.90; 95% CI, 0.85-0.96; $P = .001$).

Aortic Valve Reoperation

The incidence rate of aortic valve reoperation per 100 patient years was 0.4 (95% CI, 0.3-0.5) and 0.3 (95% CI, 0.2-0.3) in the porcine and bovine groups, respectively (Table 2). The cumulative incidence of aortic valve reoperation at 15 years in patients with porcine and bovine prostheses was 3.5% (95% CI, 2.7%-4.3%) and 2.3% (95% CI, 1.8%-2.7%), respectively (Figure 2). Patients in the porcine group had a significantly increased risk of aortic valve reoperation compared with patients in the bovine group (HR, 1.48; 95% CI, 1.11-1.98; $P = .007$).

Heart Failure Hospitalization

The incidence rate per 100 patient years of heart failure hospitalization was 2.8 (95% CI, 2.6-3.0) and 2.7 (95% CI, 2.5-2.9) in the porcine and bovine groups, respectively (Table 2). The cumulative incidence of heart failure hospitalization at 15 years in patients with porcine and bovine prostheses was 25% (95% CI, 23%-27%) and 23% (95% CI, 22%-25%), respectively (Figure 2). There was no significant difference in the risk of heart failure hospitalization between the groups (HR, 1.02; 95% CI, 0.92-1.14; $P = .664$).

Outcomes in Isolated AVR

Survival and secondary outcomes in patients who underwent isolated AVR were similar and is reported in detail in the Supplemental Material.

Comment

We found a small but significant increase in survival associated with the use of porcine bioprostheses after a 15-year follow-up period. However, in the isolated AVR subset, this difference was no longer significant. The clinical significance of this difference is likely to be negligible. The use of porcine prostheses was associated with an increased risk of reoperation. As for the survival data, the difference in risk of reoperation was not observed in the isolated AVR subset, likely because of a smaller population. It has been suggested that porcine and bovine valves have different failure modes. Porcine valves tend to fail because of cusp tears and valve incompetence, whereas bovine valves tend to fail more gradually with increasing stenosis.[27,28] It can be hypothesized that a more dramatic failure, like sudden cusp tears, would make it easier to identify a problem with the valve, allowing earlier intervention, which could explain the increased risk of reoperation with porcine valves. Although we do not have access to the reasons for reintervention, this finding was expected considering previous studies that reported superior hemodynamic characteristics with bovine compared with porcine valves.[5-7]

However, reports regarding clinical outcomes, such as survival, after AVR with porcine vs bovine prostheses, are limited and show conflicting results. In a recent systematic review and meta-analysis from our institution, the overall HR for long-term mortality between porcine and bovine valves was 1.00 (95% CI, 0.92-1.09).[12] The largest study included in the meta-analysis covered 38,040 patients undergoing bioprosthetic AVR with or without concomitant CABG during the period 2003 to 2013.[9] That study reported an adjusted HR of 0.98 (95% CI, 0.93-1.03) for mortality favoring porcine prostheses but did not reach statistical significance. In a subgroup analysis of patients less than 60 years of age, the trend also favored porcine valves in intervention-free survival ($P = .055$). They argued that the body of evidence regarding the superiority of hemodynamic characteristics with bovine bioprostheses did not translate into improved outcomes or survival.[9] The second-largest study in the meta-analysis by Said and colleagues[11] included 2979 patients who underwent bioprosthetic AVR with or without concomitant CABG between 1993 and 2007. They reported a significant association between porcine prostheses and survival, with an HR of 0.88 (95% CI, 0.78-0.98). In their study, the most common bovine valves were the

