Midterm results after aortic valve neocuspidization

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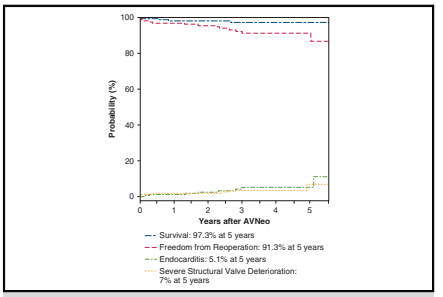
ABSTRACT

Objectives: Aortic valve neocuspidization with autologous pericardium is gaining increasing attention as a surgical treatment option for aortic valve disease. However, little is known about midterm durability and valve-related events.

Methods: Patients undergoing aortic valve neocuspidization between 2016 and 2021 were included. Transthoracic echocardiography was performed before the operation, at discharge, and annually thereafter. Data were analyzed for incidences of structural valve deterioration, bioprosthetic valve failure, survival, freedom from reoperation, and hemodynamic performance.

Results: A total of 162 patients underwent aortic valve neocuspidization (mean age, 52.6 ± 16.6 years; range, 13-78 years); 114 (70.4%) were male. A total of 132 patients presented with a bicuspid aortic valve (81.5%) and 126 patients presented with aortic valve stenosis (77.8%). Concomitant procedures were performed in 63 patients (38.9%). Mean follow-up was 3.5 ± 1.2 years. At discharge, peak and mean pressure gradients were 15.6 ± 7.2 mm Hg and 8.4 ± 3.7 mm Hg, respectively, with a mean effective orifice area of 2.4 ± 0.8 cm^2. After 5 years, peak and mean pressure gradients were 14.5 ± 4.6 mm Hg and 7.5 ± 2.2 mm Hg, respectively, with a mean effective orifice area of 2.3 ± 0.8 cm^2. At 5 years, cumulative incidences of moderate and severe structural valve deterioration and bioprosthetic valve failure were 9.82% ± 3.87%, 6.96% ± 3.71%, and 12.1% ± 4.12%, respectively. Survival was 97.3% ± 1.4%, and freedom from reoperation was 91.3% ± 2.4%.

Conclusions: Aortic valve neocuspidization accomplishes low pressure gradients early after initial surgery and during follow-up. Survival in this young patient population is excellent. The main reason for reoperation is endocarditis, and rates for structural valve degeneration are low. (JTCVS Techniques 2024;25:35-42)



Years after AVNeo.

CENTRAL MESSAGE

AVNeo achieves low peak and mean pressure gradients with large EOAs that remain stable over a 5-year follow-up.

PERSPECTIVE

AVNeo is an additional tool to treat aortic valve disease. Prospective randomized trials with long-term follow-up are necessary to determine durability and valve-related events of AVNeo in comparison with aortic valve replacement with mechanical or biological prostheses and its role in the treatment of diseased aortic valves.

Surgical treatment options suited for aortic valve disease depend on the underlying valve pathology and in most cases result in replacement of the aortic valve with a biological or mechanical prosthesis. Despite all medical progress, available prostheses have their well-known drawbacks, such as degeneration with biological prostheses, need for lifelong anticoagulation with mechanical prostheses, and an increased risk for endocarditis. In cases of aortic regurgitation, aortic valve repair is a feasible option in experienced institutions, but results are highly dependent on the quality of the native valve.[1,2]

Duran and colleagues[3] presented an alternative technique creating an aortic valve with autologous pericardium, which never gained widespread application because of its technical difficulties, as well as the use of polytetrafluorethylene or decellularized bovine pericardium due to its limited durability and tendency of early calcification.[4-7] In 2011, Ozaki and colleagues[8] presented the initial results of patients undergoing a highly standardized de novo reconstruction of the aortic valve with autologous pericardium (aortic valve neocuspidization [AVNeo]), showing encouraging results with low peak pressure gradients and no reoperations after 3 years of follow-up, with stable results in a larger cohort with longer follow-up time.[9] Our own institutional data

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Abbreviations and Acronyms

AVNeo = aortic valve neocuspidization
BVF = bioprosthetic valve failure
CPB = cardiopulmonary bypass
EOA = effective orifice area
SVD = structural valve deterioration
TTE = transthoracic echocardiography

showed large orifice areas, low pressure gradients, and excellent short-term survival after AVNeo.[10] The procedure is technically complex, requiring longer bypass and cross-clamp times, and its role in the treatment of aortic valve disease is not fully defined, because the questions of durability, reoperation rates, hemodynamic parameters, and incidence of endocarditis remain. In the present study, we present the midterm results from our institution, the largest single-center population outside of Japan, with special focus on hemodynamic parameters, structural valve deterioration (SVD), reoperation rates, and survival.

