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ORIGINAL RESEARCH

Aortic Valve Reconstruction With Autologous Pericardium Versus a Bioprosthesis: The Ozaki Procedure in Perspective

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BACKGROUND: We assessed the Ozaki procedure, aortic valve reconstruction using autologous pericardium, with respect to its learning curve, hemodynamic performance, and durability compared with a stented bioprosthesis.

METHODS AND RESULTS: From January 2007 to January 2016, 776 patients underwent an Ozaki procedure at Toho University Ohashi Medical Center. Learning curves, aortic regurgitation (AR), and peak gradient, assessed by serial echocardiograms, valve rereplacement, and survival were investigated. Valve performance and durability were compared with 627 1:1 propensity-matched patients receiving stented bovine pericardial valves implanted from 1982 to 2011 at Cleveland Clinic. Learning curves were observed for aortic clamp and cardiopulmonary bypass times, AR prevalence, and early mortality. Decreased aortic clamp time was observed over the first 300 cases. New surgeons performing parts of the procedure after case 400 resulted in a slight increase in aortic clamp and cardiopulmonary bypass times. Among matched patients, the Ozaki cohort had more AR than the PERIMOUNT cohort (severe AR at 1 and 6 years, 0.58% and 3.6% versus 0.45% and 1.0%, respectively; *P*[trend]=0.006), although with a steep learning curve. Peak gradient showed the opposite trend: 14 and 17 mm Hg for Ozaki and 24 and 28 mm Hg for PERIMOUNT at these times (*P*[trend]<0.001). Freedom from rereplacement was similar (*P*=0.491). Survival of the Ozaki cohort was 85% at 6 years.

CONCLUSIONS: Patients undergoing the Ozaki procedure had lower gradients but more recurrent AR than those receiving PERIMOUNT bioprostheses. Although recurrent AR is concerning, results confirm low risk and good midterm performance of the Ozaki procedure, supporting its continued use.

Key Words: aortic valve reconstruction ■ aortic valve replacement ■ autologous pericardium ■ Ozaki procedure

Bioprosthetic valves are increasingly used in younger patients wanting to avoid anticoagulation, a trend bolstered by the possibility of treating eventual structural valve deterioration (SVD) with valve-in-valve transcatheter aortic valve replacement (TAVR). However, despite advances in bioprosthesis design, hemodynamic degradation and SVD persist. Patients are attracted by repair and use of autologous tissue, but aortic valve repair is realistic only for aortic regurgitation (AR).

Methods for reconstructing aortic valves using autologous pericardium have been reported since 1964.[1] In 1986, Love and Love[2] introduced pericardial tanning with 0.6% glutaraldehyde to prevent retraction and scarring. Using this technique, Al Halees and

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CLINICAL PERSPECTIVE

What Is New?

- The Ozaki procedure is a new technique to reconstruct the aortic valve introduced by Shigeyuki Ozaki at Toho University Ohashi Medical Center in 2007 using individual autologous pericardial cusps and reported by Ozaki and colleagues in 2011.
- The aortic valve reconstructed using this technique results in a lower gradient but more aortic regurgitation compared with a standard bioprosthetic valve.
- Risk of reoperation and survival were similar.

What Are the Clinical Implications?

- The Ozaki procedure adds another alternative for aortic valve replacement.
- Anticoagulation is not required, which could be an attractive alternative for younger patients who want to avoid a mechanical valve.
- Calcification and stenosis are rare, but there are a few reports of successful transcatheter aortic valve replacements after an Ozaki procedure.

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
CPB	cardiopulmonary bypass
SVD	structural valve deterioration
TAVR	transcatheter aortic valve replacement

colleagues reported 16-year results in 2005,[3] followed by Chan and colleagues in 2011.[4] Both groups cut the pericardium in the shape of 3 cusps and sutured it to the anulus. However, they were unable to demonstrate superiority over bovine pericardial prostheses, so this technique was not widely adopted.[5] In 2011, Ozaki and colleagues[6] described a new technique using a standardized toolset with sizers and a template to create 3 independent pericardial cusps. Midterm results were promising.[7] This study aims to further assess outcomes of the Ozaki procedure with respect to its learning curve, and to compare valve hemodynamic performance and midterm durability with those of a well-characterized, widely used stented bovine pericardial bioprosthesis.

METHODS

The method of the analysis will be made available from the corresponding author on request.

Study Population

From April 2007 to January 2016, 776 adults underwent consecutive Ozaki procedures at Toho University Ohashi Medical Center.[7] During the study time frame, <10 prosthetic valve implants were performed at Toho University. Use of these data in research was approved by the Toho University Institutional Review Board (No. H16063; approved December 16, 2016), with patient consent waived. Data were provided for analysis by Shigeyuki Ozaki under a data use agreement with Cleveland Clinic. Seventy-four procedures, performed by Professor Ozaki at other hospitals with which we had no data use agreement, were not included, but were included in a 2018 article.[7]

A subgroup of 412 isolated Ozaki procedures was used to study complexity of the procedure by learning curve analysis of aortic clamp and cardiopulmonary bypass (CPB) times, valve performance, and mortality, because these metrics are confounded by concomitant procedures. The entire cohort was used for longitudinal post-Ozaki hemodynamic performance, as was valve explant and endocarditis. Propensity-matched pairs (627 pairs) of Ozaki procedures were used to compare valve hemodynamics and valve explant, with 12 569 patients undergoing aortic valve replacement with a stented bovine pericardial bioprosthesis (PERIMOUNT; Edwards Lifesciences, Irvine, CA) at Cleveland Clinic from June 1982 to January 2011 (Figure 1).[8]

Variables corresponding to those in the Ozaki data set were retrieved from Cleveland Clinic's Cardiovascular Information Registry. Use of these data for research was approved by the Clinic's Institutional Review Board (No. 17–781; approved April 20, 2017), with patient consent waived.

Ozaki Procedure

All procedures were performed using autologous pericardium. Briefly, a large piece of pericardium is harvested, and redundant tissue and fat are carefully removed.[6] The excised pericardium is stretched on a metal plate and treated with a 0.6% glutaraldehyde solution, then rinsed in normal saline for 6 minutes ×3.

After commencing CPB and achieving cardioplegic arrest, diseased valve cusps are excised and anular calcification is removed. Size of the new cusps is determined by the intercommissural distance, measured using Ozaki sizers (Tokyo Research Center for Advanced Surgical Technology Co, Ltd, Tokyo, Japan). Three cusps are cut from the treated pericardium using a template designed to create generous coaptation and appropriate shape. With the smooth surface of the pericardium facing the ventricle, cusps are individually sutured to the anulus with 4–0 monofilament running suture. (With the rough surface facing

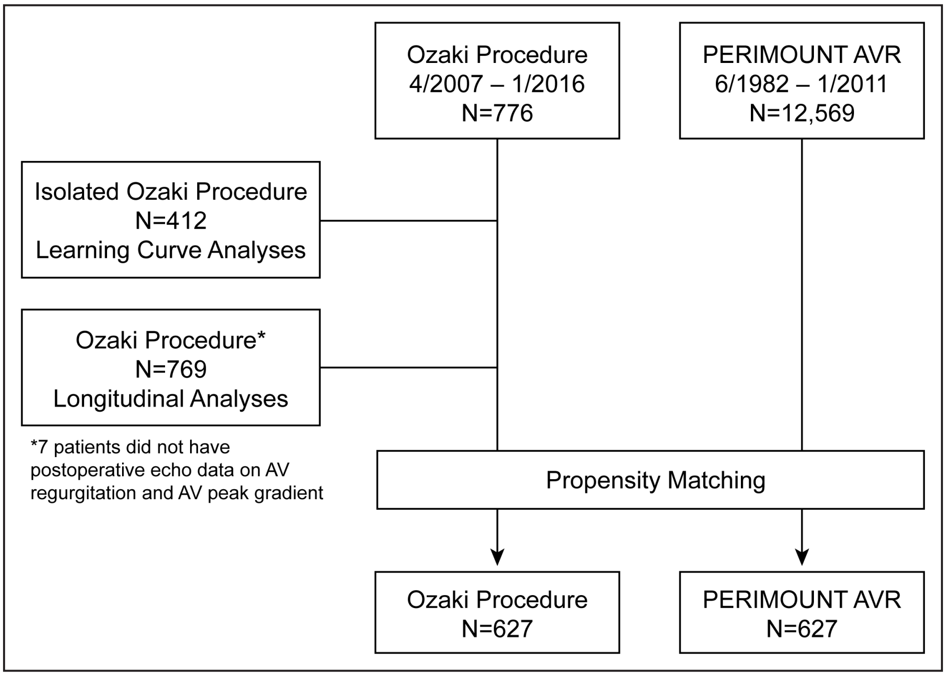

Figure 1. Consolidated Standards of Reporting Trials–style diagram of study cohort.
AV indicates aortic valve; AVR, AV replacement; and echo, echocardiographic.

the ventricle, postoperative thrombocytopenia was observed, prompting reversal.) Patients undergoing the Ozaki procedure are prescribed aspirin for 6 months after discharge.

Technical modifications made by Professor Ozaki over the study period included adding a 5-mm "wing" extension of the pericardial cusps for commissural fixation beginning at case 291, and equal tricuspidization with implantation of 3 equal-sized cusps, adjusting the position of commissures as needed in patients with bicuspid and unicuspid valves beginning at case 513. This was done to mitigate the risk of uneven movement of cusps and to potentially decrease the risk of endocarditis[7] (Video S1).

End Points

End points for complexity-related learning curves were aortic clamp and CPB times, valve performance, and mortality. Valve hemodynamic metrics were longitudinal peak gradient and AR grade by transthoracic echocardiography. Valve durability was assessed by aortic valve rereplacement and its indications. Mortality was assessed according to time-varying change in the hazard function.

Echocardiographic Follow-Up

Ozaki Cohort

Echocardiograms were performed at 1 week, 1 month, and every 6 months thereafter, yielding 6060 echocardiogram records for 769 patients (99% of study cohort), censored at aortic valve rereplacement. More than 75% of patients had echocardiographic follow-up at >1 year, and 9% had follow-up at >6 years (Figure S1A).