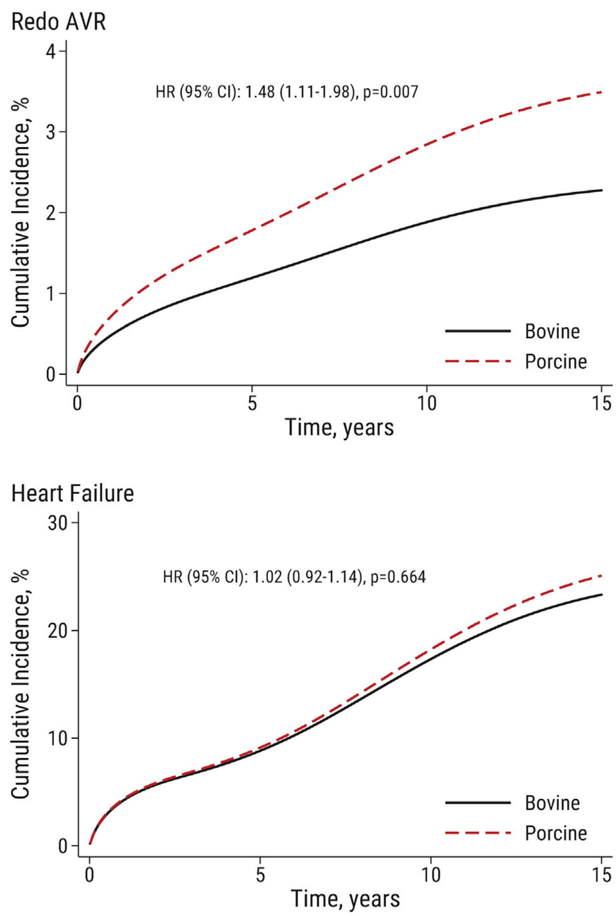

Figure 2. The cumulative incidence function for aortic valve reoperation (upper panel) and heart failure hospitalization (lower panel) stratified according to type of bioprosthesis (bovine or porcine) in the weighted sample. Bovine bioprostheses are the reference group. (AVR, aortic valve replacement; CI, confidence interval; HR, hazard ratio.)

Carpentier-Edwards and Mitroflow valves, together constituting 99% of the prostheses in the bovine group. The most common porcine valve was the Mosaic prosthesis (39%).[11] This is comparable to our study in which the Perimount and Mitroflow valves together constituted 87.6% in the bovine group, and the Mosaic valve was the second most common after the Biocor valve in the porcine group, comprising 16%. In the study by Hickey and colleagues,[9] the most common bovine valves were the Perimount valves, which made up 81% of the bovine group. The Mosaic valve constituted 26.4% of the porcine group.[9] This highlights that bovine valves are predominantly Perimount valves, whereas porcine valves are more variable, and in fact, the comparisons made in these studies could reflect the model as opposed to the species. The use of porcine xenograft material in surgical AVR has declined during the last decades.[9] However, porcine xenograft material is used in transcatheter AVR (commonly made from pericardial tissue rather than from cusp material as in surgical AVR) and might gain traction in the development of these prostheses. Naturally, long-term studies are needed to examine the performance of these valves and the xenograft materials used. The conflicting and limited body of evidence regarding comparisons of outcomes after bovine vs porcine bioprosthetic AVR supports the idea that the xenograft material used has no causal effect on survival, but that any potential differences in outcome may stem from varying performance of different prosthesis models.

Strengths and Limitations

Strengths of the study included the population-based nationwide design and the high quality of Swedish health data registers. The SWEDEHEART register has recently been subject to extensive validation that concluded a high level of validity.[16] Follow-up and ascertainment of vital status was 100% complete. There is a risk of incomplete follow-up regarding reoperation and heart failure hospitalization rates for individuals outside of Sweden. However, because of Swedish health care benefits, we strongly believe that most patients would return to Sweden for a necessary aortic valve reintervention. If some patients were lost to follow-up, we do not believe that valve type received is associated with tendency to move abroad. Thus, any such loss to follow-up would yield lower absolute event counts but would not bias the results when comparing the groups. Known confounders were accounted for using inverse probability of treatment weighting; however, residual confounding could remain. One plausible example of this could be that as bovine pericardial prostheses gained popularity, they were chosen more frequently for patients with a perceived frailty that would need and benefit more from the possible improved hemodynamic outcomes of these prostheses. Thus, if given systematically to frail patients, the results of the bovine prostheses might be impaired. It is of course equally likely that the same reasoning leads to the conclusion that these prostheses is a good choice for young and otherwise healthy patients with a long-expected survival, in which case the survival benefit associated with porcine prostheses in this study could not be explained by this bias. Another limitation was the lack of echocardiographic data such as valve gradients. The inclusion of multiple valve types could be a weakness because if one particular valve model had a low performance related to construction rather than xenograft material, this could affect the results of the entire group. The most common valves in our study have similar performance according to the literature, and therefore we do not believe that our results were affected in a clinically meaningful way. The fact that this study was population-based increases external validity.

Conclusion

During the study period, the preference for bovine valve types increased. Porcine prostheses were associated with improved long-term survival compared with bovine prostheses. Consistent with previous reports of inferior hemodynamic performance, we found that patients receiving porcine prostheses had a higher rate of reoperation. The use of bioprosthetic aortic valves has excellent long-term outcomes, regardless of the xenograft material used.

The authors wish to thank the SWEDEHEART steering committee for providing data for this study. This work was supported by the Swedish Heart-Lung Foundation (grant numbers 20160522, 20160525, and 20180400 to US, and 20190570 to NG), Åke Wiberg Foundation (grant number 2018: M18-0016 to US), Karolinska Institutet Foundations and Funds (grant number 2018-01784 to US), the regional ALF agreement between Stockholm County Council and Karolinska Institutet (grant number 20180114 to US), Capio Research Foundation (grant number 2019-3239 to NG), and a donation from Mr Fredrik Lundberg (to AF-C).