MATERIAL AND METHODS

The study was approved by the local ethics committee (548-S-SB, 10/30/2023), and need for informed consent was waived.

All patients who successfully underwent the AVNeo procedure at our institution between 2016 and 2021 were included in this "as-treated" analysis. We offered AVNeo only to elective patients scheduled for aortic valve replacement, excluding patients with endocarditis. We limited concomitant procedures to supracoronary replacement of the ascending aorta, 1- or 2- vessel coronary artery bypass grafting, and closure of patent foramen ovale.

Ozaki and colleagues[8] described the surgical procedure in detail, which we applied accordingly as follows: Before cardiopulmonary bypass (CPB), autologous pericardium was harvested, cleaned from fat and redundant tissue, and treated with 0.6% glutaraldehyde solution for 10 minutes and rinsed in physiological saline solution 3 times for 6 minutes. After initiation of CPB and induction of cardioplegic arrest, the native valve was excised and the annulus thoroughly debrided. To construct the AVNeo, we measured the exact size of each new leaflet with a commercially available sizer (JOMDD). If the native valve was bicuspid, each AVNeo was created as a tricuspid valve. If the new leaflets differed in more than 1 size, we placed an extra-anatomic neocommissure to achieve equal size distribution of the 3 leaflets, as proposed earlier.[11] After determination of the required size, leaflets were cut out of the pericardium using commercially available templates. Subsequently, the leaflets were sutured to the native aortic annulus. A detailed description of the surgical technique used in our institution was published in 2021.[12]

Every patient underwent transthoracic echocardiography (TTE) before the operation and before discharge. Patients were followed annually by TTE in our outpatient clinic or echocardiographic reports were obtained from the referring cardiologist. Mean follow-up time was 3.5 ± 1.2 years, and follow-up was completed for all patients. To obtain a more detailed understanding of valvular function after AVNeo over time, TTE examinations were analyzed for SVD or bioprosthetic valve failure (BVF), according to the definitions of Capodanno and colleagues.[13]

Statistical analysis was performed using IBM SPSS Version 23 (IBM) and R (Version 4.2.3). Continuous variables were reported as mean ± SD. For all categorical variables, absolute and relative frequencies were provided. For paired samples, *t* tests were performed. Survival and freedom from reoperation were displayed by Kaplan–Meier curves. For SVD and BVF, competitive risk analyses were performed.

RESULTS

Starting in 2016, we performed the AVNeo procedure in 162 patients with a mean age of 52.9 ± 16.1 years (range, 13-78 years), of whom 114 (70.4%) were male. Baseline demographic data are presented in Table 1.

The leading indication for AVNeo was aortic valve stenosis in 126 cases (77.8%), and the majority of patients presented with bicuspid aortic valves (132 patients, 81.5%). Mean preoperative annulus size was 24.6 ± 3.1 mm. This resulted in a mean size of the neocusps of 28.9 ± 2.9 mm for the right coronary cusp, 28.4 ± 3 mm for the left coronary cusp, and 28.9 ± 2.8 mm for the noncoronary cusp. Mean CPB time was 162.5 ± 29.9 minutes with an aortic crossclamp time of 134.6 ± 20.4 minutes. Concomitant surgical procedures were performed in 63 cases (38.9%). Early operative outcome and details of concomitant surgical procedures are depicted in Table 2.

At discharge, peak and mean pressure gradients were 15.6 ± 7.2 mm Hg and 8.4 ± 3.7 mm Hg, respectively, with a mean effective orifice area (EOA) of 2.4 ± 0.8 cm^2, showing significant changes between preoperative and discharge values ($P < .001$ each). A total of 24 patients (14.3%) had up to mild aortic regurgitation. During the follow-up period, the average peak and mean pressure gradients were less than 20 mm Hg and 10 mm Hg, respectively. Statistical analysis of the annual time points showed no significant differences between peak and mean gradients and EOA (Figure 1, *A-C*).