Matched PERIMOUNT Cohort

Echocardiograms were performed routinely before hospital discharge and at the discretion of referring physicians during follow-up, yielding 1392 echocardiogram records for 562 patients routinely followed at Cleveland Clinic (84% of matched PERIMOUNT cohort). More than 30% of patients had echocardiographic follow-up at >1 year, and 12% had follow-up at >6 years (Figure S1B).

Clinical Events Follow-Up

Ozaki Cohort

Follow-up was performed by hospital visit every 6 months or by telephone contact. If unreachable, patients were classified as lost to follow-up. Of the Ozaki cohort, 50% were followed up for >3.5 years, 25% were followed up for >5.3 years, and 10% were followed up for >6.4 years, with 2755 patient-years of data available for analysis.

Matched PERIMOUNT Cohort

Patients received a mailed questionnaire or telephone call at 2 years, 5 years, and every 5 years thereafter. Of the matched PERIMOUNT cohort, 50% were followed up for >4.3 years, 25% were followed for >7.5 years, and 10% were followed for >11 years, with 3124 patient-years of data available for analysis.

Statistical Analysis

Analyses were performed using SAS v9.2 (SAS Institute, Cary, NC). Continuous variables are summarized as mean±SD or as median (15th–85th percentiles), consistent with the SD, if distribution of values is skewed.

Learning-Curve Analyses

Among isolated Ozaki procedures, learning curves for aortic clamp and CPB times (n=379 available values) were constructed with each patient's sequence number within the entire series of 776 patients entered as the sole independent variable. Learning curves were estimated using locally weighted scatterplot smoothing (loess) estimation. Mean estimates and CIs for each patient number were obtained by fitting linear regression models to localized subsets of the data around the selected sequence number. Smoothness was determined by window width.

Additional aspects of learning included analysis of postprocedure peak gradient and AR grade by nonparametric regression modeling, and time-related mortality by multiphase hazard modeling.

Echocardiographic Analysis

Temporal trends of postoperative ordinal AR grade were estimated using a nonlinear multiphase mixed-effects cumulative logistic regression model.[9] Estimated prevalence of each grade was obtained by averaging patient-specific model profiles. Temporal trend of continuous peak transvalvular gradient was estimated using a nonlinear multiphase mixed-effects regression model.[10] To account for correlation among repeated echocardiographic measurements, the patient identifier was included as a random effect. Shaping and scaling parameters of the follow-up time function were fixed effects. Uncertainty of estimates is expressed by bootstrap confidence bands equivalent to ±1 SE (68%).

Time-to-Event Analysis

Aortic valve rereplacement and mortality probabilities were estimated nonparametrically by the Kaplan-Meier method and parametrically by a multiphase hazard model.[11]

Comparison of Ozaki Procedure and PERIMOUNT Implant Results

Propensity-score 1:1 matching was used to find equivalent cohorts for comparing outcomes of Ozaki and PERIMOUNT cohorts. Thirteen preoperative variables were included in the propensity model, including demographics, valve pathology, and renal function (Data S1). Some variables had sporadic missing values, which were imputed using 5-fold multiple imputation by chained equations. Then, using multivariable logistic regression, we created a saturated model (C=0.89) that was replicated for each imputed data set. A propensity score was next calculated for each patient by solving each of the 5 models for the probability of being in the Ozaki cohort and averaging them.[12] Then, using the logit of the propensity score, Ozaki cases were matched to PERIMOUNT cases using greedy matching[13] and a caliper width of 0.2 times the SD of the logit of the propensity score.[14] This yielded 627 patient pairs (Table 1). Bias reduction between the groups before and after propensity matching was assessed using standardized mean difference (Figure S2). A standardized mean difference <10% was interpreted as acceptable matching.

To account for possible correlation between matched pairs, longitudinal and time-to-event models incorporated matched pairs as a random effect, the former with patient nested within a matched pair.

To estimate intrinsic risk of valve rereplacement in the absence of mortality, a competing-risks analysis was performed by considering the mutually exclusive outcomes of rereplacement and death before rereplacement. Conditional probability for rereplacement, assuming mortality was eliminated, was estimated by the nonparametric product-limit method, with variance based on the Greenwood formula; and parametrically by integrating the independent, simultaneously operative transition rates (hazard functions) from living patients into rereplacement or death before rereplacement.[15]

RESULTS

Ozaki Procedure

Learning Curves (Isolated Cohort)

Aortic clamp time for *isolated* Ozaki procedures decreased from >2 hours to about 105 minutes by the 300th case (Figure 2A). CPB time mirrored this (Figure S3). Case numbers 400 to 600 showed an increase in aortic clamp and CPB times, coinciding with 3 surgeons at Toho University starting to perform the procedure under Professor Ozaki's supervision.

Severe AR at 5 years sharply declined to case 300 (Figure 2B). An elevated early phase for risk of mortality rapidly decreased within the first 50 cases (Figure S4). There was no evidence of a learning curve for peak pressure gradient (Figure S5).

Valve Hemodynamic Performance

Following the Ozaki procedure, 16 patients developed severe AR, 9 from endocarditis, 1 from early suture break, 5 from sinus dilatation causing central regurgitation, and 1

Table 1. Patient Characteristics and Procedure Details: Overall and Matched Cohorts

Variable	Overall cohorts					Matched cohorts				
	Ozaki (n=776)		PERIMOUNT (n=12 569)			Ozaki (n=627)		PERIMOUNT (n=627)		
	n*	No. (%) or mean±SD	n*	No. (%) or mean±SD	Std. Diff., %	n*	No. (%) or mean±SD	n*	No. (%) or mean±SD	Std. Diff., %
Demographics										
Age, y	775	69±14	12 569	71±11	−18	626	69±14	627	69±13	1.4
Female sex	776	369 (48)	12 569	4304 (34)	27	627	310 (49)	627	318 (51)	−2.6
Preoperative body mass index, kg/m²	776	22±3.5	11 142	28±5.7	−122	627	23±3.4	569	23±4.3	2.6
Aortic valve details										
Indication for surgery	776		12 569			627		627		
Aortic stenosis		496 (64)		6168 (49)	22		373 (59)		371 (59)	0.65
Aortic regurgitation		223 (29)		2424 (19)	30		200 (32)		200 (32)	0.0
Mixed aortic stenosis/ regurgitation		33 (4.2)		2335 (19)	−46		31 (4.9)		33 (5.3)	−1.4
Endocarditis		15 (1.9)		223 (1.8)	1.2		15 (2.4)		16 (2.6)	−1.0
Others/unknown		8 (1.0)		1419 (11)	−44		8 (1.3)		7 (1.1)	1.5
Preoperative aortic valve peak gradient, mm Hg	632	69±36	9876	69±29	−0.39	498	69±36	487	65±36	8.6
Preoperative aortic regurgitation	770		12089		22	621		627		−0.69
None		205 (27)		4661 (39)			190 (31)		188 (30)	
Mild		204 (26)		2308 (19)			177 (29)		185 (30)	
Moderate		97 (13)		2361 (20)			36 (5.8)		32 (5.1)	
Moderately severe		178 (23)		1565 (13)			139 (22)		142 (23)	
Severe		86 (11)		1194 (9.9)			79 (13)		80 (13)	
Bicuspid aortic valve	776	207 (27)	11 379	1888 (17)	25	627	165 (26)	579	158 (27)	−2.2
Renal function										
Preoperative creatinine, mg/dL†	775	0.92 (0.66–2.0)	12 107	1.04 (0.80– 1.5)	35	626	0.89 (0.64–1.4)	617	1.0 (0.70–1.7)	−0.89
Preoperative renal dialysis	776	98 (13)	10 598	137 (1.3)	46	627	43 (6.9)	556	44 (7.9)	−1.7
Ozaki procedure										
Left coronary cusp, mm	761	25±3.5	N/A	N/A	N/A	616	25±3.5	N/A	N/A	N/A
Noncoronary cusp, mm	768	27±3.5	N/A	N/A	N/A	619	27±3.5	N/A	N/A	N/A

(Continued)

Table 1. Continued

Variable	Overall cohorts					Matched cohorts				
	Ozaki (n=776)		PERIMOUNT (n=12 569)			Ozaki (n=627)		PERIMOUNT (n=627)		
Right coronary cusp, mm	765	27±3.2	N/A	N/A	N/A	619	25±3.2	N/A	N/A	N/A
Support										
Ischemic time, min‡§	386	107±28	11 927	85±36	69	319	106±27	612	80±36	83
CPB time, min‡§	386	150±30	12 569	109±49	101	319	150±31	627	103±49	116
Concomitant procedures§	776	364 (47)	12 569	9250 (74)	−57	627	286 (46)	627	442 (70)	−52
Date of operation										
January 1, 2007, to index operation§	775	30±2.2	12 569	21±5.8	208	626	30±2.1	627	22±4.9	224

CPB indicates cardiopulmonary bypass; N/A, not applicable; SD, standard deviation; and Std. Diff., standardized difference.
*Patients with data available.
†Median (15th–85th percentiles).
‡Available for isolated procedures only.
§These variables were not included in propensity-score model.

from cusp thickening. Severe AR increased from 0.60% at 1 year to 4.9% at 6 years (Figure 3A). However, there was a steep learning curve, with prevalence of severe AR at 5 years leveling at <0.5% after 200 cases; some new cases of severe AR at 1 year occurred after procedures performed by new surgeons between cases 400 and 700 (Figure 2B). Peak aortic gradient averaged 14 and 17 mm Hg at 1 and 6 years, respectively (Figure 3B). There was slightly greater aortic regurgitation (P=0.141), but lower peak gradient (P=0.002), after replacement of bicuspid compared with tricuspid aortic valves (Figure S6).

Aortic Valve Rereplacement and Infectious Endocarditis

During follow-up, 14 rereplacements occurred, 13 for infective endocarditis and 1 for broken sutures. Actuarially, occurrence of aortic valve rereplacement was 0.5% at 1 year and 3.2% at 6 years (Figure S7). Conditional probability of reoperation adjusted for the competing risk of death was 0.38% at 1 year and 3.3% at 6 years (Figure S8). There was no learning curve for occurrence of endocarditis (P=0.824), and only 1 case of infectious endocarditis was observed after introduction of equal tricuspidization.

