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Physical and mental recovery after aortic valve surgery in non-elderly patients: Native valve preservation vs. prosthetic valve replacement

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Physical and Mental Recovery after Aortic Valve Surgery in Non-Elderly Patients: Native Valve-Preserving Surgery vs. Prosthetic Valve Replacement

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Abstract: Background: Exercise capacity and patient-reported outcomes are increasingly considered crucial following aortic valve (AV) surgery in non-elderly adults. We aimed to prospectively evaluate the effect of native valve preservation compared with prosthetic valve replacement. **Methods:** From October 2017 to August 2020, 100 consecutive non-elderly patients undergoing surgery for severe AV disease were included. Exercise capacity and patient-reported outcomes were evaluated upon admission, and 3 months and 1 year postoperatively. **Results:** In total, 72 patients underwent native valve-preserving procedures (AV repair or Ross procedure, NV group), and 28 patients, prosthetic valve replacement (PV group). Native valve preservation was associated with an increased risk of reoperation (weighted hazard ratio: 10.57 (95% CI: 1.24–90.01), $p = 0.031$). The estimated average treatment effect on six-minute walking distance in NV patients at 1 year was positive, but not significant (35.64 m; 95% CI: −17.03–88.30, adj. $p = 0.554$). The postoperative physical and mental quality of life was comparable in both groups. Peak oxygen consumption and work rate were better at all assessment time points in NV patients. Marked longitudinal improvements in walking distance (NV, +47 m (adj. $p < 0.001$); PV, +25 m (adj. $p = 0.004$)) and physical (NV, +7 points (adj. $p = 0.023$); PV, +10 points (adj. $p = 0.005$)) and mental quality of life (NV, +7 points (adj. $p < 0.001$); PV, +5 points (adj. $p = 0.058$)) from the preoperative period to the 1-year follow-up were observed. At 1 year, there was a tendency of more NV patients reaching reference values of walking distance. **Conclusions:** Despite the increased risk of reoperation, physical and mental performance markedly improved after native valve-preserving surgery and was comparable to that after prosthetic aortic valve replacement.

Keywords: aortic valve repair; Ross procedure; aortic valve replacement; quality of life; exercise capacity

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1. Introduction

Prosthetic aortic valve replacement (AVR) using mechanical or biological aortic valve (AV) substitutes is considered the standard of care in the treatment of non-elderly adults (i.e., age < 65 years) with AV disease, despite being associated with increased risk of anticoagulation-related thromboembolic/bleeding complications, infective endocarditis and structural valve deterioration impacting long-term survival and freedom from cardiovascular events [1–5].

Native valve- or living tissue-preserving procedures including AV repair and the Ross procedure are evolving alternative strategies in well-selected patients aimed at overcoming the inherent drawbacks of artificial valve substitutes and restoring survival comparable to that of the general population [6,7]. In recent decades, both procedures have become an integral part of the surgical treatment protocols in non-elderly adults presenting with severe AV disease, especially when performed at dedicated centers [8]. Both AV repair and the Ross procedure offer the potential benefit of reduced risk of valve-related complications compared with prosthetic AVR, but at the potential expense of increased risk of valve-related reoperation [6,7,9–11]. Moreover, both procedures potentially allow postoperative hemodynamics similar to those of well-functioning, native valves to be achieved due to the absence of a rigid sewing ring and the preservation of native aortic root geometry, permitting transvalvular flow characteristics and left ventricular dynamics to be preserved [12]. Yet, currently, no firm evidence confirming the believed superiority of native valve-preserving procedures over conventional prosthetic AVR exists, and the advantages of native valve preservation in terms of postoperative outcome determinants other than morbidity and mortality (e.g., postoperative recovery of exercise capacity as well as patient-reported outcomes) still have to be defined. Currently, only few retrospective, cross-sectional reports investigating differences in either exercise capacity [13] or patient-reported outcomes [14–17] among AV repair, Ross procedure and prosthetic AVR are available. Moreover, only two prospective studies evaluated longitudinal changes in exercise capacity alone [18] or combined with mental well-being [19] following AV surgery but without differentiating among surgical techniques. Prospective data on longitudinal changes with emphasis on the effect of the different surgical strategies (i.e., native valve-preserving procedures vs. conventional prosthetic AVR) are, however, still lacking.

The aim of this study, therefore, was to prospectively observe and evaluate the effects of living/native valve-preserving surgery (NV group) compared with prosthetic valve replacement (PV group) in non-elderly adults undergoing AV surgery as differences in potential indicators of superiority, namely, cardiopulmonary functional capacity and self-reported QoL 1 year postoperatively. Moreover, we aimed to assess any postoperative longitudinal change in physical performance and mental well-being in the cohorts (i.e., NV and PV groups).

2. Materials and Methods

2.1. Study Population

This prospective observational trial was approved by the ethics committee of General Medical Council, Hamburg, Germany (PV5723), and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. From October 2017 until August 2020, all patients aged 18–65 years and referred to our institution for elective AV surgery for severe isolated/predominant aortic regurgitation (AR) and non-elderly patients aged < 60 years with severe mixed congenital AV disease or severe isolated congenital aortic stenosis (AS) were considered eligible for inclusion in this study. Patients were excluded if AV dysfunction was only mild to moderate; if they suffered from isolated non-congenital aortic stenosis or syndromic congenital heart disease; if they had undergone previous cardiac surgery or intervention in childhood; or if they required concomitant mitral/tricuspid valve surgery, coronary artery bypass grafting or treatment for active endocarditis. Further exclusion criteria comprised musculoskeletal disorders or severe obesity (i.e., body weight > 150 kg) impairing mobility and thus cardiopulmonary exercise testing, or insufficient knowledge of the German language to fill out health-related questionnaires. Written informed consent was obtained from all individual subjects prior to inclusion. In total, 100 consecutive patients were prospectively included and observed during the postoperative follow-up.

2.2. Surgical Procedure

Preoperative work-up included transthoracic/transesophageal echocardiography assessing the underlying mechanism of AV pathology and pulmonary valve function. A surgical attempt to preserve the living/native valvular tissue was decided together with all patients after they had been informed in detail about all three surgical options (i.e., AV repair, Ross procedure and prosthetic AVR), and their relevant benefits and drawbacks. However, the final choice of the type of AV surgery was made intraoperatively after valve exposure and detailed assessment using a standardized protocol, including the assessment of AV (and if necessary pulmonary valve) annulus diameter; the number and localization of fenestrations; the localization of calcifications; details on number of cusps and cusp fusion (i.e., right-/left-coronary, right-/non-coronary, left-/non-coronary, right-/left-coronary + right-/non-coronary, right-/left-coronary + left-/non-coronary or right-/non-coronary + left-/non-coronary, complete or partial fusion), in case of unicuspid and bicuspid AV, and commissural orientation, in case of bicuspid AV; commissural height; geometric cusp height; and effective cusp height before AV repair, Ross procedure or AVR. AV repair was performed as planned in all the patients with isolated AR in whom the tissue quality seemed sufficient for successful repair. In patients aged < 60 years with isolated/concomitant congenital AS due to a severely restrictive raphe (i.e., exclusively patients with unicuspid/bicuspid morphology), the Ross procedure was pursued as planned. In cases in whom the aortic and pulmonary valve tissue appeared unsuspectedly deficient for successful preservation upon intraoperative inspection and in cases with moderate-to-severe residual AR after a first attempt at native valve preservation, a biological or mechanical valve prosthesis was implanted according to the patient's wish. With respect to the choice of artificial valve substitute, we deliberately advocated bioprosthetic AVR in all patients, in combination with simultaneous annulus enlargement in small aortic annuli to enable the implantation of bioprostheses with internal diameters $\geq$ 25 mm to be achieved to prevent postoperative patient–prosthesis mismatch and make future valve-in-valve procedures possible. If concomitant aortic root aneurysm was present, root replacement with valve reimplantation or remodeling (i.e., David or Yacoub procedure), or composite graft replacement of the AV and aortic root (i.e., Bentall procedure) was performed.

2.3. Study Protocol

The study protocol included the assessment of AV and left ventricular function using transthoracic echocardiography (including the quantification of AV dysfunction, and left ventricular ejection fraction and end-diastolic diameter); measures of cardiopulmonary functional capacity (including six-minute walk test (6MWT) distance [20]; cardiopulmonary exercise testing on a cycle ergometer (Vyntus CPX; Vyaire Medical, Hoechberg, Germany) using a ramp protocol and involving the estimation of peak oxygen consumption (peak VO_2) and peak work rate); and measures of patient-reported outcomes (including the well-established 12-Item Short Form Health Survey (SF-12), evaluating self-reported physical and mental QoL with 12 items on 2 subscales [21], and Hospital Anxiety and Depression Scale (HADS), evaluating anxiety and depression with 14 items on 2 subscales [22]). All patients were assessed by a single investigator upon admission (i.e., the day before surgery) and subsequently 3 months (after having completed a cardiac rehabilitation program) and 1 year postoperatively during routine postoperative follow-up assessments at our institution. Consequently, the physical and self-reported data of each individual patient were gathered at the same time. If patients missed their follow-up appointments, they were contacted via telephone and questionnaires were subsequently mailed to them. Moreover, their referral cardiologists were contacted, and all available information (i.e., echocardiographic images and results of cardiopulmonary exercise testing) from outpatient follow-up assessments was requested for further systematic analysis.

