Mid-term Results after Aortic Valve Neocuspidization

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**Mid-term Results after Aortic Valve Neocuspidization**

Aortic Valve Neocuspidization (AVNeo) is an additional tool in the treatment of diseased aortic valves. Little is known about mid-term durability and valve-related events.

162 patients underwent AVNeo and were followed annually by echocardiography. Data were analyzed for incidence of severe structural valve degeneration (SVD), bioprosthesis valve failure, survival, and freedom from reoperation after 5 years.

<table>
<thead>
<tr>
<th>Event</th>
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<tr>
<td>Survival</td>
<td>97.3%</td>
</tr>
<tr>
<td>Reoperation</td>
<td>8.7%</td>
</tr>
<tr>
<td>SVD</td>
<td>7%</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>4.5%</td>
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</table>

Survival is excellent in patients after AVNeo. Incidence of structural valve degeneration is low and the main indication for redo surgery is endocarditis.
Mid-term Results after Aortic Valve Neocuspidization

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Moderna and has received speakers’ honoraria from Medtronic and Terumo.

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Key words: Heart Valve, Aortic Valve, Aortic Valve Neocuspidization, Autologous Pericardium

Abbreviations:

AVNeo: Aortic valve neocuspidization
BVF: Bioprosthetic Valve Failure
CPB: Cardiopulmonary Bypass
EOA: Effective orifice area
SVD: Structural Valve Deterioration
TTE: Transthoracic Echocardiography

Central Message: Aortic Valve Neocuspidization achieves low peak and mean pressure gradients with large effective orifice areas which remain stable over a 5 year follow-up.

Perspective Statement: Aortic Valve Neocuspidization 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 to aortic valve replacement with mechanical or biological prostheses and its role in the treatment of diseased aortic valves.

Central Picture

Years after AVNeo
Abstract

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

Methods:
Patients undergoing AVNeo between 2016 to 2021 were included. Transthoracic echo was performed prior to 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:
162 patients underwent AVNeo (mean age 52.6 ± 16.6 years; range: 13 – 78 years), 114 (70.4%) were male. 132 patients presented with a bicuspid aortic valve (81.5%) and 126 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 and 8.4 ± 3.7 mmHg, respectively, with a mean EOA of 2.4 ± 0.8 cm² and after 5 years 14.5 ± 4.6 and 7.5 ± 2.2 mmHg and 2.3 ± 0.8 cm². At 5 years, cumulative incidence 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 91.3%±2.4.
Conclusion

AVNeo 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 while rates for structural valve degeneration are low.
Introduction

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 life-long 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 et al. presented an alternative technique creating an aortic valve with autologous pericardium, which never gained widespread application due to its technical difficulties (3), as well as the use of polytetrafluorethylene (PTFE) or decellularized bovine pericardium due to its limited durability and tendency of early calcification (4-7). In 2011 Ozaki et al. presented initial results of patients undergoing a highly standardized de novo reconstruction of the aortic valve with autologous pericardium (AVNeo), showing encouraging results with low peak pressure gradients and no reoperations after three years of follow-up (8) with stable results in a larger cohort with longer follow-up time (9). Own institutional data showed large orifice areas, low pressure gradients and excellent short-term survival after AVNeo (10). But 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, as the questions of durability, reoperation rates, hemodynamic parameters and incidence of endocarditis remain. In the present study we present mid-term results from our institution, the largest single center population outside of Japan, with special focus on hemodynamic parameters, structural valve deterioration, 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 underwent successfully the AVNeo- procedure at our institution between 2016 - 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 described the surgical procedure in detail (8), which we applied accordingly as follows: prior to 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 three times for six minutes. After initiation of CPB and induction of cardioplegic arrest, the native valve was excised and the annulus thoroughly debried. In order to construct the AVNeo, we measured with commercially available sizer (JOMDD, Tokyo, Japan) the exact size of each new leaflet. If the native valve was bicuspid, each AVNeo was created as a tricuspid valve. If the new leaflets differed in more than one size, we placed an extraanatomical neocommissure in order to achieve equal size distribution of the three 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 trans- thoracic echocardiography (TTE) prior to the operation and before discharge. Patients were either 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 get a more detailed understanding of valvular function after AVNeo over time, TTE- examinations were analyzed for
signs of valve deterioration (SVD) or bioprosthetic valve failure (BVF), according to the definitions of Cappodano et al. (13).

Statistical analysis was performed using IBM SPSS Version 23 (IBM, Armonk, NY, USA) and R (Version 4.2.3). Continuous variables were reported as mean ± standard deviation. 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 (Tab.) 1.

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 neo-cusps 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 non-coronary cusp. Mean CPB- time was 162.5 ± 29.9 minutes with an aortic cross-clamp 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 Tab. 2.