Mortality

Time-related mortality exhibited both an early high-risk phase and a nearly constant risk after about 1.5 years of 1.6%/year (Figure S9, inset). Survival was 99% at 30 days, 92% at 1 year, and 85% at 6 years (Figure S9). Six-year survival after isolated Ozaki procedures (88%) was greater than after combined procedures (81%; P=0.008; Figure S10).

Ozaki Procedure Versus Matched PERIMOUNT Implant Outcomes

Hemodynamic Performance

In contrast with the steady increase in severe AR across follow-up time after the Ozaki procedure (0.58% and 3.6% at 1 and 6 years, respectively, among matched patients undergoing the Ozaki procedure), in the propensity-matched PERIMOUNT cohort, severe AR was 0.45% and 1.0% at 1 and 6 years, respectively (P for difference in trends=0.006; Figure 4A). Peak aortic valve gradient was lower after the Ozaki procedure (14 and 17 mm Hg at 1 and 6 years, respectively) than after PERIMOUNT valve replacement (24 and 28 mm Hg at 1 and 6 years, respectively) (P for difference in trends <0.001; Figure 4B).

Aortic Valve Rereplacement and Endocarditis

Aortic valve rereplacement at 6 years was similar for matched Ozaki (2.4% occurrence) and PERIMOUNT (2.4% occurrence) cohorts (P=0.491; Figure 5). The

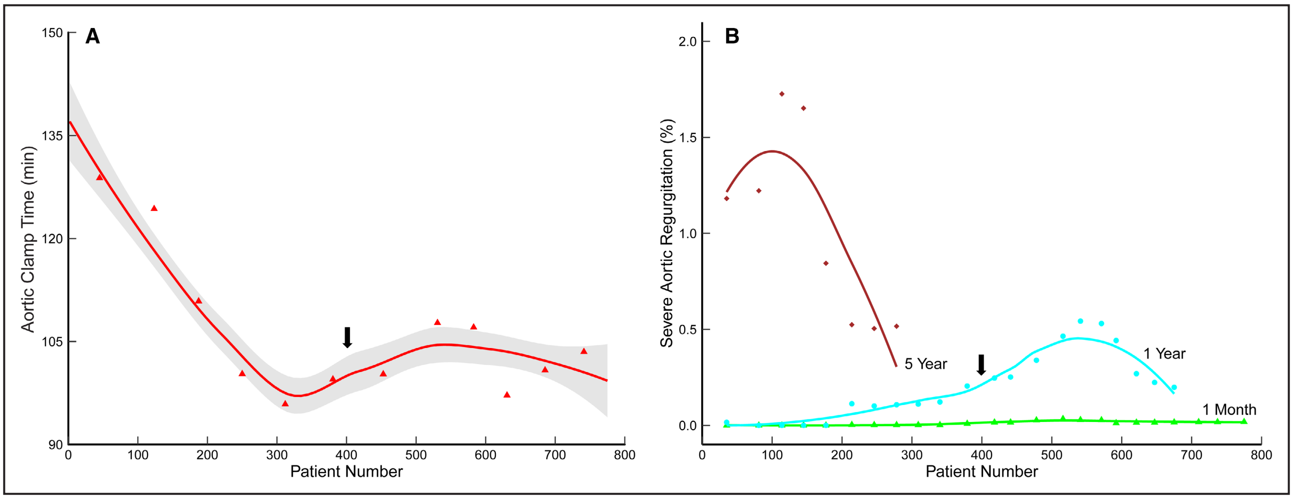

Figure 2. Isolated Ozaki procedure learning curves.
Numbers on horizontal axis are sequence number of patients undergoing a primary isolated procedure. Solid lines represent a nonparametric or parametric estimate of the learning curve. Black arrows point to when new surgeons became involved. **A**, Aortic clamp time. Symbols represent data within groups of 32 patients. Gray shaded area is a 68% confidence band equivalent to ±1 SE. **B**, Prevalence of severe aortic valve (AV) regurgitation at 1 month (green), 1 year (blue), and 5 years (red). Symbols represent data within groups of patients to provide crude verification of model fit. Note steep decrease in intermediate-term (5-year) severe AV regurgitation.

predominant indication for rereplacement after the Ozaki procedure was infective endocarditis (13 of 14), similar to 9 of 13 PERIMOUNT valves rereplaced for endocarditis in the midterm (*P*=0.741).

DISCUSSION

Principal Findings

The Ozaki procedure is complex! We addressed complexity by examining learning curves for the originator of the procedure, Shigeyuki Ozaki, with his own institutional experience. Using aortic clamp and CPB times, valve performance, and early mortality as surrogate quantitative metrics for complexity in isolated procedures, the Ozaki procedure exhibited learning curves for these. AR risk is greater than with the PERIMOUNT bioprosthesis, but has a steep learning curve; peak transvalvular gradient is lower than with a PERIMOUNT bioprosthesis; and risk of valve rereplacement is similar through intermediate-term follow-up.

Findings in Context

Since the first report in 2011,[6] an increasing number of centers in Asia, Europe, and the United States have

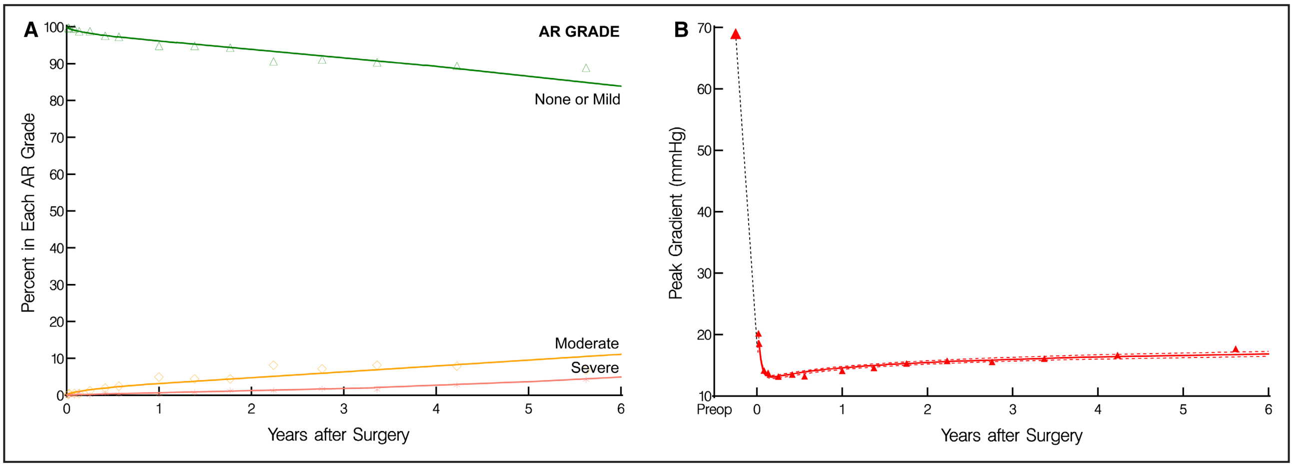

Figure 3. Aortic regurgitation (AR) and peak gradient after an Ozaki procedure in the entire cohort.
Symbols represent raw data (without regard to repeated measurements) within time frames to provide a crude verification of model fit. **A**, Longitudinal trend of each AR grade. Solid lines represent parametric measurements of percentage of patients in each grade postoperatively. **B**, Peak aortic gradient. Solid line represents parametric estimate of ensemble average of peak gradient after procedure. Dashed lines are a 68% confidence band equivalent to ±1 SE. Preop indicates preoperative.

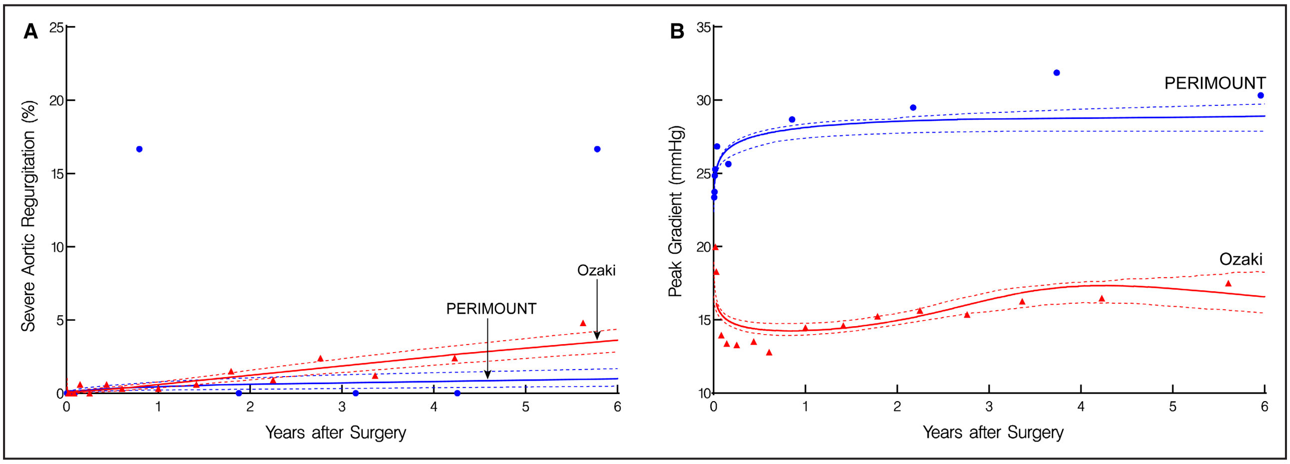

Figure 4. Comparison of aortic regurgitation (AR) and peak gradient.