2.4. Statistical Analysis

Categorical variables are expressed as absolute and relative frequencies, and continuous variables are presented as medians (interquartile ranges) throughout the manuscript unless otherwise specified. Statistical analysis comprised three parts: (1) between-group comparison at the 1-year follow-up, and evaluation of longitudinal changes from baseline to 1-year follow-up within the (2) NV group and (3) PV group. All *p*-values were adjusted for multiple comparisons using the Bonferroni method and considered statistically significant if <0.05. In each part of the analysis, a hierarchical test procedure involving three parameters in a fixed sequence (i.e., 6MWT distance representing physical capacity → self-reported physical QoL → self-reported mental QoL) was applied. Testing was performed until the first non-rejection of the respective null hypothesis. The estimation of the average treatment effect on the treated cohort (ATT, i.e., the increase/decrease in 6MWT distance/physical QoL/mental QoL in NV patients (test group) resulting from not having required prosthetic AVR as PV patients (reference group)) at the 1-year follow-up was conducted using augmented inverse probability weighting (AIPW), a propensity score-based method involving a special form of inverse probability of treatment weighting (IPW), namely, the calculation of the so-called treated weights, with an extension to augment the estimator with a regression model for the outcome variable. This doubly robust estimator is consistent if at least one of the two models (i.e., the propensity score or the outcome model) is correctly specified. Details can be found in the published literature [23,24]. Within-group comparisons were made using the Wilcoxon sign-ranked test. Moreover, the 1-year follow-up values of patients were compared with gender- and age-specific published data on healthy individuals [21,25–27]. No imputation for missing values was performed. The characteristics of the remaining parameters (i.e., peak VO_2, work rate, anxiety and depression) were summarized descriptively. Peak VO_2 values were only included for a subset of patients (n = 65) due to a defective gas concentration sensor leading to invalid measurements until November 2018. Statistical analysis was performed until treatment failure (i.e., AV reoperation or death) as follow-up ended at that point. Time to treatment failure was analyzed using a weighted Cox regression model incorporating the ATT IPW weights. R Statistical Software (v4.0.2; R Core Team 2020), including RStudio (v1.3.1093) and the dplyr (v.1.0.7), PSW (v1.-3), survival (v3.1-12) and ggplot2 (v1.0.7) packages, was used for all statistical analyses and visualizations.

3. Results

3.1. Patient Characteristics

Baseline patient characteristics are outlined in Table 1.

The preservation of the native valve (i.e., AV repair (n = 58) or Ross procedure (n = 14)) was possible in 72 patients, while prosthetic AVR was required in 28 patients. In total, 15/72 (21%) NV patients received valve-sparing root replacement, including 13 David procedures and 2 Yacoub procedures. In total, 2/28 (7%) PV patients received composite graft replacement of the aortic valve and root (i.e., Bentall procedure). The predominant indication for surgery was isolated AR in both groups (NV, 59/72 patients (82%); PV, 21/28 patients (75%)). The remaining patients were mostly referred for isolated AS in the NV group (10/72 patients (14%)) and for mixed AV disease in the PV group (6/28 patients (21%)). Most NV patients (78%) presented with congenital AV disease (i.e., 58% bicuspid and 19% unicuspid), while the proportions of patients with congenital AV disease (50%) and tricuspid morphology (50%) were similar in PV patients. Additionally, both groups markedly differed in terms of age, sex, sum of cardiac risk factors, severity of symptoms and overall perioperative risk profile. After IPW with the ATT as the estimand to correct for baseline differences, more patient characteristics were homogeneously distributed in both groups, as indicated by standardized mean differences ≤ 0.2 (Table 1). In Supplementary Table S1, further information on perioperative patient characteristics is summarized, including cardiopulmonary bypass duration; aortic cross-clamp time; ICU stay; and the incidence of perioperative coronary artery distortion, perioperative neurological deficit, postoperative permanent pacemaker implantation, and reintervention for complication before discharge.

Table 1. Baseline patient characteristics.

	NV (n = 72)	PV before Weighting (n = 28)	PV after Weighting (Weight: 76.92)	SMD before Weighting	SMD after Weighting
Age (years) #$	41 ± 12	52 ± 12	40 ± 13	0.92	0.10
Male sex #$	62 (86%)	20 (71%)	68 (88%)	0.37	0.07
Sum of cardiac risk factors *#$					
0	9 (13%)	2 (7%)	11 (14%)	0.20	0.04
1	20 (28%)	5 (18%)	15 (20%)	0.24	0.18
2	30 (42%)	9 (32%)	16 (21%)	0.21	0.47
3	9 (13%)	8 (29%)	18 (24%)	0.40	0.29
≥4	4 (6%)	4 (14%)	17 (22%)	0.27	0.54
AV morphology #					
Unicuspid	14 (19%)	4 (14%)	15 (20%)	0.14	0.00
Bicuspid	42 (58%)	10 (36%)	49 (64%)	0.45	0.11
Tricuspid	16 (22%)	14 (50%)	13 (17%)	0.61	0.14
Reason for surgery $					
Isolated regurgitation	59 (82%)	21 (75%)	54 (70%)	0.17	0.28
Isolated stenosis	10 (14%)	1 (4%)	1 (1%)	0.35	0.50
Mixed AV disease	3 (4%)	6 (21%)	22 (29%)	0.53	0.70
NYHA class #$					
I	33 (46%)	8 (29%)	37 (48%)	0.36	0.03
II	28 (39%)	9 (32%)	34 (44%)	0.15	0.10
III	11 (15%)	11 (39%)	7 (9%)	0.56	0.21
IV	0 (0%)	0 (0%)	0 (0%)	0.00	0.00
Preoperative proBNP (ng/L) #$	332 ± 634	1102 ± 1882	372 ± 594	0.55	0.07
Preoperative LVEF (%) #$	56 ± 7	52 ± 8	55 ± 8	0.53	0.04
Preoperative $LVESD_{ind}$ (mm/m^2)	21 ± 3	24 ± 6	22 ± 2	0.63	0.10
STS-PROM (%) #$	0.75 ± 0.59	0.92 ± 0.51	0.82 ± 0.37	0.31	0.14
EuroSCORE II (%) #$	1.19 ± 0.99	1.20 ± 0.65	1.29 ± 0.54	0.11	0.12

Data presented as means ± SD or absolute and relative frequencies. * includes hypertension, hyperlipidemia, diabetes, BMI, obesity, smoking, creatinine level, coronary artery disease, extracardiac arteriopathy, previous stroke and previous cardiac surgery in adulthood. # parameters included in propensity score model. $ parameters included in outcome model. AV, aortic valve; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NV, native valve; PROM, predicted risk of mortality; PV, prosthetic valve; proBNP, brain natriuretic peptide; SMD, standardized mean difference (i.e., difference in means divided by the standard deviation).

3.2. Time to Treatment Failure

Patients were only followed up until treatment failure occurred, which was defined as either the need for AV reoperation or death. In the NV group, one patient died from small-cell lung carcinoma 8 months after surgery, and nine patients required re-do surgery for residual/recurrent severe AR during the early postoperative follow-up after initial AV repair, whereas no Ross patient required reoperation. In the PV group, one patient died from sudden cardiac death 2 months after surgery, and no patient needed re-do surgery. AV and left ventricular functional parameters in both groups determined using transthoracic echocardiography at discharge, and 3 months and 1 year postoperatively are summarized in Supplementary Table S2. Weighted Cox regression analysis incorporating the IPW-treated weights (based on parameters marked with # in Table 1) revealed increased confounder-adjusted risk of treatment failure in NV patients (weighted hazard ratio: 10.57 (95% CI: 1.24–90.01), $p = 0.031$) (Supplementary Figure S1).

3.3. Treatment Effect as Difference 1 Year Postoperatively

In terms of the 6MWT 1 year postoperatively, the ATT (i.e., increase in walking distance in NV patients (test group) resulting from not having required prosthetic AVR as PV patients (reference group)) was estimated to be 35.64 m (Figure 1).