Estimated survival after 1, 3, and 5 years was 98.1% ± 1.1% and 97.3% ± 1.4%, respectively, and remained stable in the following years, resulting in an overall survival of 97.3% (Figure 2). Estimated freedom from reoperation was 96.9% ± 1.4% at 1 year, 92.3% ± 2.2% at 3 years, and 91.3% ± 2.4% at 5 years (Figure 3) with a mean freedom from reoperation of 92%. Reoperations had to be performed in 13 patients (8%), 5 (3.1%) for recurrent aortic valve regurgitation and 8 (4.9%) for acute infective endocarditis, corresponding to a rate of 1% endocarditis/patient-year. A detailed depiction of time after initial surgery, indication for reoperation, and background for reoperation is presented in Table 3.

In our series, 4 patients (2.5%) developed moderate SVD over the course of follow-up and 6 patients presented with severe SVD. Of these, 5 (3.1%) developed severe aortic regurgitation and 1 (0.6%) had an increased mean gradient. Endocarditis occurred in 8 patients (4.5%). BVF had to be reported in 13 cases (8%), including the patients with endocarditis and severe SVD, who underwent reoperation. Two of the patients underwent reoperation within the initial admission before discharge. The cumulative incidence for

TABLE 1. Baseline demographics

Variable	Value
Age (y)	52.9 ± 16.1
Male	114 (70.4)
Coronary artery disease	20 (12.3%)
Arterial hypertonus	79 (48.8%)
Hyperlipidemia	51 (31.5%)
Diabetes mellitus	14 (8.6%)
Renal insufficiency	1 (0.6%)
euroSCORE	3.81 ± 1.8
Log euroSCORE	3.31 ± 2.2
euroSCORE II	0.62 ± 0.7

Continuous variables: Mean value ± SD. Categorial variables: number (%). *euroSCORE*, European System for Cardiac Operative Risk Evaluation.

moderate SVD after 1, 3, and 5 years was 2.5% ± 1.2,% 6.5% ± 2.1%, and 9.8% ± 3.9%, respectively. The incidence for severe SVD after 1, 3, and 5 years was 1.8% ± 1.1%, 3.5% ± 1.5%, and 7% ± 3.7%, respectively. For endocarditis, the cumulative incidence after 1, 3, and 5 years was 1.2% ± 0.9%, 4.2% ± 1.7%, and 5.1% ± 1.9%, respectively, and for BVF was 3.1% ± 1.4%, 7.7% ± 2.3%, and 12.1% ± 4.1%, respectively (Figure 4, *A-D*).

DISCUSSION

The AVNeo procedure, as described by Ozaki and colleagues,[8] is gaining more interest as an alternative treatment modality for diseased aortic valves. Because the technical feasibility with excellent early hemodynamic results and low perioperative mortality has been independently reproduced by several groups around the world,[8,10,14-16] the remaining issue is the longevity of the reconstructed valve and its long-term hemodynamic performance.

TABLE 2. Concomitant procedures and periprocedural data

Concomitant procedures	63 (38.9)
Supracoronary ascending aorta	39 (24.1)
CABG	9 (5.6)
PFO closure	9 (5.6)
Pulmonary vein ablation	5 (3.1)
Subvalvular myectomy	7 (4.3)
Other	4 (2.5)
30-d mortality	1 (0.6)
Ventilation time [h]	7.3 (IQR 5.3-9.9)
Reexploration for bleeding	1 (0.6)
Early postoperative stroke	1 (0.6)
Renal failure requiring dialysis	3 (1.9)
Pacemaker	0

Continuous variables: Mean value ± SD. Categorial variables: number (%). *CABG*, Coronary artery bypass grafting; *PFO*, persistent foramen ovale.