Solid lines represent parametric estimates enclosed within a 68% confidence band equivalent to ±1 SE. Symbols represent raw data (without regard to repeated measurements) within time frames to provide a crude verification of model fit. **A**, Temporal trend of prevalence of severe postoperative AR after aortic valve replacement in Ozaki vs PERIMOUNT matched cohorts. See Figure S1 for number of patients at risk and number of observations across time. **B**, Longitudinal trend of aortic valve peak gradient after valve replacement in the Ozaki and PERIMOUNT propensity-matched cohorts. Preoperative gradient is not shown.

enthusiastically adopted the Ozaki procedure.[16–20] A limitation of these reports is lack of a comparison group to provide context. The natural comparator is a standard, widely used bioprosthesis: The PERIMOUNT 2700 stented bovine pericardial bioprosthesis, although now off the market, is the most used and characterized bioprosthesis worldwide. There is no evidence that its structural properties and hemodynamics have changed since the premarket cohort of the early 1980s. Cleveland Clinic has the largest experience with this bioprosthesis.[8]

Aortic Regurgitation

Compared with the PERIMOUNT cohort, which had minimal AR, the Ozaki cohort experienced more AR. Although the 5-year risk of severe AR rapidly decreased over the first 300 cases, the Ozaki procedure

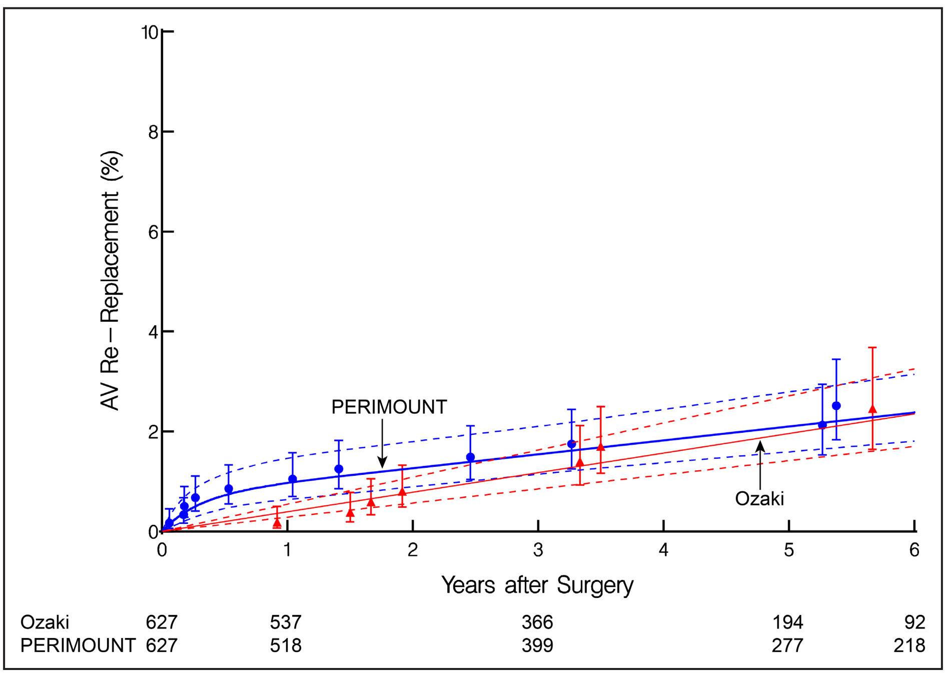

Figure 5. Aortic valve (AV) rereplacement after Ozaki procedure and PERIMOUNT bioprosthesis implant in propensity-matched cohorts.

Each symbol is a rereplacement, with Kaplan-Meier estimates and 68% confidence bars. Numbers below horizontal axis are patients remaining at risk.

was modified twice to address possible causes of AR. A 5-mm “wing” extension was added to improve commissure fixation. Equal tricuspidization was also introduced to reduce AR, but longer-term follow-up is needed to confirm the effectiveness and durability of these modifications. AR after an Ozaki procedure was higher after bicuspid than tricuspid valve repair, and the bump in AR at 1 year (Figure 2B) coincides with initiation of equal tricuspidization for bicuspid valves, suggesting that moving the commissures by tricuspidization adds to surgical complexity, adding another learning experience.

Larger Orifice Area With Low Gradient

We demonstrate lower peak valve gradient after the Ozaki procedure compared with the PERIMOUNT bioprosthesis, which may translate into slower development of SVD.[8]

The effective orifice area of stented bioprostheses is limited by the rigid frame, which also inhibits normal aortic anulus motion.[21] The Ozaki procedure reconstructs the cusps with 3 individually tailored pieces of pericardium, preserving normal anulus size and motion as well as increasing systolic-phase effective orifice area.[22] Rosseykin and colleagues[23] compared immediate postoperative echocardiographic findings of 20 patients who underwent the Ozaki procedure with those of patients undergoing aortic valve replacement with the Hancock II (n=41) and PERIMOUNT valves (n=35), reporting lower gradients and larger effective orifice area index with the Ozaki procedure ($P<0.001$).

In 57 patients with aortic stenosis and small anulus (average, 20±2.5 mm^2) who underwent an Ozaki procedure, postoperative effective orifice area index was 1.2±0.4 cm^2/m^2.[18] Ozaki and colleagues[24] reported an average anular diameter of 20±2.5 mm in 86 Japanese patients aged ≥80 years who underwent the Ozaki procedure. Three died in hospital, and 56-month survival was 87%, comparable to survival in octogenarians undergoing surgical or transcatheter aortic valve replacement.[25,26] Average peak gradient was 15 mm Hg at 3.5 years, demonstrating excellent hemodynamic results in patients with a small aortic anulus. Johnston and colleagues[8] showed that a higher gradient across PERIMOUNT valves was associated with higher probability of valve explant.

Structural Valve Deterioration and Endocarditis

We demonstrate at midterm follow-up valve rereplacement comparable to matched PERIMOUNT bioprostheses. In the Ozaki cohort, other than 1 patient whose suture broke, there were no replacements for SVD. In the PERIMOUNT cohort, risk of rereplacement for SVD increased slightly after 5 years,[8] whereas risk of rereplacement remained stable in the matched Ozaki cohort.

Patients who underwent the Ozaki procedure did not have a lower risk of endocarditis than observed in patients who underwent the PERIMOUNT procedure, with endocarditis being the primary indication for rereplacement. Johnston and colleagues[8] reported a cumulative occurrence of rereplacement for endocarditis after aortic valve replacement of only 1.4% at 20 years; some report higher occurrences.[27]

Avoiding foreign material in the Ozaki procedure was anticipated to protect against endocarditis, but it did not. Previous reports of using glutaraldehyde-treated autologous pericardium have raised similar concerns. Chan and colleagues[4] reported a 27% occurrence of endocarditis at 7.5 years, with endocarditis the indication for surgery in 2 patients, and Al Halees and colleagues[3] reported that 11% of patients developed endocarditis within 16 years that occurred between 1 and 163 months after surgery. They had a comparable bovine pericardium group with similar baseline characteristics who underwent aortic valve replacement with less postoperative endocarditis. Until proven otherwise, endocarditis may be inherent in the use of autologous pericardium, suggesting that endocarditis prophylaxis should be given after an Ozaki procedure. Until 2012, Professor Ozaki used the raphe as a commissure for bicuspid valves, accepting unequal size cusps. Driven by concerns about AR and endocarditis, since 2012, equal tricuspidization, creating “new commissures,” has been performed, resulting in more symmetrical movements of the 3 cusps.[7] Equal tricuspidization is technically more demanding and increases CPB time, but only 1 case of endocarditis occurred after its introduction. This suggests that cusp design and function could play a role in risk of endocarditis. However, changes in perioperative management, patient selection, and awareness of the need for standard antibiotic prophylaxis similar to that for prosthetic valves may also have been factors.

Mortality

The increased risk of mortality early in the Ozaki cohort reflects complexity of this operation, which initially required aortic clamp times exceeding 2 hours. A 30-day mortality of 1% is comparable to recently reported outcomes for aortic valve replacement.[28]

Clinical Implications and Barriers to Widespread Use of the Ozaki Procedure

We demonstrate at midterm follow-up valve rereplacement comparable to matched PERIMOUNT bioprostheses. The Ozaki procedure may have a particular and important niche in younger patients with unrepairable valves who on the one hand do not want to be saddled for life with anticoagulation and on the other hand are concerned about accelerated prosthesis deterioration.

Despite excellent midterm results, the Ozaki procedure is not widely used given its technical complexity and perceived unsuitability for valve-in-valve TAVR attributable to large high cusps that increase risk of coronary occlusion. However, there is a report of successful TAVR after Ozaki procedures using newer-generation TAVR systems.[29] Cusp laceration, as in the BASILICA (Bioprosthetic or Native Aortic Scallop Intentional Laceration to Prevent Iatrogenic Coronary Artery Obstruction during TAVR) trial, should enable valve-in-valve TAVR in most cases.[30] Another obstacle is that the Ozaki procedure has been performed through a full sternotomy. However, Nguyen and colleagues[31] report 9 Ozaki procedures performed with a less invasive approach using thoracic endoscopy to harvest the pericardium during CPB.

Limitations

The "learning curve" analyses are confounded by modifications of the Ozaki procedure over time and introduction of surgeons who performed it under Professor Ozaki's supervision. However, these changes occurred after the learning curves plateaued. In addition, we do not know where in the sequence of operations the 74 Ozaki procedures done at other institutions fit.

Intermediate-term follow-up is too short to identify rate of SVD and thus durability of the Ozaki procedure. However, follow-up is informative of early deterioration of performance, such as the AR noted in this report. We recognize that using valve explant as a surrogate for SVD is subject to biases like surgeons being reluctant to replace a valve in older, frail patients. Longitudinal study of valve regurgitation and stenosis, as in this study, is more reflective of valve deterioration.

The most commonly reported competing-risk estimate of valve rereplacement after the Ozaki procedure, cumulative incidence, could be confounded by inherent differences in Japanese survival compared with other parts of the world. This was mitigated by use of a different competing-risk metric, conditional probability, which is intended to remove the influence of death on explant estimates.[15]

Follow-up echocardiograms for hemodynamic valve performance in patients having undergone an Ozaki procedure were done on a regular basis; most follow-up echocardiograms for patients with a PERIMOUNT bioprosthesis were obtained from a subgroup of patients followed routinely at Cleveland Clinic, which may not be representative.