At discharge, peak and mean pressure gradients were 15.6 ± 7.2 and 8.4 ± 3.7 mmHg, respectively, with a mean EOA of 2.4 ± 0.8 cm², showing significant changes between preoperative and discharge values (p < 0.001 each). 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 mmHg and 10 mmHg, respectively. Statistical analysis of the annual time points showed no significant differences between peak and mean gradients and EOA (see Fig. 3 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 [Fig.] 1). 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 (Fig. 2) with a mean freedom from reoperation of 92 %. Reoperations had to be performed in 13 patients (8%), five (3.1%) for recurrent aortic valve regurgitation and eight (4.9%) for acute infective endocarditis, corresponding to a rate of 1.8% endocarditis/ patient- year. A detailed depiction of time after initial surgery, indication for reoperation and background for reoperation is presented in Tab. 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 one patient (0.6%) 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 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 3.1 ± 1.4, 7.7 ± 2.3 and 12.1 ± 4.1% (see Figure 4 A-D).
Discussion

The AVNeo- procedure, as described by Ozaki, is gaining more interest as an alternative treatment modality for diseased aortic valves. Since 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.

Hemodynamic performance

In 2018, Ozaki and colleagues published mid-term 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 mmHg, despite the small annulus size of 20.9 ± 3.3 mm (9). Similar results were presented by Iida and colleagues with peak and mean gradients of 19.2 ± 9.7 mmHg and 9.7 ± 5.5 mmHg after 20 months. The EOA was 1.8 ± 0.6 cm². Here, the mean annulus diameter was only 20.5 ± 2.5 mm (17). In both studies, leading indication for surgery was aortic stenosis. Interestingly, the same group published data of patients younger 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 mmHg for peak gradients with an EOA of 2.2 ± 0.8 cm² (18).

Koechlin and colleagues reported results from 35 AVNeo- patients 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 days follow-up, median peak and mean pressure gradients were 12 and 6 mmHg, respectively. (19).

In our cohort, the peak gradient at discharge and at 5-year follow-up were comparable with 15.6 ± 7.2 mmHg and 14.5 ± 4.6 mmHg, respectively (Fig. 3A). Correspondingly, we also report mean gradients and EOA, which were significantly lower compared to preoperative values and remained also stable over time (Fig. 3B, 3C).
In summary, the AVNeo procedure resulted in reproducible low peak and mean pressure gradients with corresponding large EOA also in small aortic valve annuli. This excellent hemodynamic performance is stable at least up to five years.

Long-term survival and freedom from reoperation

In our series, survival rate was 98.1% and freedom from reoperation at 5 years was 91.3%. Ozaki and colleagues reported a survival of 85.9% and a freedom from reoperation of 95.8% (9). The superior survival rate may be due to the younger mean age at surgery in our patient population (52.9 ± 16.1 vs. 71 years). Iida and colleagues reported a survival rate of 77.2% after 60 months and a freedom from reoperation of 95.3% after 81 months (17). In their second series, survival and freedom from reoperation after 72 months was 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 rates and freedom from reoperation are comparable, considering a one year shorter follow up time. In the study from Koechlin and colleagues, survival was 91% and freedom from reoperation 97% after a median follow-up of 645 days (19).

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 with endocarditis.

In summary, promising outcomes for survival and freedom from reoperation rates are reproducible and comparable in different institutions from different surgeons worldwide.

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 rate in a large study of patients aged between 50 – 69 years was 89% after 5 years and rate of reoperation
5.2% after 16 years of follow-up (20). Another study by Vitanova and colleagues reports an estimated survival of 97 ± 2% and 79.1 ± 5.8% after 10 years in patients below or above 60 years of age (21). Although no direct comparison of patients after AVNeo and biological valve replacement has been conducted so far, survival rates in patients after AVNeo are very promising. One may speculate that a selection bias may contribute to this finding, as 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 is available. Our group published two 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 sAVR 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 (EOAI) were analyzed and in both cases, multiple regression favored AVNeo for larger EOA and EOAI (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, who matched patients after either AVNeo or biological aortic valve replacement. Comparison of pressure gradients showed significantly lower values after AVNeo for peak and mean pressure gradients, compared to biological prosthesis (23).

SVD, BVF and Endocarditis

In a recent publication, Unai and colleagues matched 776 patients, after AVNeo with patients who received biological prosthetic valve replacement, leading to 627 1:1-matched pairs. They report only one patient after AVNeo, who had to undergo reoperation due to SVD. However,
13 out of 14 reoperations were caused by endocarditis. Notably, the AVNeo patients were derived from the cohort of Ozaki whereas the patients with surgical aortic valve replacement had been operated at Cleveland Clinic (23). Ozaki and colleagues report in their own publication from 2018 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 (9). Compared to our data, the incidence of severe AR causing reoperation and the incidence for endocarditis (1%/ patient-year) after AVNeo was higher in our study population. Iida and colleagues report in their series rates of endocarditis of 5.5% (18) and 3.5% (17), respectively.

In large studies of patients undergoing implantation of biological prostheses, the incidence of endocarditis varies between 1.3% (24), 1.6% (25) and 4.4% (26). Comparing these results to 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 two different types of bioprosthesis, Lange and colleagues report an overall rate of BVF of 6.1%. At 5 years, the cumulative incidence for BVF in patients younger 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 (27). In a study by Mayr and colleagues, 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 compared to the younger AVNeo population with a mean age of 52.9 ± 16.1 years.