Hemodynamic Performance

In 2018, Ozaki and colleagues[9] published midterm follow-up data of 850 patients, presenting the largest single-center cohort with the longest mean follow-up time of 53.7 ± 28.2 months with a mean peak gradient of 15.2 ± 6.3 mm Hg, despite the small annulus size of 20.9 ± 3.3 mm. Similar results were presented by Iida and colleagues[17] with peak and mean gradients of 19.2 ± 9.7 mm Hg and 9.7 ± 5.5 mm Hg after 20 months. The EOA was 1.8 ± 0.6 cm^2. Here, the mean annulus diameter was only 20.5 ± 2.5 mm. In both studies, the leading indication for surgery was aortic stenosis. Interestingly, the same group published data of patients aged less than 65 years with aortic regurgitation in the majority of the cases. These patients were younger (55 ± 10.4 years) and had larger annuli with 22.8 ± 3.1 mm. Midterm values here were 19 ± 8.6 mm Hg for peak gradients with an EOA of 2.2 ± 0.8 cm^2.[18]

Koechlin and colleagues[19] reported results from 35 patients who received AVNeo with a median age of 72 years and a median annulus size of 23 mm. Aortic stenosis was the main indication for surgery, and at the end of the 645-day follow-up, median peak and mean pressure gradients were 12 mm Hg and 6 mm Hg, respectively.

In our cohort, the peak gradient at discharge and at 5-year follow-up were comparable with 15.6 ± 7.2 mm Hg and 14.5 ± 4.6 mm Hg, respectively (Figure 1, *A*). Correspondingly, we also report mean gradients and EOA, which were significantly lower compared with preoperative values and remained stable over time (Figure 1, *B* and *C*).

The AVNeo procedure resulted in reproducible low peak and mean pressure gradients, with corresponding large EOA in small aortic valve annuli. This excellent hemodynamic performance is stable at least up to 5 years.

Long-Term Survival and Freedom From Reoperation

In our series, the survival was 98.1% and freedom from reoperation at 5 years was 91.3%. Ozaki and colleagues[9] reported a survival of 85.9% and a freedom from reoperation of 95.8%. The superior survival may be due to the younger mean age at surgery in our patient population (52.9 ± 16.1 years vs 71 years). Iida and colleagues[17] reported a survival of 77.2% after 60 months and a freedom from reoperation of 95.3% after 81 months. In their second series, survival and freedom from reoperation after 72 months were 88.9% and 87.3%, respectively.[18] Interestingly, the mean age in their series was 55 ± 10.4 years and comparable to our study population. In our cohort, survival and freedom from reoperation are comparable, considering a 1-year shorter follow-up time. In the study by Koechlin