This is an observational study that in part compares data obtained from 2 institutions in different parts of the world. Inherent differences between Japanese and US patients and differences in health care systems may have influenced the results. However, this study is primarily about aortic valve performance. Performance of the PERIMOUNT bioprosthesis has been well characterized over the past 40 years. A consistent finding has been a strong association between age at implant and SVD, which we have accounted for by propensity matching, despite the small number of other factors available for developing the propensity score. Furthermore, there was no evidence that PERIMOUNT hemodynamics have drifted over time, making us confident that the temporal disparity of these between the Ozaki and PERIMOUNT propensity-matched experiences is not heavily biased. There is also no evidence that the PERIMOUNT bioprosthesis behaves differently in the Japanese population; to the contrary, the Japanese experience is similar to the US experience.[32,33]

CONCLUSIONS

Intermediate-term outcomes of the Ozaki procedure are promising and comparable to those of a well-studied stented bioprosthetic valve. These results confirm the effectiveness and relative safety of the Ozaki procedure, even accounting for an important learning curve. Although midterm follow-up cannot address all aspects of bioprosthesis durability, this study demonstrates absence of a signal for early valve failure, as has been seen with bioprostheses such as the Trifecta and Mitroflow aortic bioprostheses before that.[34,35] Recurrent AR and risk of endocarditis remain valid concerns. Larger, multi-institutional studies with longer follow-up are needed to determine optimal patient selection and to better define the role of the Ozaki procedure in aortic valve treatment algorithms, particularly in younger patients. Further modifications of the procedure can be anticipated.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Figures S1–S10
Video S1

REFERENCES

1. Bjoerk VO, Hultquist G. Teflon and pericardial aortic valve prostheses. *J Thorac Cardiovasc Surg.* 1964;47:693–701. doi: 10.1016/S0022-5223(19)33497-X
2. Love CS, Love JW. The autogenous tissue heart valve: current status. *J Card Surg.* 1991;6:499–507. doi: 10.1111/j.1540-8191.1991.tb00351.x
3. Al Halees Z, Al Shahid M, Al Sanei A, Sallehuddin A, Duran C. Up to 16years follow-up of aortic valve reconstruction with pericardium: a stentless readily available cheap valve? *Eur J Cardiothorac Surg.* 2005;28:200–205. doi: 10.1016/j.ejcts.2005.04.041
4. Chan KM, Rahman-Haley S, Mittal TK, Gavino JA, Dreyfus GD. Truly stentless autologous pericardial aortic valve replacement: an alternative to standard aortic valve replacement. *J Thorac Cardiovasc Surg.* 2011;141:276–283. doi: 10.1016/j.jtcvs.2010.09.038
5. Banbury MK, Cosgrove DM III, White JA, Blackstone EH, Frater RW, Okies JE. Age and valve size effect on the long-term durability of the Carpentier-Edwards aortic pericardial bioprosthesis. *Ann Thorac Surg.* 2001;72:753–757. doi: 10.1016/S0003-4975(01)02992-7
6. Ozaki S, Kawase I, Yamashita H, Uchida S, Nozawa Y, Matsuyama T, Takatoh M, Hagiwara S. Aortic valve reconstruction using self-developed aortic valve plasty system in aortic valve disease. *Interact Cardiovasc Thorac Surg.* 2011;12:550–553. doi: 10.1510/icvts.2010.253682
7. Ozaki S, Kawase I, Yamashita H, Uchida S, Takatoh M, Kiyohara N. Midterm outcomes after aortic valve neocuspidization with glutaraldehyde-treated autologous pericardium. *J Thorac Cardiovasc Surg.* 2018;155:2379–2387. doi: 10.1016/j.jtcvs.2018.01.087
8. Johnston DR, Soltesz EG, Vakil N, Rajeswaran J, Roselli EE, Sabik JF III, Smedira NG, Svensson LG, Lytle BW, Blackstone EH. Long-term durability of bioprosthetic aortic valves: implications from 12,569 implants. *Ann Thorac Surg.* 2015;99:1239–1247. doi: 10.1016/j.athoracsur.2014.10.070
9. Rajeswaran J, Blackstone EH. A multiphase non-linear mixed effects model: an application to spirometry after lung transplantation. *Stat Methods Med Res.* 2017;26:21–42. doi: 10.1177/0962280214537255
10. Rajeswaran J, Blackstone EH, Ehrlinger J, Li L, Ishwaran H, Parides MK. Probability of atrial fibrillation after ablation: using a parametric nonlinear temporal decomposition mixed effects model. *Stat Methods Med Res.* 2018;27:126–141. doi: 10.1177/0962280215623583
11. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc.* 1986;81:615–624. doi: 10.1080/01621459.1986.10478314
12. Mitra R, Reiter JP. A comparison of two methods of estimating propensity scores after multiple imputation. *Stat Methods Med Res.* 2016;25:188–204. doi: 10.1177/0962280212445945
13. Austin P. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med.* 2008;27:2037–2049. doi: 10.1002/sim.3150
14. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharma Stat.* 2011;10:150–161. doi: 10.1002/pst.433
15. Rajeswaran J, Blackstone EH. Competing risks: competing questions. *J Thorac Cardiovasc Surg.* 2017;153:1432–1433. doi: 10.1016/j.jtcvs.2017.03.017
16. Reuthebuch O, Koechlin L, Schurr U, Grapow M, Fassl J, Eckstein FS. Aortic valve replacement using autologous pericardium: single centre experience with the Ozaki technique. *Swiss Med Wkly.* 2018;148:w14591. doi: 10.4414/smw.2018.14591
17. Nguyen DH, Vo AT, Le KM, Vu TT, Nguyen TT, Pham CVT, Truong BQ. Minimally invasive Ozaki procedure in aortic valve disease: the preliminary results. *Innovations (Phila).* 2018;13:332–337. doi: 10.1097/IMI.0000000000000556
18. Iida Y, Fujii S, Akiyama S, Sawa S. Early and mid-term results of isolated aortic valve neocuspidization in patients with aortic stenosis. *Gen Thorac Cardiovasc Surg.* 2018;66:648–652. doi: 10.1007/s11748-018-0976-0
19. Krane M, Boehm J, Prinzing A, Ziegelmueller J, Holfeld J, Lange R. Excellent hemodynamic performance after aortic valve neocuspidization using autologous pericardium. *Ann Thorac Surg.* 2021;111:126–133. doi: 10.1016/j.athoracsur.2020.04.108
20. Ngo HT, Nguyen HC, Nguyen TT, Le TN, Camilleri L, Doan HQ. Reconstruction of aortic valve by autologous pericardium (Ozaki's procedure): single center experience in Vietnam. *Asian Cardiovasc Thorac Ann.* 2021;29:394–399. doi: 10.1177/0218492320981468
21. Hamdan A, Guetta V, Konen E, Goitein O, Segev A, Raanani E, Spiegelstein D, Hay I, Di Segni E, Eldar M, et al. Deformation dynamics and mechanical properties of the aortic annulus by 4-dimensional computed tomography: insights into the functional anatomy of the aortic valve complex and implications for transcatheter aortic valve therapy. *J Am Coll Cardiol.* 2012;59:119–127. doi: 10.1016/j.jacc.2011.09.045
22. Iida Y, Akiyama S, Shimura K, Fujii S, Hashimoto C, Mizuuchi S, Arizuka Y, Nishioka M, Shimura N, Moriyama S, et al. Comparison of aortic annulus dimensions after aortic valve neocuspidization with those of normal aortic valve using transthoracic echocardiography. *Eur J Cardiothorac Surg.* 2018;54:1081–1084. doi: 10.1093/ejcts/ezy190
23. Rosseykin EV, Bazylev VV, Batrakov PA, Karnakhin VA, Rastorguev AA. Immediate results of aortic valve reconstruction by using autologous pericardium (Ozaki procedure). *Patologiya krovoobrashcheniya i kardiokhirurgiya = Circulation Pathology and Cardiac Surgery.* 2016;20:26–30. (In Russ.).
24. Ozaki S, Kawase I, Yamashita H, Uchida S, Nozawa Y, Takatoh M, Hagiwara S, Kiyohara N. Aortic valve reconstruction using autologous pericardium for ages over 80years. *Asian Cardiovasc Thorac Ann.* 2014;22:903–908. doi: 10.1177/0218492314520748
25. Gavalaki A, Roussakis A, Zoubourlis P, Contrafouris C, Zarkalis D, Perreas K. Outcomes and quality of life after aortic valve surgery in octogenarians. *J Card Surg.* 2020;35:341–344. doi: 10.1111/jocs.14377
26. Lemor A, Villablanca P, Hernandez G, Dyal M, Jain T, Frisoli TM, Wang DD, Eng MH, O'Neill W. Comparison of outcomes and transcatheter versus surgical aortic valve replacement in patients ≥80years of age. *Am J Cardiol.* 2019;123:1853–1858. doi: 10.1016/j.amjcard.2019.03.006
27. Poirer NC, Pelletier LC, Pellerin M, Carrier M. 15-year experience with the Carpentier-Edwards pericardial bioprosthesis. *Ann Thorac Surg.* 1998;66:S57–S61. doi: 10.1016/S0003-4975(98)01110-2
28. Ghoreishi M, Thourani VH, Badhwar V, Massad M, Svensson L, Taylor BS, Pasrija C, Gammie JS, Jacobs JP, Cox M, et al. Less-invasive aortic valve replacement: trends and outcomes from the society of thoracic surgeons database. *Ann Thorac Surg.* 2021;111:1216–1223. doi: 10.1016/j.athoracsur.2020.06.039
29. Tada N, Tanaka N, Abe K, Hata M. Transcatheter aortic valve implantation after aortic valve neocuspidization using autologous pericardium: a case report. *Eur Heart J Case Rep.* 2019;3:ytz105. doi: 10.1093/ehjcr/ytz105
30. Khan JM, Greenbaum AB, Babaliaros VC, Rogers T, Eng MH, Paone G, Leshnower BG, Reisman M, Satler L, Waksman R, et al. The BASILICA trial: prospective multicenter investigation of intentional leaflet laceration to prevent TAVR coronary obstruction. *JACC Cardiovasc Interv.* 2019;12:1240–1252. doi: 10.1016/j.jcin.2019.03.035
31. Nguyen DH, Vo AT, Nguyen TT, Le KM, Truong BQ, Nguyen BH. Minimally invasive aortic valve reconstruction with autologous pericardium: how we do it. *Ann Cardiothorac Surg.* 2019;8:444–446. doi: 10.21037/acs.2019.05.12
32. Minakata K, Tanaka S, Okawa Y, Shimamoto M, Kaneko T, Takahara Y, Yaku H, Yamanaka K, Usui A, Tamura N, et al. Long-term outcome of the Carpentier-Edwards pericardial valve in the aortic position in Japanese patients. *Circ J.* 2014;78:882–889. doi: 10.1253/circj.CJ-13-1068
33. Sakamoto Y, Hashimoto K, Okuyama H, Ishii S, Inoue T, Kinouchi K, Abe T. Carpentier-Edwards pericardial aortic valve in middle-aged patients: comparison with the St. Jude medical valve. *Jpn J Thorac Cardiovasc Surg.* 2005;53:465–469. doi: 10.1007/s11748-005-0088-5
34. Yongue C, Lopez DC, Soltesz EG, Roselli EE, Bakaeen FG, Gillinov AM, Pettersson GB, Semple ME, Rajeswaran J, Tong MZ, et al. Durability and performance of 2298 trifecta aortic valve prostheses: a propensity-matched analysis. *Ann Thorac Surg.* 2021;111:1198–1205. doi: 10.1016/j.athoracsur.2020.07.040
35. Nielsen PH, Hjortdal V, Modrau IS, Jensen H, Kimose HH, Terp K, Poulsen SH, Smerup M, Nielsen SL. Durability after aortic valve replacement with the mitroflow versus the perimount pericardial bioprosthesis: a single-centre experience in 2393 patients. *Eur J Cardiothorac Surg.* 2016;49:1705–1710. doi: 10.1093/ejcts/ezv432