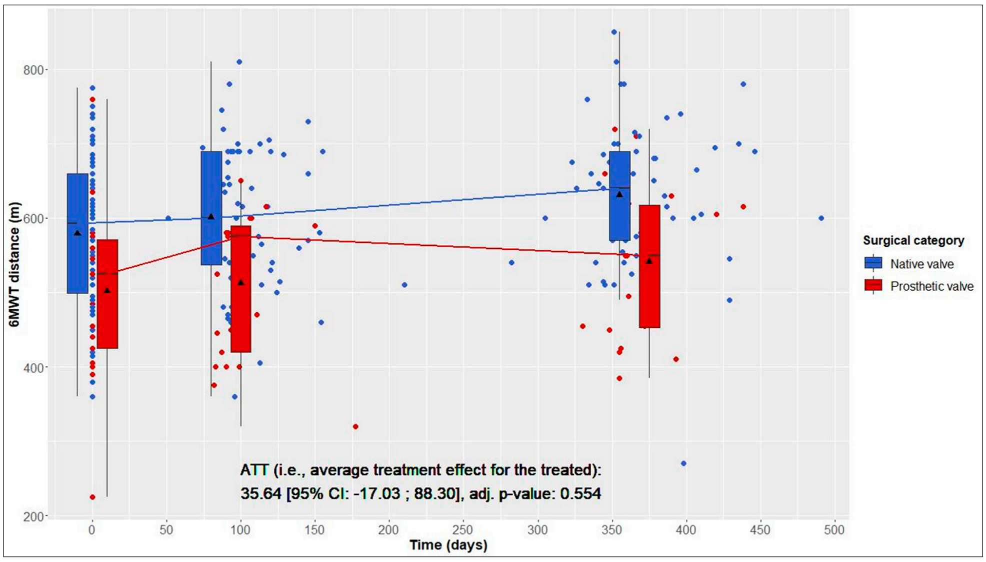

Figure 1. Six-minute walk test (6MWT) distance over time in native valve vs. prosthetic valve patients; boxes and whiskers indicate medians, IQRs, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend; displayed *p*-value corresponds to ATT testing after inverse probability of treatment weighting.

This average treatment effect on the treated group was positive, but not significant (95% CI: −17.03–88.30; adj. $p = 0.554$). According to the hierarchical test procedure, no further ATT testing was performed with respect to physical and mental QoL. According to Figures 2 and 3, it can, however, be deduced that physical and mental QoL scores were similar in both groups at the 1-year follow-up (median physical QoL score, 55 (6) in NV vs. 54 (7) in PV patients; median mental QoL score, 56 (7) in NV vs. 56 (13) in PV patients).

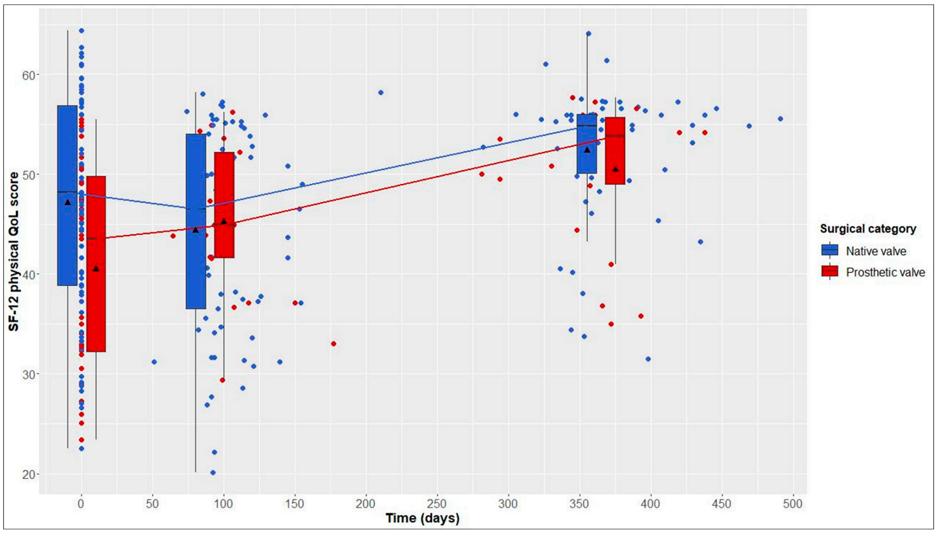

Figure 2. 12-Item Short Form Health Survey (SF-12) physical quality of life (QoL) score over time in native valve vs. prosthetic valve patients; boxes and whiskers indicate medians, IQRs, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend.

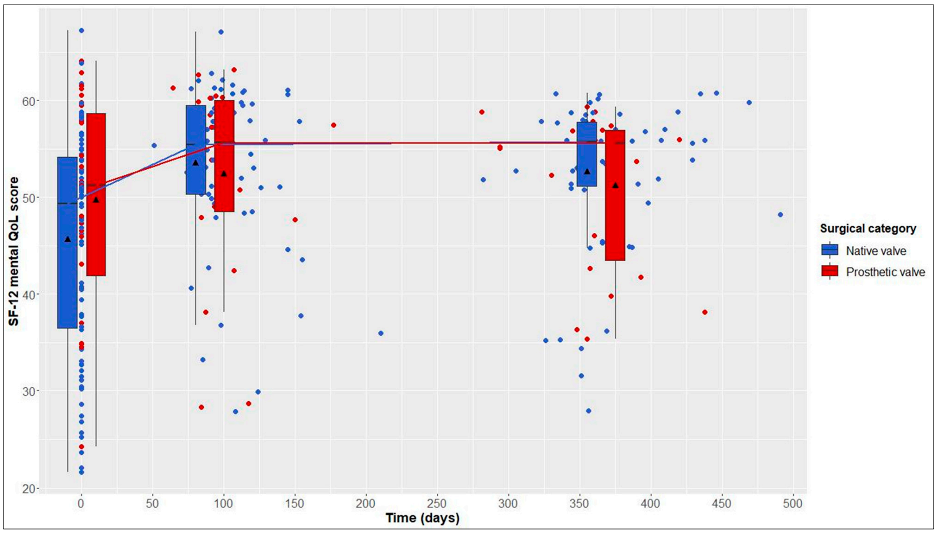

Figure 3. 12-Item Short Form Health Survey (SF-12) mental quality of life (QoL) score over time in native valve vs. prosthetic valve patients; boxes and whiskers indicate medians, IQRs, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend.

3.4. Longitudinal Changes after Native Valve-Preserving Surgery

From baseline to 1-year follow-up, NV patients showed significant improvements in 6MWT distance, from 593 (161) to 640 (120) m (+47 m, adj. $p < 0.001$); in the physical QoL score, from 48 (18) to 55 (6) (+7, adj. $p = 0.023$); and in the mental QoL score, from 49 (18) to 56 (7) (+7, adj. $p < 0.001$) (Table 2 and Figures 1–3).

Table 2. Longitudinal changes from baseline to 1-year follow-up.

		Baseline	One-Year Follow-Up	Adj. *p*-Value *
6MWT distance	Native valve	593 (161)	640 (120)	<0.001
	Prosthetic valve	525 (146)	550 (165)	0.004
SF-12 physical QoL	Native valve	48 (18)	55 (6)	0.023
	Prosthetic valve	44 (18)	54 (7)	0.005
SF-12 mental QoL	Native valve	49 (18)	56 (7)	<0.001
	Prosthetic valve	51 (17)	56 (13)	0.058

Data presented as medians (IQRs). * derived from Wilcoxon sign-ranked test. 6MWT, six-minute walk test; QoL, quality of life; SF-12, 12-Item Short Form Health Survey.

3.5. Longitudinal Changes after Prosthetic Valve Replacement

From baseline to 1-year follow-up, PV patients also showed significant improvements in 6MWT distance, from 525 (146) to 550 (165) m (+25 m, adj. $p = 0.004$), and in the physical QoL score, from 44 (18) to 54 (7) (+10, adj. $p = 0.005$). Although not statistically significant, improvements in the mental QoL score were also observed (baseline, 51 (17), vs. 1 year postoperatively, 56 (13); +5, adj. $p = 0.058$) (Table 2 and Figures 1–3).

3.6. Differences between Our Data and Gender- and Age-Specific Published Data on Healthy Individuals

One year postoperatively, the percentages of patients reaching reference values of the 6MWT derived from published data on healthy individuals were 16.9% of the NV group and only 5.3% of the PV group (Figure 4).

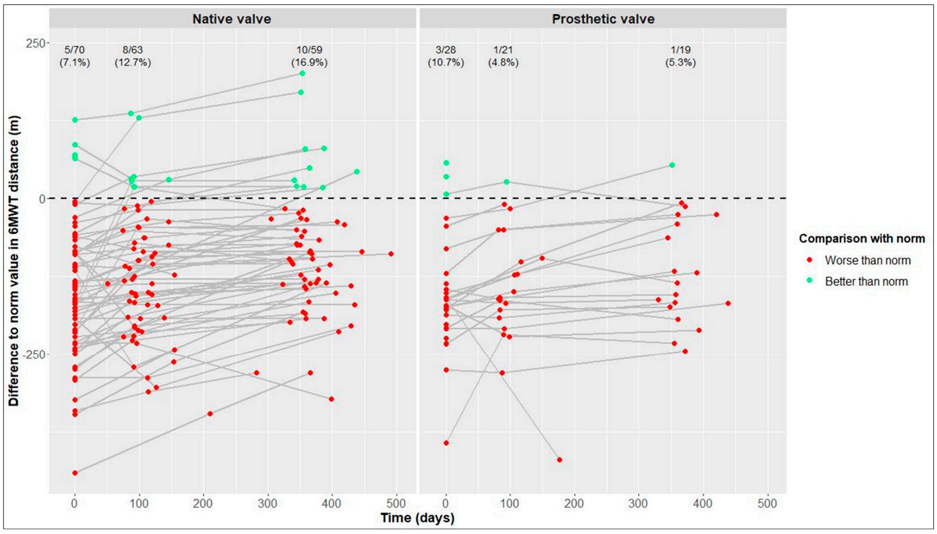

Figure 4. Differences between our values and reference values of six-minute walk test (6MWT) distance [25] in native valve vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data).