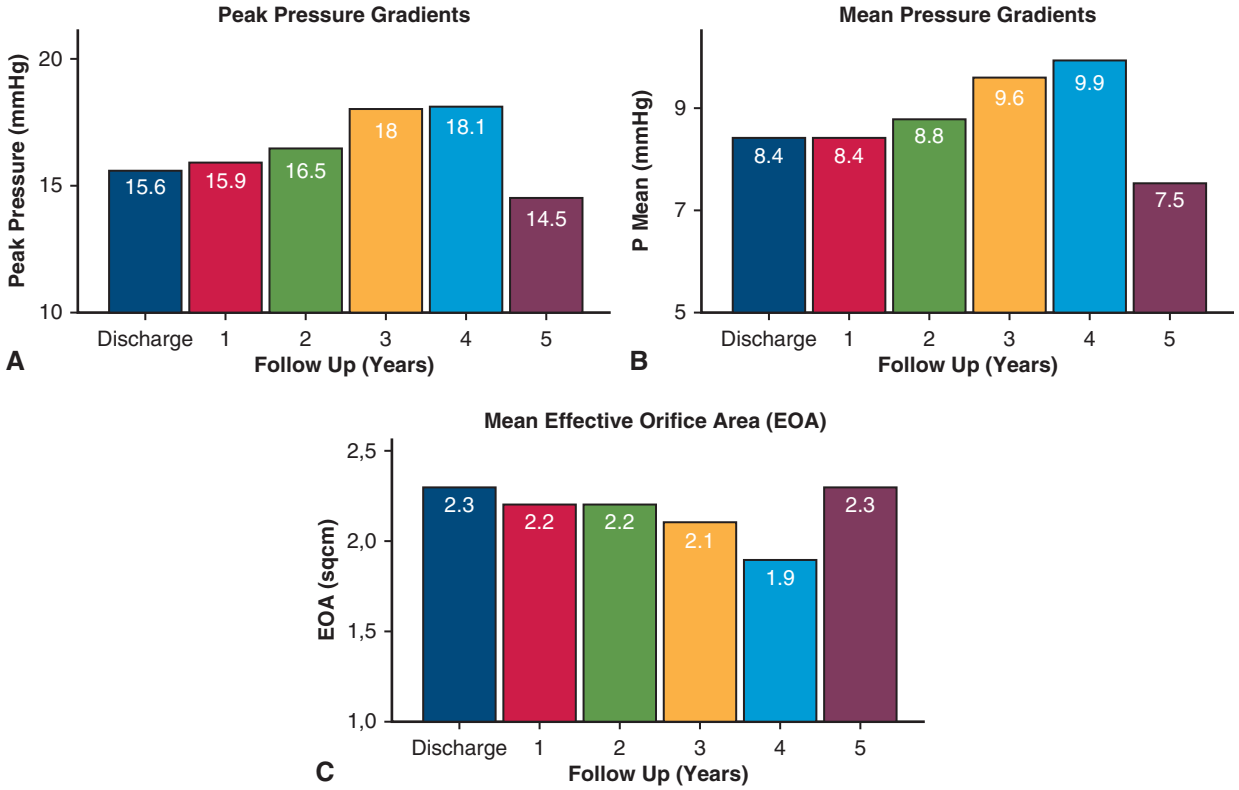

FIGURE 1. A, Peak pressure gradients during follow-up. Gradients (mm Hg). B, Mean pressure gradients during follow-up. Gradients (mm Hg). C, Mean EOA (cm^2) during follow-up.

and colleagues,[19] survival was 91% and freedom from reoperation was 97% after a median follow-up of 645 days.

However, one needs to keep in mind that our patient cohort consists of highly selected patients in an elective setting, excluding patients with high surgical risk, need for multiple concomitant procedures, or endocarditis.

Promising outcomes for survival and freedom from reoperation rates are reproducible and comparable in different institutions from different surgeons worldwide.

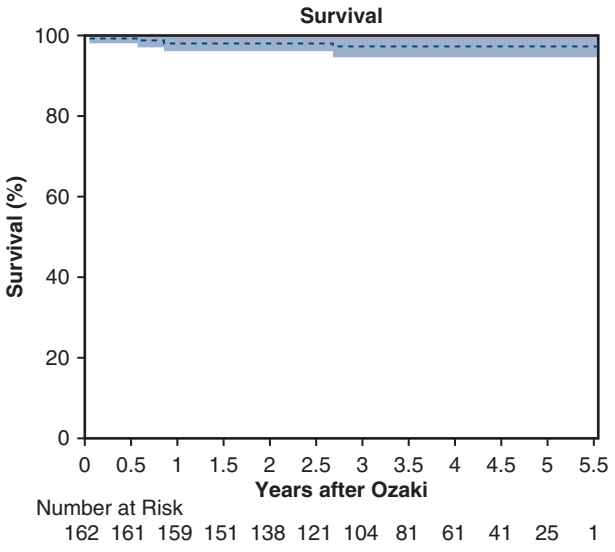

FIGURE 2. Kaplan–Meier curve: Overall survival. 95% CI.

Comparison With Biological Prosthesis

Until now, the gold standard in treatment of aortic valve disease is replacement with a prosthesis, mainly a biological prosthesis. Therefore, AVNeo needs to stand comparison with biological prostheses. For patients after biological valve replacement, the survival in a large study of patients aged 50 to 69 years was 89% after 5 years and rate of reoperation was 5.2% after 16 years of follow-up.[20] Another study by Vitanova and colleagues[21] reports an estimated survival of 97% ± 2% and 79.1% ± 5.8% after 10 years in patients aged less than and more than 60 years, or older. Although no direct comparison of patients after AVNeo and biological valve replacement has been conducted so far, survival in patients after AVNeo is promising. One may speculate that a selection bias may contribute to this finding, because patients undergoing AVNeo are most likely highly elective cases.