SUPPLEMENTAL MATERIAL

Data S1.

Variables Included in the Propensity Model

Demographics:	Age (y), female, body mass index (kg/m^2)
Valve pathology:	Aortic valve regurgitation; bicuspid aortic valve; aortic valve peak gradient (mmHg); indication for surgery: aortic regurgitation, aortic stenosis, mixed regurgitation–stenosis; endocarditis
Renal function:	Creatinine (mg/dL), history of dialysis

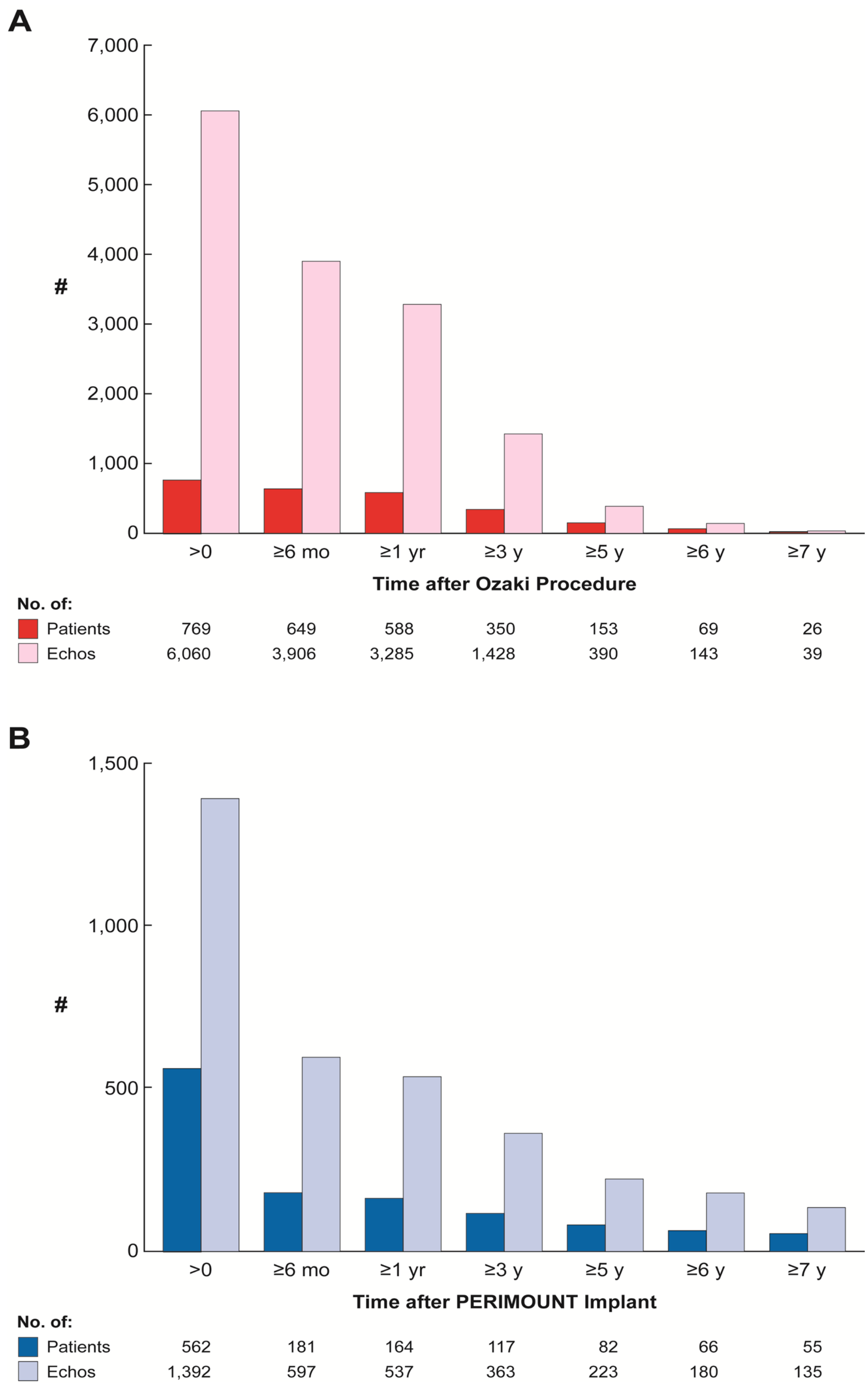
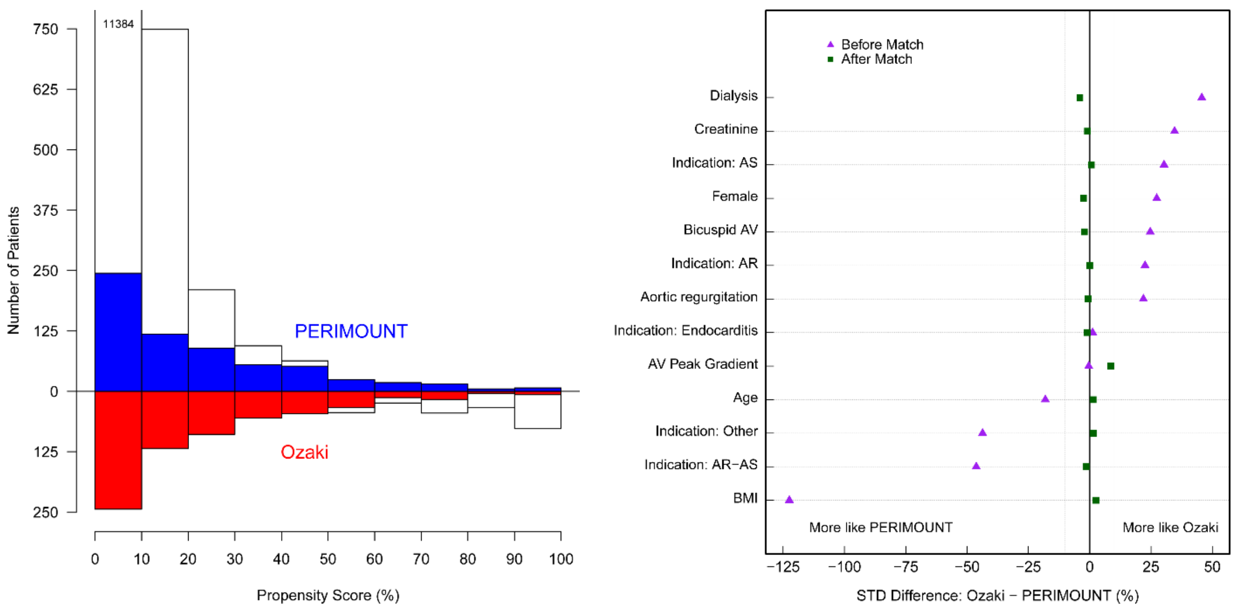


Figure S1. Number of echocardiograms and number of patients with echocardiograms across follow-up time after Ozaki procedure and PERIMOUNT bioprosthesis implant. **A,** Ozaki procedure. **B,** PERIMOUNT bioprosthesis implant.



A **B**

Figure S2. Quality of balancing score matching of Ozaki and PERIMOUNT patients.
A, Mirrored histogram of distribution of propensity scores for Ozaki and PERIMOUNT cohorts before and after 1:1 propensity matching. Shaded areas indicate matched patient pairs, showing that they cover the complete spectrum of cases. **B,** Standardized differences before and after matching for all variables available and included in propensity model. Vertical dashed lines at -10% and +10% indicate boundaries of desirable matching. Purple triangles represent standardized differences before propensity score–based matching, with positive values indicating variables more common in the Ozaki group and negative values indicating variables more common in the PERIMOUNT group. Green squares represent values after matching. Key: *AR,* aortic regurgitation; *AS*, aortic stenosis; *AV*, aortic valve; *BMI*, body mass index; *STD,* standardized.