In terms of physical and mental QoL (Figures 5 and 6), the percentages of patients reaching reference values at the 1-year follow-up were similar in the NV and PV cohorts (physical QoL, 69.5% vs. 72.7%, respectively; mental QoL, 66.1% vs. 63.6%, respectively).

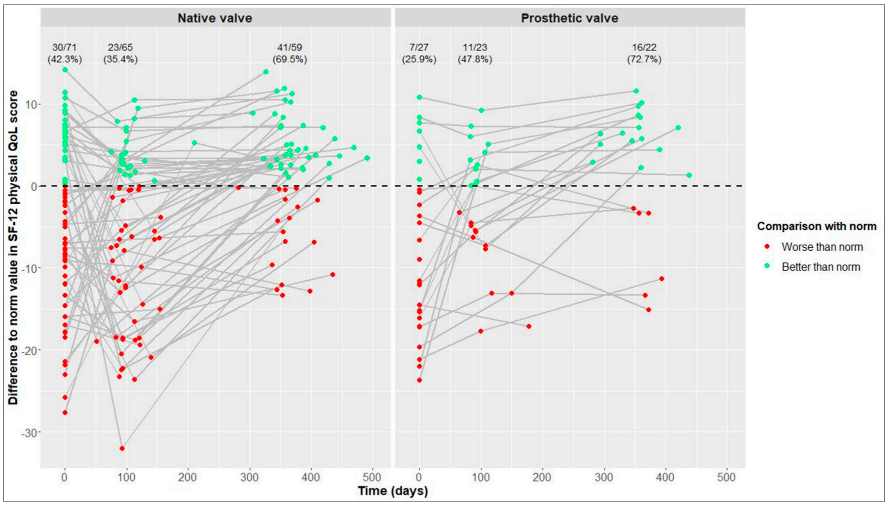

Figure 5. Differences between our values and reference values of 12-Item Short Form Health Survey (SF-12) physical quality of life (QoL) [21] in native valve vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data).

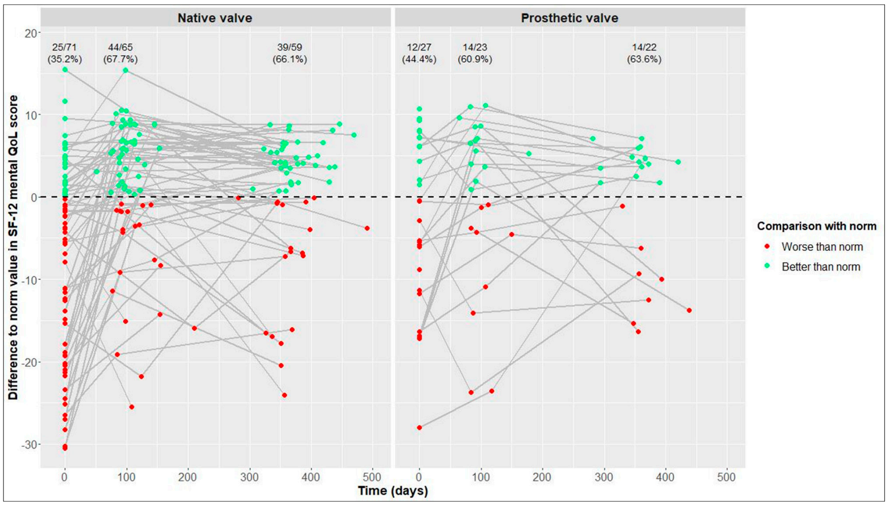

Figure 6. Differences between our values and reference values of 12-Item Short Form Health Survey (SF-12) mental quality of life (QoL) [21] in native valve vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data).

3.7. Descriptive Statistics of Peak VO_2, Work Rate, Anxiety and Depression

From baseline to 1 year postoperatively, improvements in median peak VO_2 and work rate were +3.7 mL/kg/min and +33.5 Watts in NV patients vs. +1.35 mL/kg/min and +13.5 Watts in PV patients. During the same period, median anxiety and depression scores decreased by 3 and 3 points in NV patients vs. 2 and 2.5 points in PV patients, respectively. At all times, including baseline assessment, median peak VO_2 and peak work rate were better in NV patients than in PV patients, while median anxiety and depression scores were similar in both groups (Supplementary Figures S2–S9).

4. Discussion

Despite progress in artificial AV substitutes in terms of design and function over time and the evolution of new therapeutic strategies attempting native valve preservation, the treatment of non-elderly adults with AV disease remains a challenge due to the unique characteristics of this otherwise relatively healthy patient cohort: (1) longer anticipated life expectancy imposing higher cumulative risk of valve-related complications; (2) higher levels of physical and metabolic activity; and (3) a major focus on patient-reported outcomes with greater importance of preserved or restored physical, mental and social functioning [28]. When evaluating different treatment strategies in these patients, it is thus crucial to also focus on physical capacity and patient-reported outcomes besides morbidity and mortality.

In our patients, native valve preservation was associated with increased risk of treatment failure, more specifically, AV reoperation for failed AV repair, in NV patients, which is in line with previous findings [11,29,30]. A learning curve with a more liberal/aggressive approach to AV repair at the beginning of the study (i.e., performing AV repair in unicuspid morphology using the bicuspidization procedure [31], in bicuspid morphology with large calcifications and a severely restrictive raphe, and in bicuspid/tricuspid morphology with large fenestrations necessitating patch augmentation) might have contributed to this. Patients were only followed up until treatment failure, and the statistical analysis needs to be interpreted accordingly.

The benefit of the preservation of native valve tissue, avoiding prosthetic AVR and its inherent drawbacks, including the concurring lifetime risk of either anticoagulation-related complications or structural valve deterioration [1–4], translated into a positive estimated average treatment effect of 35.64 m with respect to 6MWT distance in NV patients compared with PV patients. This positive average treatment effect in NV patients was, however, not significant. The subsequent descriptive statistical analysis of physical and mental QoL showed similar scores at the 1-year follow-up in both groups. This is in agreement with a recent study that reported no significant differences in physical and mental QoL in children and young adults following the Ross procedure vs. mechanical AVR [16], but contrary to most previous reports evaluating and comparing QoL in adult patients undergoing AV repair, the Ross procedure and mechanical AVR, Nötzold and colleagues observed that postoperative physical and mental QoL is quite influenced by the type of AV procedure and negatively linked with mechanical AVR compared with the Ross procedure [17]. These findings were later confirmed by two other groups and extended from Ross to AV repair patients [14,15]. The fact that 86% of our AVR patients had received a biological instead of mechanical valve substitute might have accounted for our results being inconsistent with those previous investigations.

Yet, we still confirmed the previous findings obtained by Aicher and colleagues with respect to HADS subscales by also observing similar anxiety and depression levels 1 year after native valve-preserving surgery and prosthetic AVR [14].

Only peak VO_2 and work rate were considerably better in NV patients than in PV patients 1 year postoperatively, which is in agreement with a recently published study that reported better initial postoperative exercise capacity assessed with cardiopulmonary exercise testing in children and young adults after the Ross procedure than after mechanical AVR at the mid-term follow-up [13]. However, it must be pointed out that the observed between-group differences in our patients were already present at baseline and were potentially linked to differences in age and sex distribution in both groups.

Physical and mental recovery in terms of notable longitudinal improvements in 6MWT distance and self-reported physical and mental QoL during the first postoperative year was observed following both native valve preservation and prosthetic AVR. Considerable decreases in self-reported anxiety and depression from baseline to 1-year follow-up were also seen in both cohorts. Our findings are in line with previous work by Petersen and colleagues [19], who assessed the course of physical and mental recovery after AV surgery during the first 6 months postoperatively using the same instruments, but without differentiating among different surgical techniques. The observed improvements in physical and mental QoL, as well as in anxiety and depression, in their patients were similar to ours, while the improvement in 6MWT distance in their patients was markedly greater. This is likely the result of both our patient cohorts already performing better in the 6MWT (i.e., walking faster and consequently further) at baseline, thus leaving less room for improvement during follow-up, as subjects are only allowed to walk and are not allowed to run, even if possible [20]. Additionally, the better baseline performance might reflect the impact of earlier indication for AV surgery in asymptomatic patients as recommended by the recent ESC/EACTS guidelines for the management of valvular heart disease [32].