References

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-2791.
2. Glaser N, Persson M, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Loss in life expectancy after surgical aortic valve replacement: Swedeheart study. *J Am Coll Cardiol*. 2019;74:26-33.
3. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. *Eur Heart J*. 2016;37:2658-2667.
4. Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. *J Thorac Cardiovasc Surg*. 2015;149:1262-1269.e3.
5. Chan V, Kulik A, Tran A, et al. Long-term clinical and hemodynamic performance of the Hancock II versus the Perimount aortic bioprostheses. *Circulation*. 2010;122:S10-S16.
6. Dalmau MJ, Gonzalez-Santos JM, Blazquez JA, et al. Hemodynamic performance of the Medtronic Mosaic and Perimount Magna aortic bioprostheses: five-year results of a prospectively randomized study. *Eur J Cardiothorac Surg*. 2011;39:844-852 [discussion: 852].
7. Ruzicka DJ, Hettich I, Hutter A, et al. The complete supraannular concept: in vivo hemodynamics of bovine and porcine aortic bioprostheses. *Circulation*. 2009;120:S139-S145.
8. Glaser N, Franco-Cereceda A, Sartipy U. Late survival after aortic valve replacement with the Perimount versus the Mosaic bioprosthesis. *Ann Thorac Surg*. 2014;97:1314-1320.
9. Hickey GL, Grant SW, Bridgewater B, et al. A comparison of outcomes between bovine pericardial and porcine valves in 38,040 patients in England and Wales over 10 years. *Eur J Cardiothorac Surg*. 2015;47:1067-1074.
10. Wang M, Furnary AP, Li HF, Grunkemeier GL. Bioprosthetic aortic valve durability: a meta-regression of published studies. *Ann Thorac Surg*. 2017;104:1080-1087.
11. Said SM, Ashikhmina E, Greason KL, et al. Do pericardial bioprostheses improve outcome of elderly patients undergoing aortic valve replacement? *Ann Thorac Surg*. 2012;93:1868-1874 [discussion: 1874-1865].
12. Glaser N, Jackson V, Franco-Cereceda A, Sartipy U. Survival after aortic valve replacement with bovine or porcine valve prostheses: a systematic review and meta-analysis. *Thorac Cardiovasc Surg*. 2019;67:282-290.
13. Benchimol EI, Smeeth L, Guttmann A, et al. The reporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS Med*. 2015;12:e1001885.
14. von Elm E, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335:806-808.
15. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). *Heart*. 2010;96:1617-1621.
16. Vikholm P, Ivert T, Nilsson J, et al. Validity of the Swedish cardiac surgery registry. *Interact Cardiovasc Thorac Surg*. 2018;27:67-74.
17. Ludvigsson JF, Svedberg P, Olen O, Bruze G, Neovius M. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) and its use in medical research. *Eur J Epidemiol*. 2019;34:423-437.
18. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
19. Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. 2017;32:765-773.
20. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24:659-667.
21. Kim DH, Uno H, Wei LJ. Restricted mean survival time as a measure to interpret clinical trial results. *JAMA Cardiol*. 2017;2:1179-1180.
22. Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol*. 2013;13:152.
23. Griffin BA, Ridgeway G, Morral AR, et al. Toolkit for weighting and analysis of nonequivalent groups (TWANG) website. Santa Monica, CA: RAND Corporation; 2014. Available at: http://www.rand.org/statistics/twang. Accessed December 17, 2019.
24. Ridgeway G, McCaffrey D, Morral A, Griffin BA, Burgette L, Cefalu M. Twang: toolkit for weighting and analysis of nonequivalent groups. Available at: https://CRAN.R-project.org/package=twang. Accessed December 17, 2019.
25. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661-3679.
26. Sally HR, Lambert PC. Extending the flexible parametric survival model for competing risks. *Stata J*. 2013;13:344-355.
27. Arsalan M, Walther T. Durability of prostheses for transcatheter aortic valve implantation. *Nat Rev Cardiol*. 2016;13:360-367.
28. Johnston DR, Soltesz EG, Vakil N, et al. Long-term durability of bioprosthetic aortic valves: implications from 12,569 implants. *Ann Thorac Surg*. 2015;99:1239-1247.

ADULT CARDIAC

Clinical Relevance and Statistical Significance

Check for updates

Invited Commentary:

In the paper by Persson and colleagues[1] published in this issue of *The Annals of Thoracic Surgery*, the authors utilized a large national data set to compare long-term outcomes in patients who underwent aortic valve replacement according to type of bioprosthesis. This analysis of 12,845 patients reported that, among propensity-matched cohorts, a statistically significant improvement in survival was noted at 15 years favoring porcine valves (15% vs

0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2020.06.103