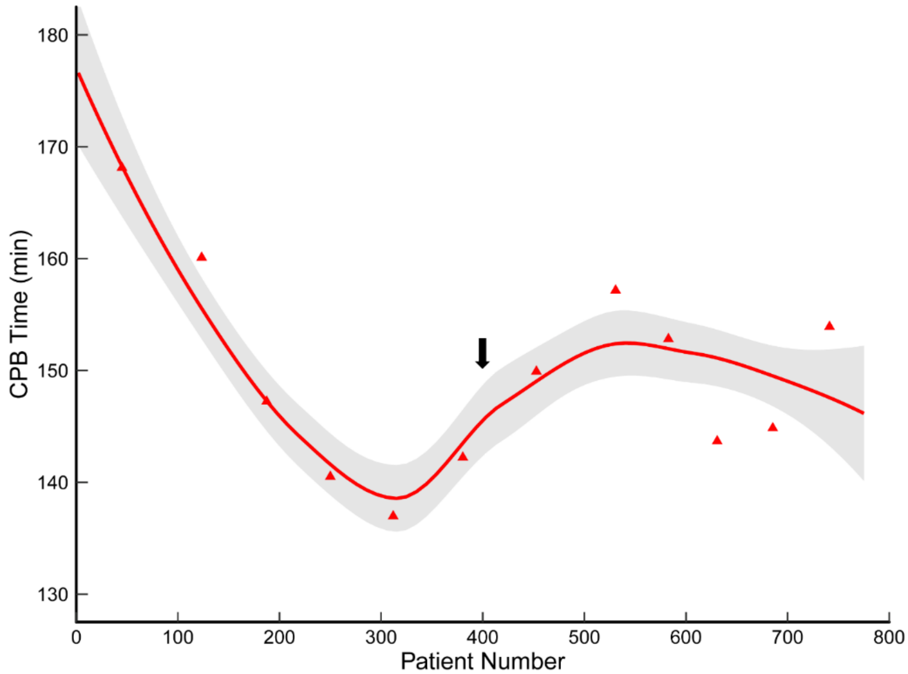


Figure S3. Ozaki procedure learning curve for cardiopulmonary bypass (CPB) time. Numbers on horizontal axis are sequence numbers of patients undergoing a primary isolated procedure. Black arrow points to when new surgeons became involved. Format as in Figure 2A.

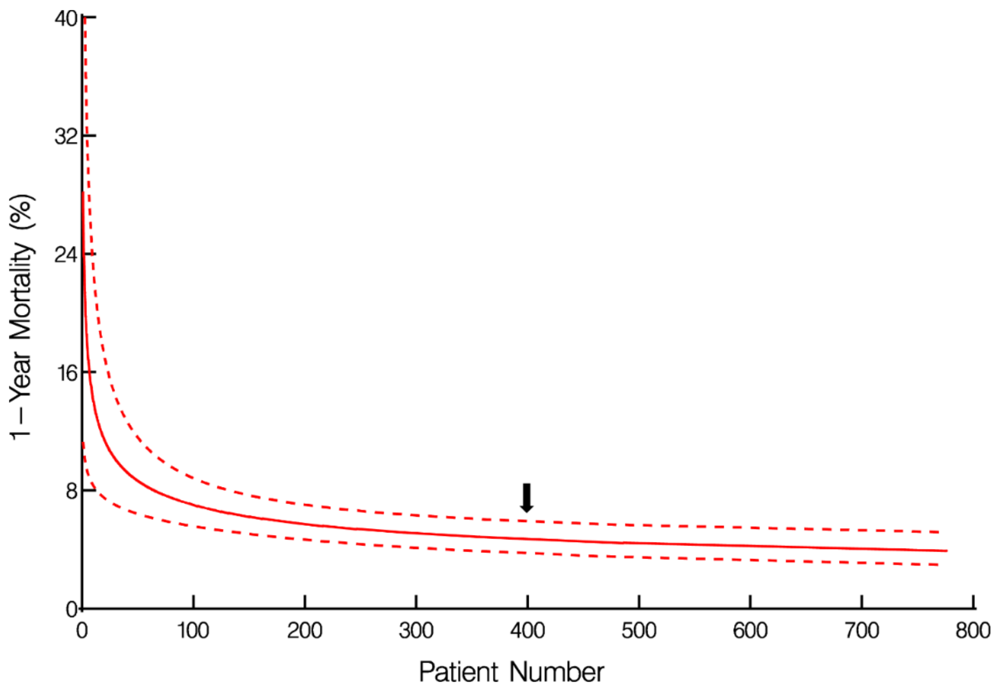


Figure S4. Isolated Ozaki procedure learning curve. Numbers along horizontal axis are sequence numbers of patients undergoing a primary isolated procedure. Solid line represents a parametric estimate of the learning curve. Black arrow points to when new surgeons became involved. One-year mortality is based on parametric mortality analysis shown in Figure S9. Dashed lines are a 68% confidence band equivalent to ±1 standard error.

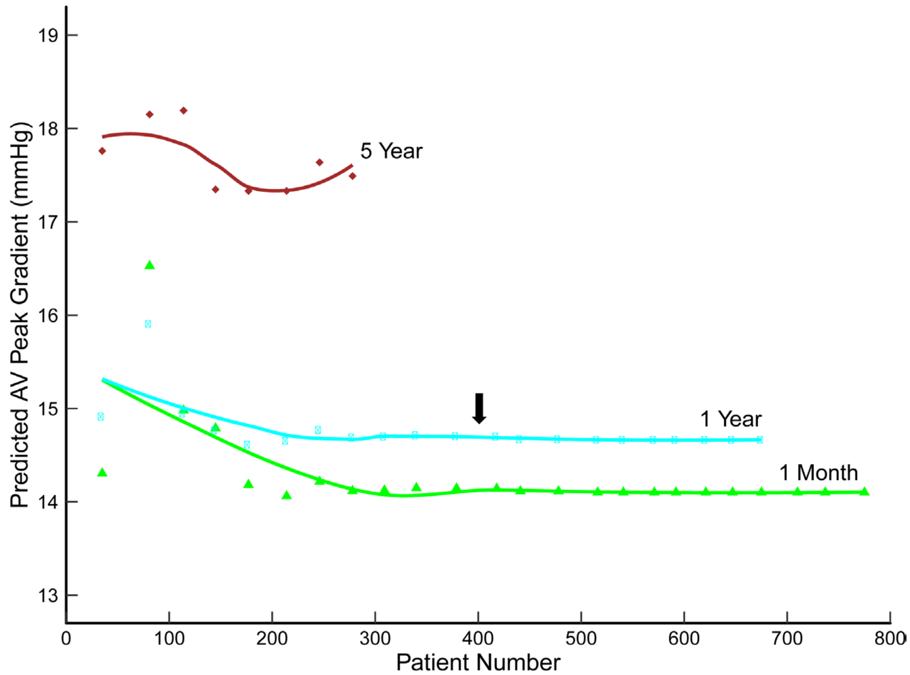
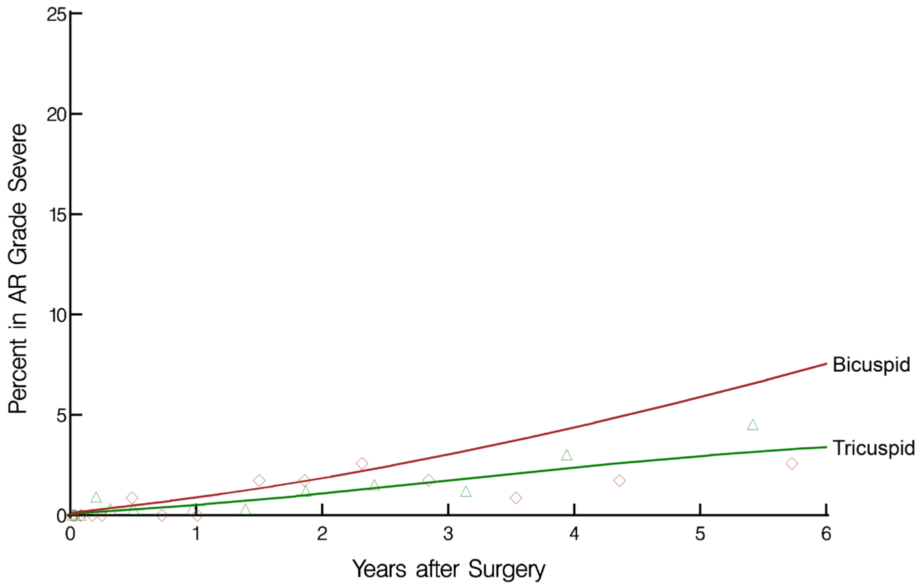
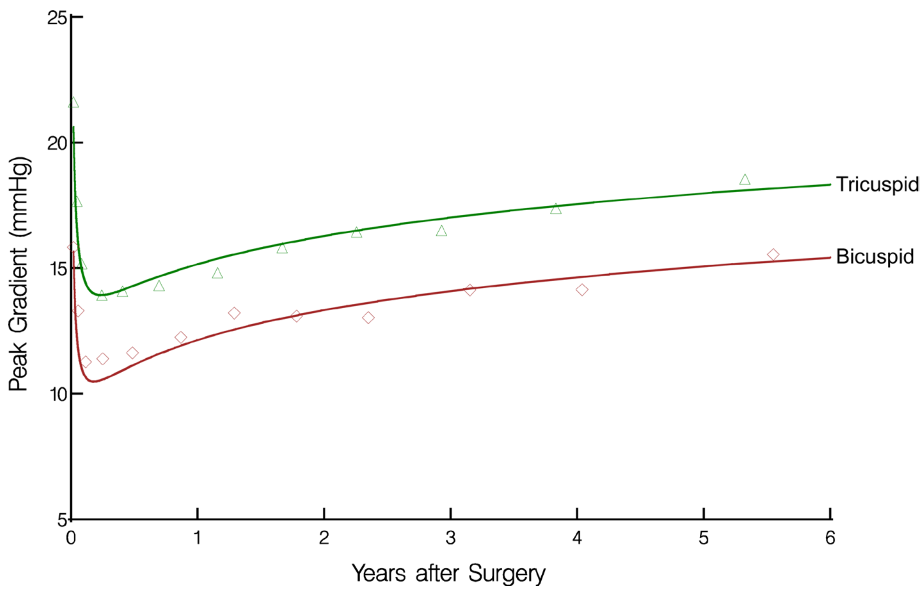


Figure S5. Ozaki procedure learning curve for aortic valve (AV) peak gradient at 1 month (green), 1 year (blue), and 5 years (red). Numbers on horizontal axis are the sequence number of patients undergoing a primary isolated procedure. Black arrow points to when new surgeons became involved. Note that the apparent decrease in gradient across sequence number is only about 1 mmHg. Format as in Figure 2B.