To our knowledge, cardiopulmonary exercise testing has not yet been investigated in great detail following AV repair or the Ross procedure specifically. We found small improvements in median peak VO_2 and work rate at 1-year follow-up in NV and PV patients. The improvements were, however, slightly more pronounced following native valve preservation than after prosthetic AVR and were also more pronounced compared with previous findings by Tamás and colleagues, who performed cardiopulmonary exercise testing before AV surgery and 6 months after AV surgery and observed steady peak VO_2 and an increase of only 12 Watts in peak work rate postoperatively. Their study cohort included mostly prosthetic AVR patients and only three patients with reconstructive surgery [18].

In previous works, average values of study cohorts were compared with reference values derived from published data on healthy individuals [14,19]. In contrast, we calculated, for each patient, the difference between his/her value and his/her gender- and age-specific reference values at baseline and follow-up and then determined the absolute/relative frequency of patients reaching reference values for each visit. One year postoperatively, there was a tendency of more NV patients than PV patients reaching the reference values of the 6MWT, while the percentages of patients reaching the reference values of physical and mental QoL were similar in both cohorts.

Limitations

As we report a single-center experience, the generalization of our findings is limited. Patients were not actively assigned to a group, and sample sizes were not determined in advance but rather resulted from the impossibility to preserve the living/native valvular tissue in some patients as established intraoperatively, which led to uneven sample sizes. Moreover, we only present short-term effects due to the limited follow-up period of 1 year. To derive conclusions on mid- and long-term benefits and risks of native valve preservation compared with prosthetic AVR, a longer follow-up is required. Furthermore, follow-up ended at the time of treatment failure, so the impact of AV reoperation on physical capacity and mental well-being could not be determined. Hence, the conclusions drawn are technically only valid until a patient requires reoperation, which might introduce a slightly biased, positive view for the NV group. The ATT estimated using AIPW should also be interpreted with caution, as the unmeasured confounders, heterogenous treatment groups and poor small sample size properties of causal inference methods might have hindered the correct specification of either the propensity score or the outcome model; therefore, results might again be slightly biased. In fact, even after IPW with the calculation of the treated weights, some patient characteristics, including the presence of two or more cardiac risk factors and the underlying AV pathology, remained heterogeneously distributed in both groups, as indicated by standardized mean differences > 0.2. In addition, the cardiopulmonary exercise testing parameters were only summarized descriptively, as peak VO_2 values were solely available for a subset of patients due to invalid measurements until November 2018. In summary, our findings should be confirmed in further prospective, ideally multicentric studies with larger sample sizes and more homogenous patient cohorts. A valve-specific questionnaire should be added to obtain more specific insights into QoL after valve surgery. Furthermore, follow-up should be continued after AV reoperation to enable results to be interpretated independently of the risk of treatment failure.

5. Conclusions

- Physical and mental performance improved during the first year after native valve preservation and prosthetic AVR.
- One year postoperatively, the reported physical and mental QoL was similar in both cohorts, while native valve preservation was associated with a positive, although not significant, treatment effect on 6MWT distance.
- A tendency of more patients reaching the 6MWT distance of healthy individuals and a trend of better peak oxygen consumption and work rate at the 1-year follow-up following native valve-preserving surgery than following prosthetic AVR were observed.
- Despite an increased risk of treatment failure, physical and mental performance after native valve-preserving surgery was comparable to that after conventional prosthetic AVR.
- Hence, shared decision making with patients to choose the appropriate treatment option adapted to their own specific needs is necessary.

Contributions to the Field

Despite its limitations, our study is the first study to provide prospective data on early longitudinal postoperative changes in both physical and mental capacity after AV surgery in non-elderly patients with an emphasis on the effect of modern living/native valve-preserving procedures compared with conventional prosthetic AVR. It underlines the value of AV repair and the Ross procedure in today's surgical armamentarium for treating AV disease in non-elderly patients by recognizing it as a reasonable alternative to prosthetic AVR, which is still considered the standard of care in most centers in spite of its inherent long-term risks and drawbacks. Patients should, therefore, have sufficient information and a sufficient understanding of the existence, as well as associated risks and benefits, of native valve-preserving procedures before making a decision about the treatment of their AV disease.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcdd10040138/s1, Figure S1: Plot of confounder-adjusted time to treatment failure (i.e., aortic valve reoperation or death) in native valve patients vs. prosthetic valve patients based on Cox regression analysis incorporating the inverse probability of treatment weights. Confounders: parameters included in the propensity score model marked with # in Table 1 of the main text, Figure S2: Peak oxygen consumption (peak VO_2) assessed with cardiopulmonary exercise testing over time in native valve patients vs. prosthetic valve patients; boxes and whiskers indicate medians, IQRs, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend, Figure S3: Work rate at peak oxygen consumption assessed with cardiopulmonary exercise testing over time in native valve patients vs. prosthetic valve patients; boxes and whiskers indicate medians, IQRs, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend, Figure S4: Self-reported anxiety on Hospital Anxiety and Depression Scale (HADS) over time in native valve patients vs. prosthetic valve patients; boxes and whiskers indicate medians, IQRs, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend, Figure S5: Self-reported depression on Hospital Anxiety and Depression Scale (HADS) over time in native valve patients vs.

prosthetic valve patients; boxes and whiskers indicate medians, IQRs, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend, Figure S6: Differences between our values and reference values of peak oxygen consumption (peak VO_2) assessed with cardiopulmonary exercise testing [26] in native valve patients vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data), Figure S7: Differences between our values and reference values of work rate at peak oxygen consumption assessed with cardiopulmonary exercise testing [26] in native valve patients vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data), Figure S8: Differences between our values and reference values of self-reported anxiety on Hospital Anxiety and Depression Scale (HADS) [27] in native valve patients vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data), Figure S9: Differences between our values and reference values of self-reported depression on Hospital Anxiety and Depression Scale (HADS) [27] in native valve patients vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data), Table S1: Perioperative patient characteristics, Table S2: Echocardiographic parameters at discharge, and 3 months and 1 year postoperatively.

Author Contributions: Conceptualization, J.P. and E.G.; methodology, J.P., B.W. and C.S.; software, S.F.; formal analysis, T.H. and S.F; investigation, T.H. and J.P.; resources, B.W., C.S., M.R. and H.R.; data curation, T.H.; writing—original draft preparation, T.H. and J.P.; writing—review and editing, S.F., B.W., C.S., M.R., H.R. and E.G.; visualization, T.H. and S.F.; supervision, H.R. and E.G.; project administration, E.G. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Hamburg Medical Association, Germany (PV5723).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data underlying this article will be shared upon reasonable request to the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

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Supplementary Materials

Physical and Mental Recovery after Aortic Valve Surgery in Non-Elderly Patients: Native Valve-Preserving Surgery vs. Prosthetic Valve Replacement

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1 Supplementary Tables

Table S1. Perioperative patient characteristics.

	NV (n=72)	**PV (n=28)**
Cardiopulmonary bypass duration (min)	139±54	123±45
Aortic cross-clamp time (min)	90±43	82±29
Intensive care unit stay (days)	1.6±1.2	2.2±1.6
Perioperative coronary artery distortion	2 (3%)	0 (0%)
Perioperative neurological deficit	0 (0%)	1 (4%)
Postoperative pacemaker implantation	4 (6%)	4 (14%)
Reintervention for complication before discharge	6 (8%)	3 (11%)

Data presented as means ± SD or absolute and relative frequencies. Raw data presented.

NV: native valve; PV: prosthetic valve

Table S2. Echocardiographic parameters at discharge and 3 months and 1 year postoperatively.

	NV (n=72)	**PV (n=28)**
Residual AR at discharge		
- *no/trace*	44 (61%)	26 (93%)
- *mild*	23 (34%)	2 (7%)
- *moderate*	1 (2%)	0 (0%)
- *severe*	0 (0%)	0 (0%)
Max. AV gradient at discharge (mmHg)	17±10	18±8
Mean AV gradient at discharge (mmHg)	9±6	10±4
LVEF at discharge (%)	49±7	46±11
$LVESD_{ind}$ at discharge (mm/m^2)	21±3	23±5
Residual AR at 3 months		
- *no/trace*	25 (37%)	22 (88%)
- *mild*	32 (48%)	3 (12%)
- *moderate*	7 (10%)	0 (0%)
- *severe*	3 (4%)	0 (0%)
Max. AV gradient at 3 months (mmHg)	15±7	16±5
Mean AV gradient at 3 months (mmHg)	8±4	9±2
LVEF at 3 months (%)	54±7	56±10
$LVESD_{ind}$ at 3 months (mm/m^2)	19±3	20±4
Residual AR at 1 year		
- *no/trace*	20 (33%)	22 (92%)

- *mild* - *moderate* - *severe*	34 (56%) 7 (12%) 0 (0%)	2 (8%) 0 (0%) 0 (0%)
Max. AV gradient at 1 year (mmHg)	13±8	17±7
Mean AV gradient at 1 year (mmHg)	7±5	9±3
LVEF at 1 year (%)	54±7	55±5
$LVESD_{ind}$ at 1 year (mm/m^2)	19±3	19±3
Data presented as means ± SD or absolute and relative frequencies. Raw data presented. AV: aortic valve; AR: aortic regurgitation; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; NV: native valve; PV: prosthetic valve		

3

2 Supplementary Figures

Figure S1. Plot of confounder-adjusted time to treatment failure (i.e., aortic valve reoperation or death) in native valve patients vs. prosthetic valve patients based on Cox regression analysis incorporating the inverse probability of treatment weights (treated weights); Confounders: parameters included in the propensity score model marked with # in **Table 1** of the main text.