Still, the question of comparability with aortic valve prosthesis remains, and up to now, no randomized data

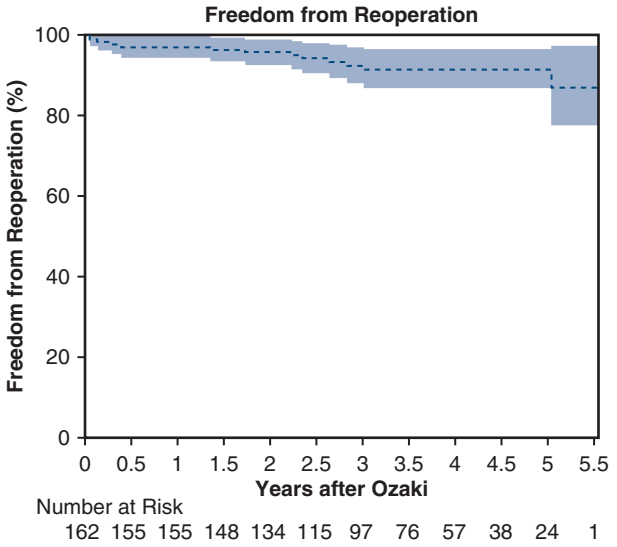

FIGURE 3. Kaplan–Meier curve: Freedom from reoperation. 95% CI.

are available. Our group published 2 retrospective studies of patients after AVNeo, comparing them with patients after biological aortic valve replacement. After measuring the aortic annulus with prosthetic biological aortic valve sizers, in one study averaged EOA and peak and mean gradients after surgical aortic valve replacement were compared with the results after AVNeo, showing significantly lower values for mean pressure gradients and significantly larger EOA in patients after AVNeo.[10] In the second study, EOA and indexed EOA were analyzed, and in both cases, multiple regression favored AVNeo for larger EOA and indexed EOA.[22] We believe that these results reflect the avoidance of the rigid stent frame in the AVNeo procedure, allowing an unobstructed outflow tract and preserved physiological annulus movement with consecutive lower pressure gradients and larger orifice areas. Our findings were confirmed by Unai and colleagues,[23] who matched patients after AVNeo or biological aortic valve replacement. Comparison of pressure gradients showed significantly lower values after AVNeo for peak and mean pressure gradients compared with a biological prosthesis.

TABLE 3. Indication for reoperation

No.	Time after surgery	Indication	Reason
1	9 d	Early SVD	Leaflet tear (technical failure)
2	13 d	Early SVD	Leaflet flipped (technical failure)
3	43 d	Endocarditis	S.p. pericardial puncture prior surgery
4	99 d	Endocarditis	S.p. steroid therapy (pericardial effusion)
5	136 d	Thrombus	Thrombus formation on neo-LCC and RCC
6	1.34 y	Endocarditis	Exacerbation of colitis ulcerosa
7	1.72 y	Endocarditis	Focus unclear
8	2.18 y	Late SVD	Leaflet prolapse
9	2.34 y	Endocarditis	S.p. chemotherapy for multiple myeloma
10	2.63 y	Late SVD	Tear left cusp
11	2.82 y	Endocarditis	S.p. carotid surgery
12	3 y	Endocarditis	Focus unclear
13	5.1 y	Endocarditis	S.p. urosepsis after urological surgery for cancer

SVD, Structural valve deterioration; *LCC*, left coronary cusp; *RCC*, right coronary cusp; *S.p.*, status post.

Structural Valve Deterioration, Bioprosthetic Valve Failure, and Endocarditis

In a recent publication, Unai and colleagues[23] matched 776 patients after AVNeo with patients who received biological prosthetic valve replacement, leading to 627 1:1 matched pairs. They report only 1 patient after AVNeo who had to undergo reoperation due to SVD. However, 13 of 14 reoperations were due to endocarditis. Notably, the patients who received AVNeo were derived from the cohort of Ozaki and colleagues, whereas the patients with surgical aortic valve replacement underwent operation at the Cleveland Clinic.[23] In their publication from 2018, Ozaki and colleagues[9] report 15 reoperations (1.7%) in which endocarditis was the indication for reoperation in 13 cases (1.5%), leading to an incidence of 0.3%/patient-year. Compared with our data, the incidence of severe aortic regurgitation causing reoperation and the incidence for endocarditis (1%/patient-year) after AVNeo were higher in our study population. Iida and colleagues report rates of endocarditis of 5.5%[18] and 3.5%.[17]

In large studies of patients undergoing implantation of biological prostheses, the incidence of endocarditis varies from 1.3%,[24] 1.6%,[25] to 4.4%.[26] Comparing these results with our data, AVNeo showed a slightly higher incidence of endocarditis.