A



B

Figure S6. Aortic valve hemodynamics after the Ozaki procedure in entire cohort, stratified by bicuspid versus tricuspid valve morphology. A, Severe aortic valve regurgitation (AR). **B,** Aortic valve peak gradient. Format as in Figure 3.

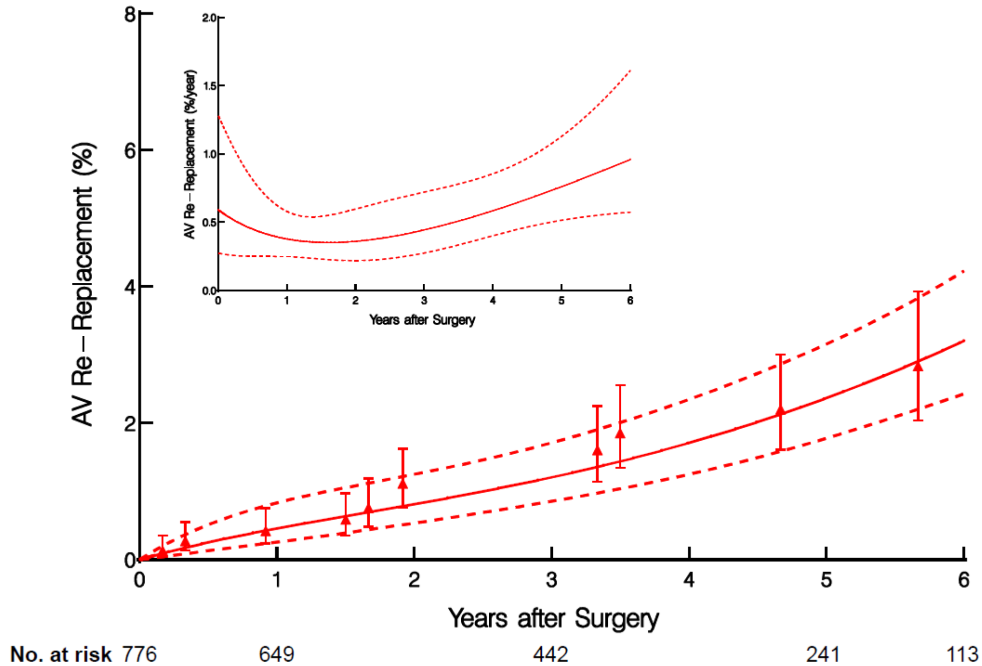


Figure S7. Aortic valve re-replacement after Ozaki procedure in the entire cohort. Symbols are Kaplan-Meier estimates with 68% confidence bars. Solid lines represent parametric estimates enclosed within a 68% confidence band equivalent to ±1 standard error. Numbers below horizontal axis are patients remaining at risk. Inset is instantaneous risk of re-replacement enclosed within a 68% confidence band.

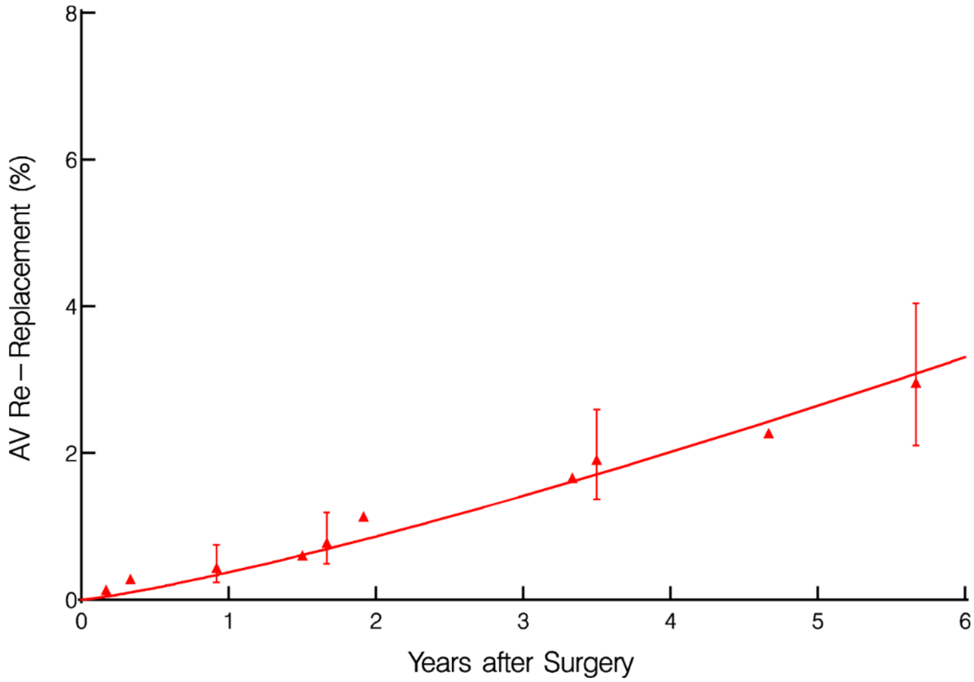


Figure S8. Conditional probability of aortic valve (AV) re-replacement after the Ozaki procedure (entire cohort), accounting for mortality as a competing risk. Solid line is parametric estimate, and symbols are nonparametric estimates with 68% confidence bars.

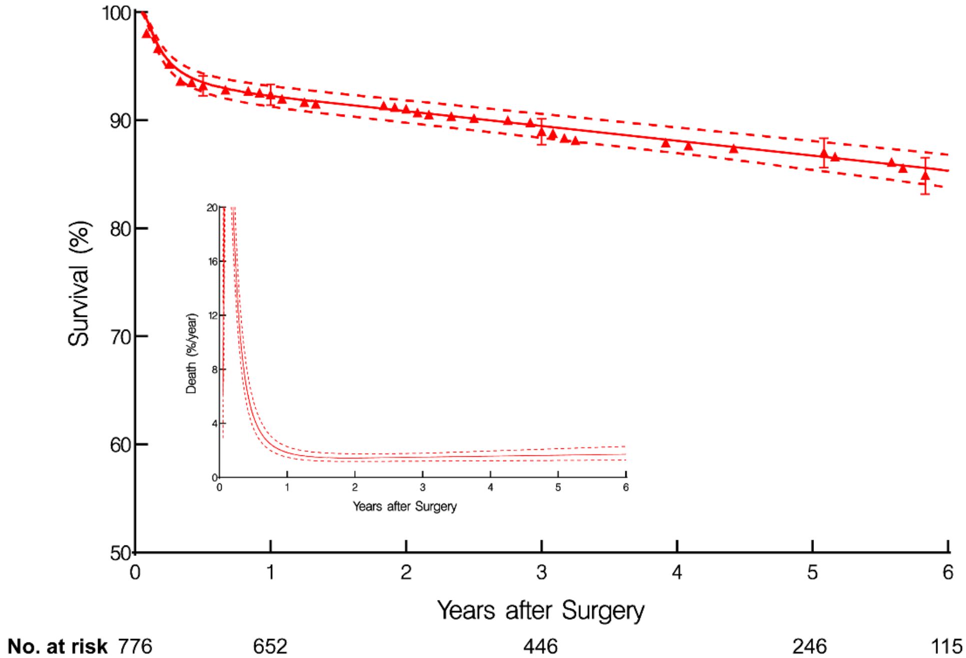


Figure S9. Survival after Ozaki procedure in the entire cohort. Numbers below horizontal axis are patients remaining at risk. Inset is instantaneous risk of death, demonstrating high postoperative risk merging with a low, nearly constant risk after about 1.5 years. Format as in Figure S7.

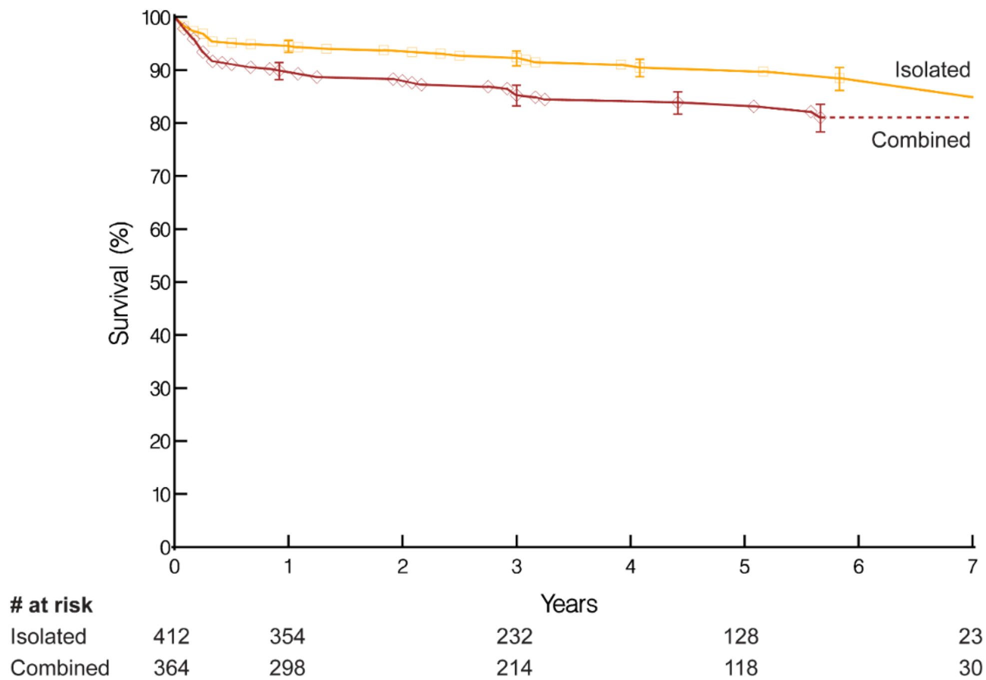


Figure S10. Survival after Ozaki procedure stratified by isolated versus combined procedures. Symbols are Kaplan-Meier estimates with 68% confidence bars.

Video S1. Intraoperative echocardiogram and surgical video showing the main steps of the operation performed by Professor Ozaki. Best viewed with Windows Media Player.