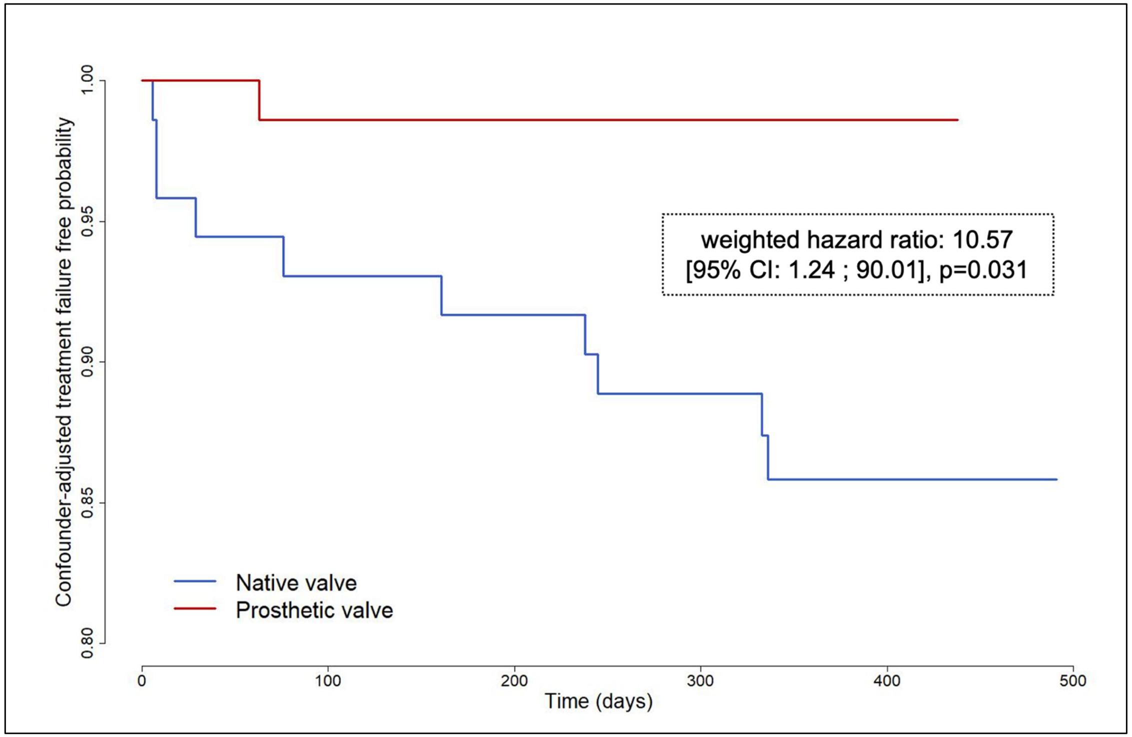


Figure S2. Peak oxygen consumption (peak VO_2) assessed with cardiopulmonary exercise testing over time in native valve patients vs. prosthetic valve patients; boxes and whiskers indicate median, IQR, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend.

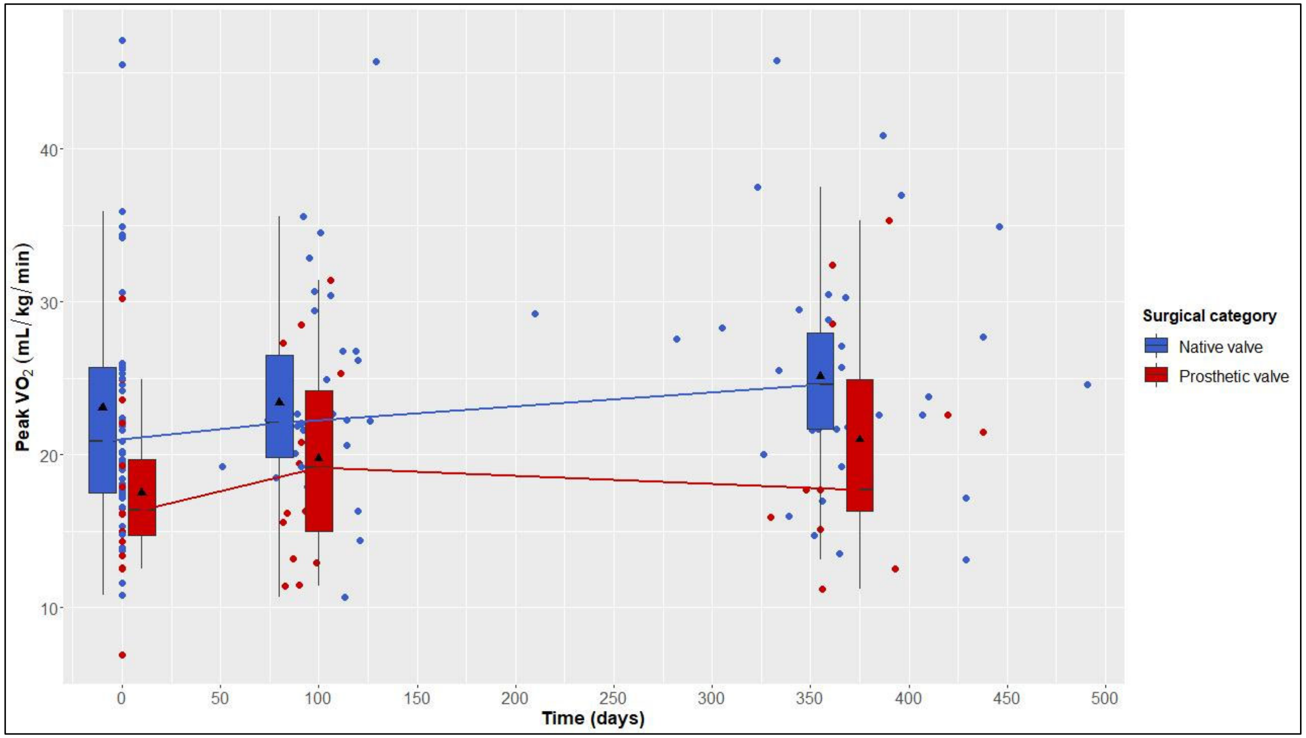


Figure S3. Work rate at peak oxygen consumption assessed with cardiopulmonary exercise testing over time in native valve patients vs. prosthetic valve patients; boxes and whiskers indicate median, IQR, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend.