In a large cohort of more than 5000 patients (mean age 69 ± 11 years) receiving 2 different types of bioprosthesis, Lange and colleagues[27] report an overall rate of BVF of 6.1%. At 5 years, the cumulative incidence for BVF in patients aged less than 65 years was 4.9% ± 0.8% in patients receiving the Edwards Perimount valve and 8.5% ± 1.1% after implantation of the Abbott Trifecta valve. In the study by Mayr and colleagues[28] using serial echocardiographic evaluation in 58 patients with an Edwards Perimount Magna Ease valve, the incidence of moderate, severe SVD, and BVF after 10 years was 20% ± 6%, 14% ± 5%, and 16% ± 5%, respectively.[28] These results must be interpreted in the context of a mean age of 66 ± 9.4 years in the published Edwards Perimount Magna Ease population

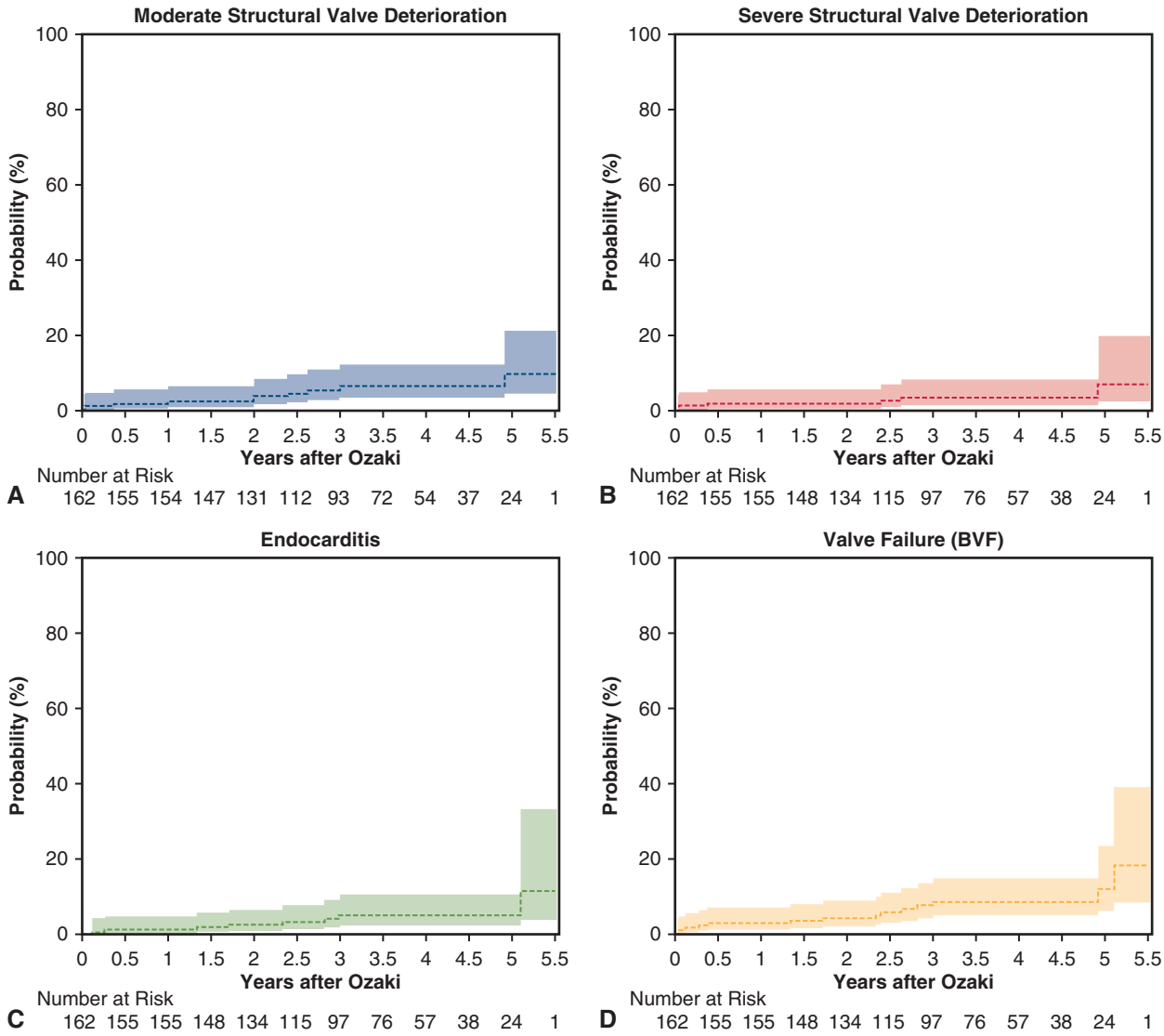

FIGURE 4. A, Cumulative incidence of moderate SVD. 95% CI. B, Cumulative incidence of severe SVD. 95% CI. C, Cumulative incidence of endocarditis. 95% CI. D, Cumulative incidence of BVF. 95% CI. *BVF*, Bioprosthetic valve failure.

compared with the younger AVNeo population with a mean age of 52.9 ± 16.1 years.

Study Limitations

The main limitation of this study is the retrospective character of the study design. We present the largest cohort outside of Japan followed routinely with annual echocardiographic examinations, and our findings are summarized in the Graphical Abstract (Figure 5).