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 a graphical abstract (Fig. 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 sAVR 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).

In conclusion, AVNeo has large EOAs as well as low peak and mean pressure gradients at discharge which remain stable up to five years. The survival rate after AVNeo is excellent. The main reason for reoperation is endocarditis while rates for structural valve deterioration are low.
References


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<th>Variable</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>52.9 ± 16.1</td>
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<tr>
<td>Male</td>
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<td>Coronary artery disease</td>
<td>20 (12.3%)</td>
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<tr>
<td>Arterial Hypertonus</td>
<td>79 (48.8%)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>51 (31.5%)</td>
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<tr>
<td>Diabetes mellitus</td>
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</tr>
<tr>
<td>Renal insufficiency</td>
<td>1 (0.6%)</td>
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<tr>
<td>Euroscore</td>
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<tr>
<td>Log Euroscore</td>
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<td>Euroscore II</td>
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Table 1: Baseline demographics. Continuous variables: Mean value ± standard deviation. Categorical variables: Number (%).
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<tr>
<th>Concomitant procedures</th>
<th>63 (38.9)</th>
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<tr>
<td>Supracoronary Ascending Aorta</td>
<td>39 (24.1)</td>
</tr>
<tr>
<td>CABG</td>
<td>9 (5.6)</td>
</tr>
<tr>
<td>PFO closure</td>
<td>9 (5.6)</td>
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<tr>
<td>Pulmonary vein ablation</td>
<td>5 (3.1)</td>
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<tr>
<td>Subvalvular Myectomy</td>
<td>7 (4.3)</td>
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<tr>
<td>Other</td>
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<td>30- day mortality</td>
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<td>Ventilation time [h]</td>
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<tr>
<td>Re-exploration for bleeding</td>
<td>1 (0.6)</td>
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<tr>
<td>Early postoperative stroke</td>
<td>1 (0.6)</td>
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<tr>
<td>Renal failure requiring dialysis</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>0</td>
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Table 2: Concomitant procedures and periprocedural data. CABG = coronary artery bypass grafting. PFO = persistent foramen ovale. Continuous variables: Median (Inter Quartile Range). Categorial variables: Number (%).
<table>
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<tr>
<td>1</td>
<td>9 days</td>
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<td>Leaflet tear (Technical failure)</td>
</tr>
<tr>
<td>2</td>
<td>13 days</td>
<td>Early SVD</td>
<td>Leaflet flipped (Technical failure)</td>
</tr>
<tr>
<td>3</td>
<td>43 days</td>
<td>Endocarditis</td>
<td>S.p. pericardial puncture prior surgery</td>
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<td>4</td>
<td>99 days</td>
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<td>S.p. steroid therapy (pericardial effusion)</td>
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<td>136 days</td>
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<td>6</td>
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<td>8</td>
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<td>S.p. chemotherapy for Multiple Myeloma</td>
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<tr>
<td>10</td>
<td>2.63 years</td>
<td>Late SVD</td>
<td>Tear left cusp</td>
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<td>11</td>
<td>2.82 years</td>
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<td>12</td>
<td>3 years</td>
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<td>5.1 years</td>
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<td>S.p. urosepsis after urological surgery for cancer</td>
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Table 3: Indication for reoperation. SVD = structural valve deterioration. LCC = left coronary cusp. RCC = right coronary cusp. S.p. = status post.
Figure 1: Kaplan-Meier curve: Overall survival. 95% CI.

Figure 2: Kaplan-Meier curve: Freedom from reoperation. 95% CI.

Figure 3A: Peak pressure gradients during follow-up. Gradients (mmHg)

Figure 3B: Mean pressure gradients during follow-up. Gradients (mmHg)

Figure 3C: Mean effective orifice area (cm²) during follow-up.

Figure 4A: Cumulative incidence of moderate structural valve deterioration. 95% CI.

Figure 4B: Cumulative incidence of severe structural valve deterioration. 95% CI.

Figure 4C: Cumulative incidence of endocarditis. 95% CI.

Figure 4D: Cumulative incidence of bioprosthetic valve failure. 95% CI.

Figure 5: Graphical abstract.
Moderate Structural Valve Deterioration

Probability (%)

Years after Ozaki

Number at Risk
162 155 154 147 131 112 93 72 54 37 24 1
- Survival: 97.3% at 5 years
- Freedom from Reoperation: 91.3% at 5 years
- Endocarditis: 5.1% at 5 years
- Severe Structural Valve Deterioration: 7% at 5 years
Mid-term Results after Aortic Valve Neocuspidization

Aortic Valve Neocuspidization (AVNeo) is an additional tool in the treatment of diseased aortic valves. Little is known about mid-term durability and valve-related events.

162 patients underwent AVNeo and were followed annually by echocardiography. Data were analyzed for incidence of severe structural valve degeneration (SVD), bioprosthesis valve failure, survival and freedom from reoperation after 5 years.

- Survival: 97.3%
- Reoperation: 8.7%
- SVD: 7%
- Endocarditis: 4.5%

Survival is excellent in patients after AVNeo. Incidence of structural valve degeneration is low and main indication for redo surgery is endocarditis.