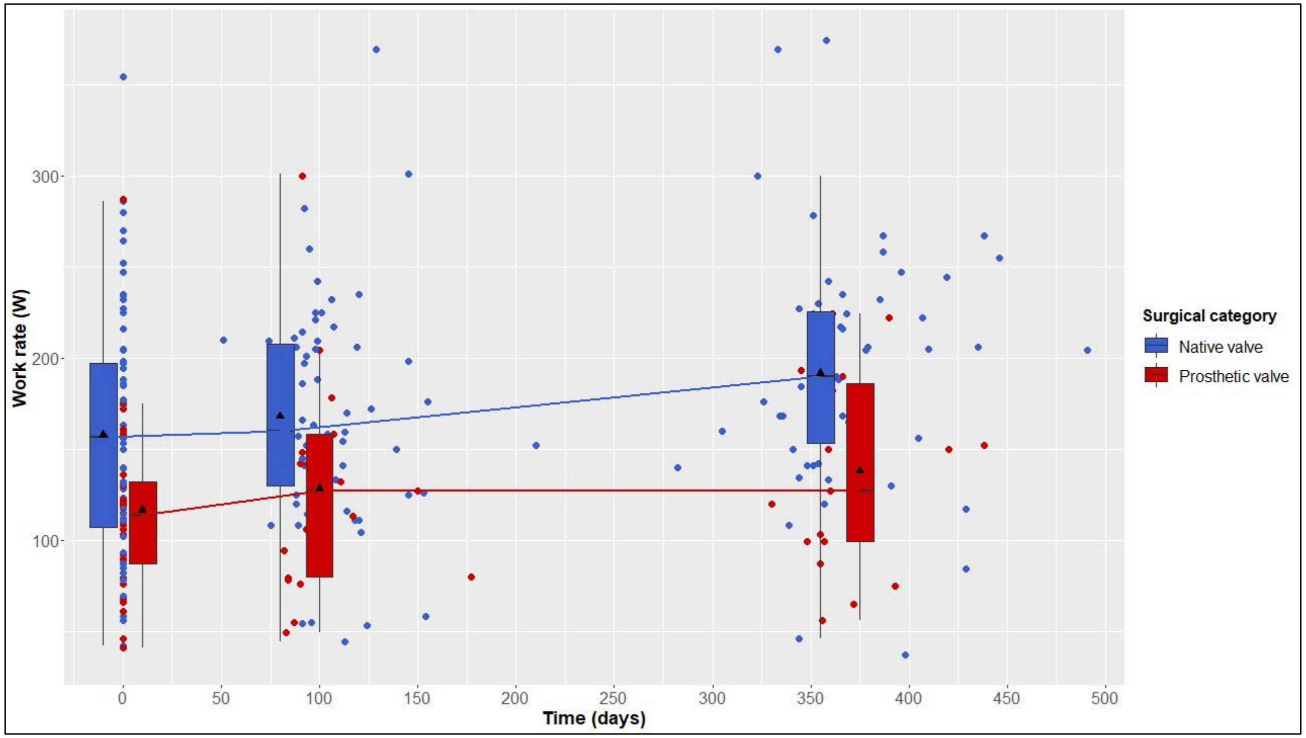


Figure S4. Self-reported anxiety on Hospital Anxiety and Depression Scale (HADS) over time in native valve patients vs. prosthetic valve patients; boxes and whiskers indicate median, IQR, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend.

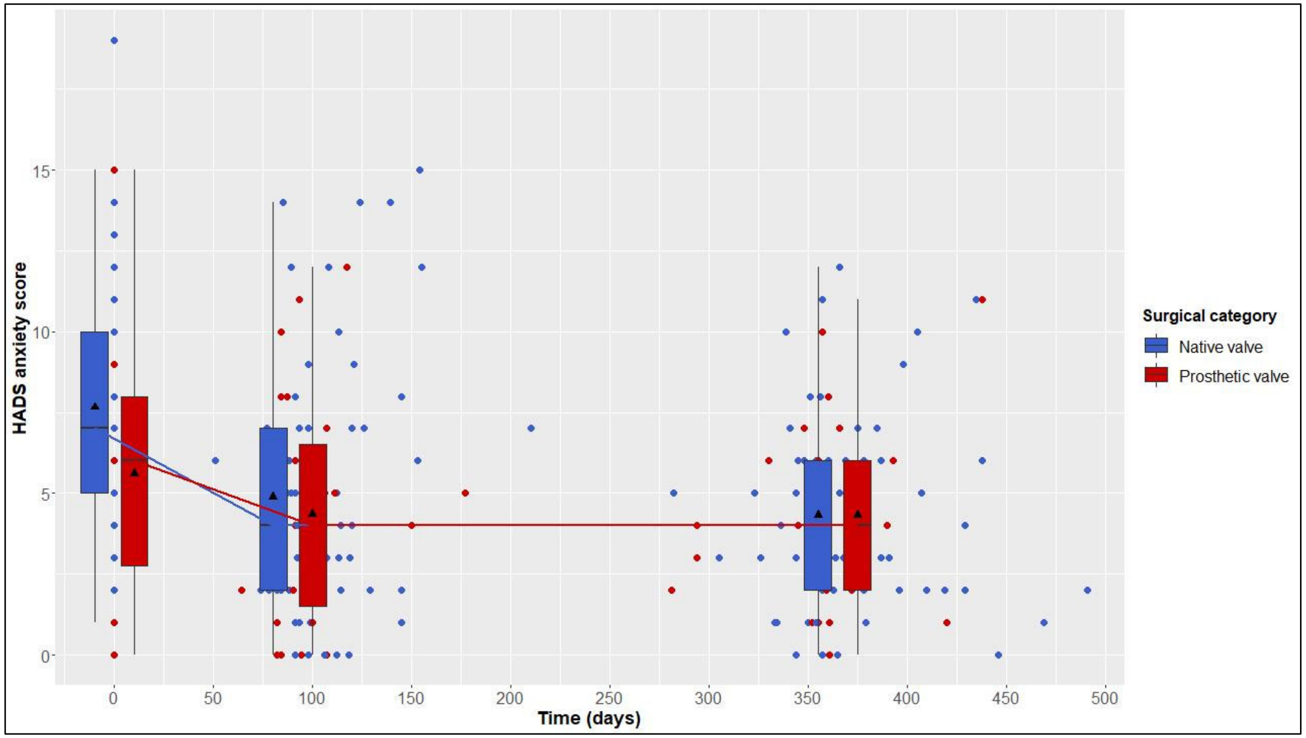


Figure S5. Self-reported depression on Hospital Anxiety and Depression Scale (HADS) over time in native valve patients vs. prosthetic valve patients; boxes and whiskers indicate median, IQR, minima and maxima (raw data); triangles indicate means (raw data); medians are connected to show time trend.

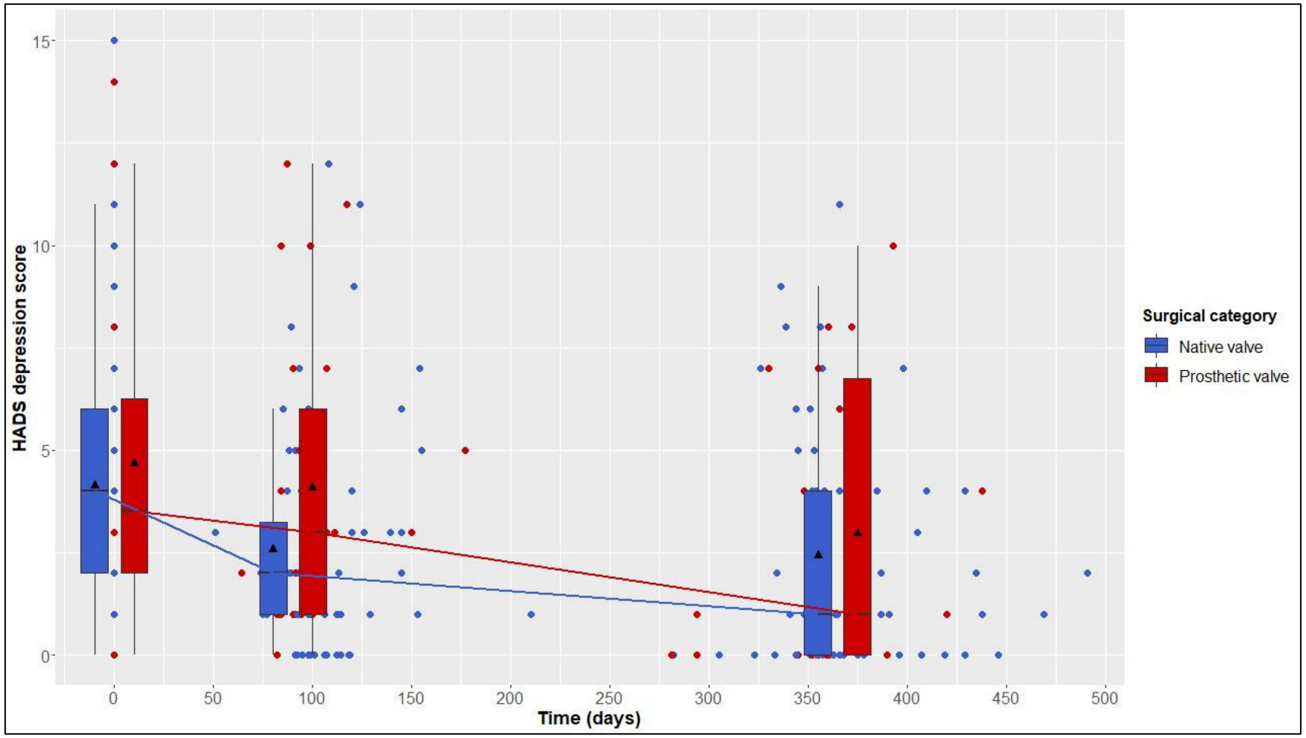


Figure S6. Difference between our values and reference values of peak oxygen consumption (peak VO_2) assessed with cardiopulmonary exercise testing (1) in native valve patients vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data).