Our cohort is highly selected, and the role of the AVNeo procedure needs to be evaluated with larger cohorts with long-term follow-up and compared with biological and mechanical surgical aortic valve replacement in prospective, randomized trials. Enrollment in a randomized controlled trial at our institution to answer parts of these questions will be completed in 2024 (ClinicalTrials.gov ID NCT03600662).

CONCLUSIONS

AVNeo has large EOAs as well as low peak and mean pressure gradients at discharge that remain stable up to 5 years. The survival after AVNeo is excellent. The main reason for reoperation is endocarditis, whereas rates for SVD are low.

Conflict of Interest Statement

Dr Krane is a physician proctor and a member of the medical advisory board for JOMDD, a physician proctor for Peter Duschek, and a medical consultant for EVOTEC and Moderna, and has received speakers' honoraria from

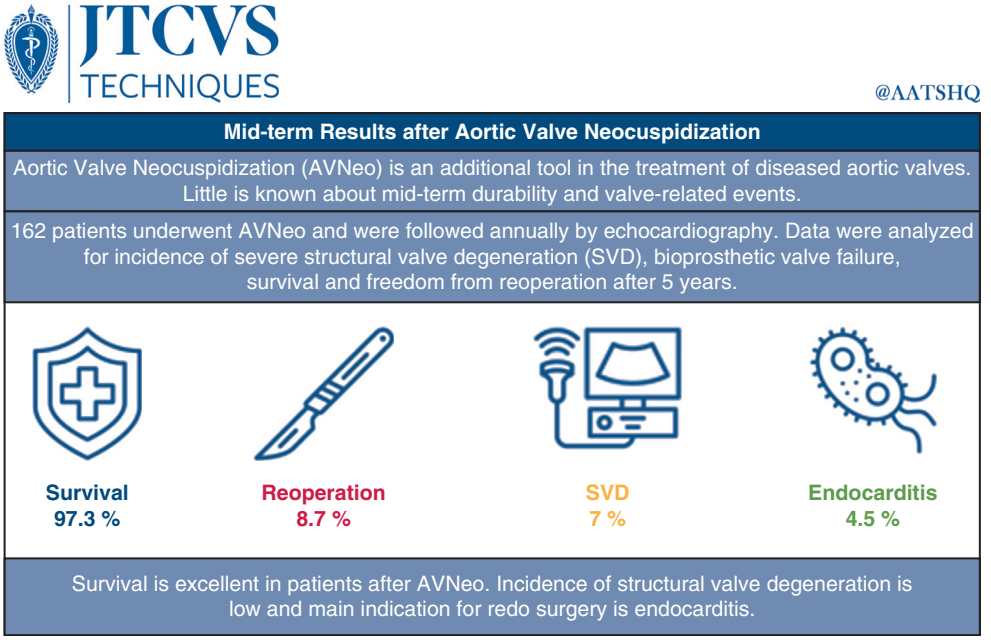

FIGURE 5. Graphical Abstract. *AVNeo*, Aortic valve neocuspidization; *SVD*, structural valve degeneration.

Medtronic and Terumo. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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