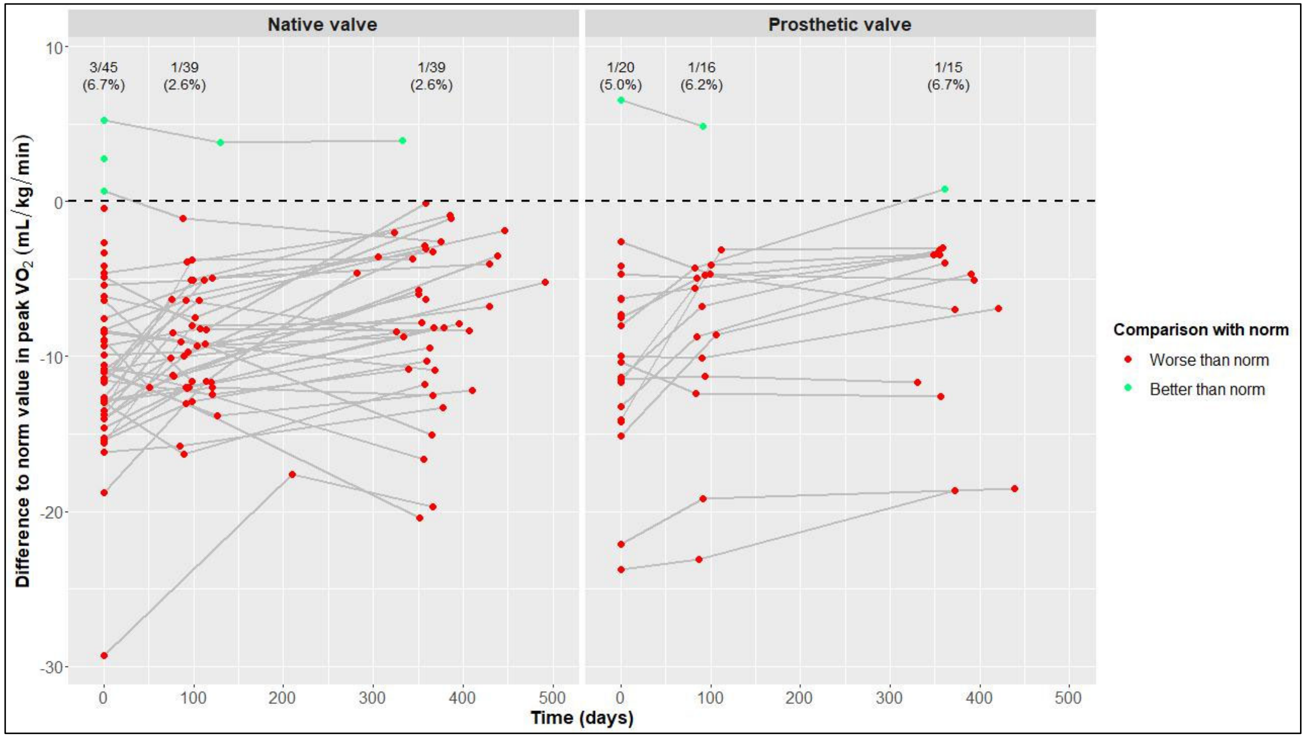


Figure S7. Difference between our values and reference values of work rate at peak oxygen consumption assessed with cardiopulmonary exercise testing (1) in native valve patients vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data).

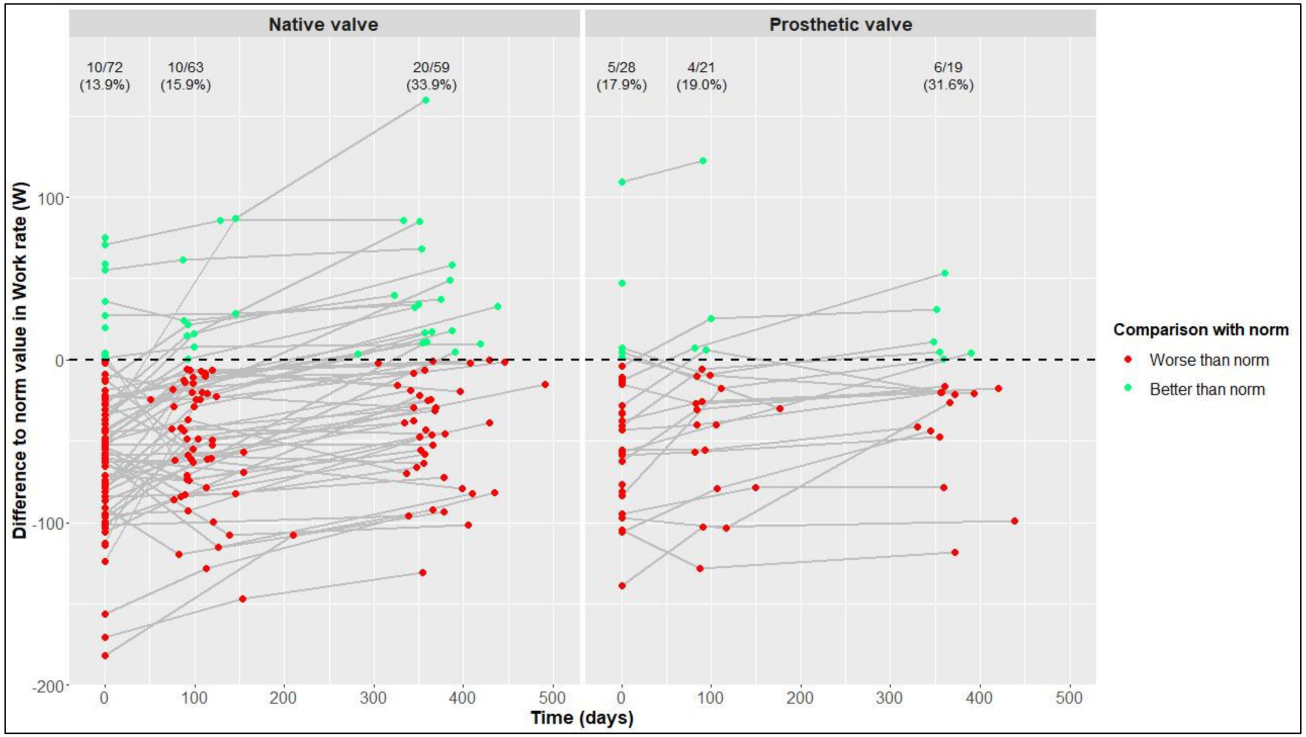


Figure S8. Difference between our values and reference values of self-reported anxiety on Hospital Anxiety and Depression Scale (HADS) (2) in native valve patients vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data).

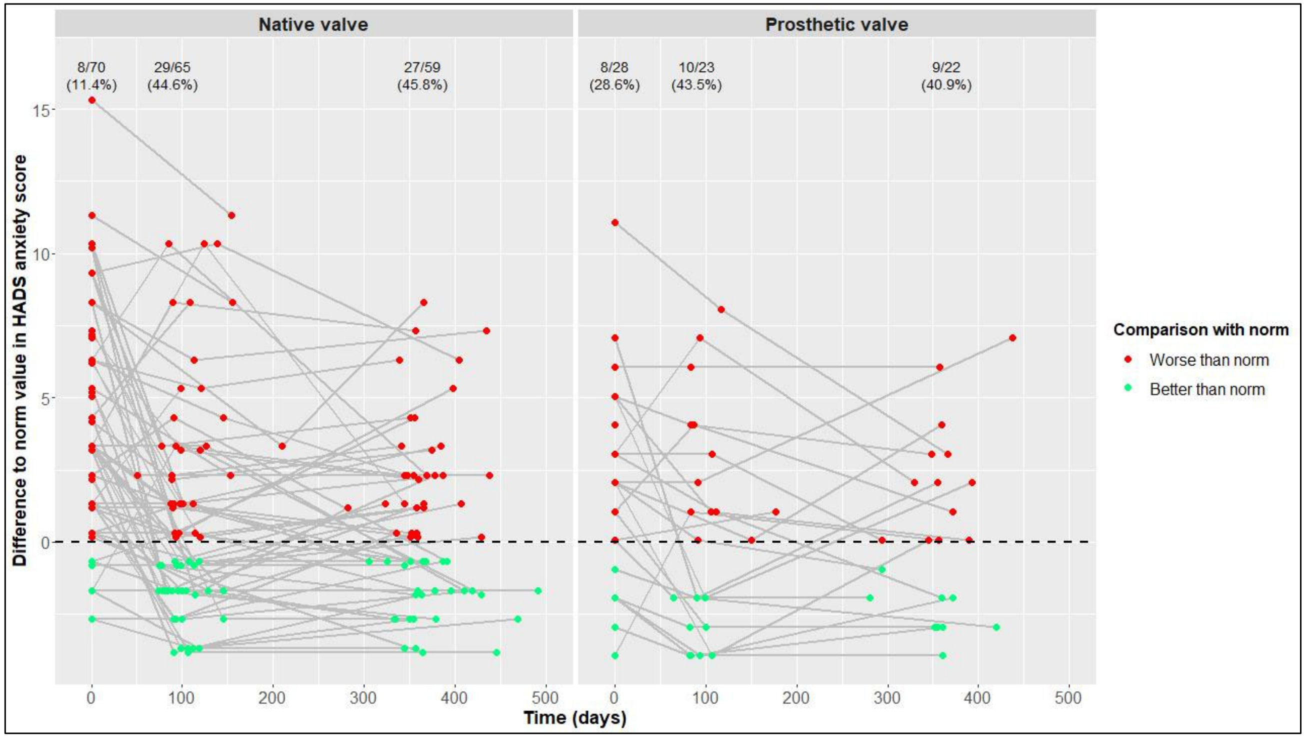
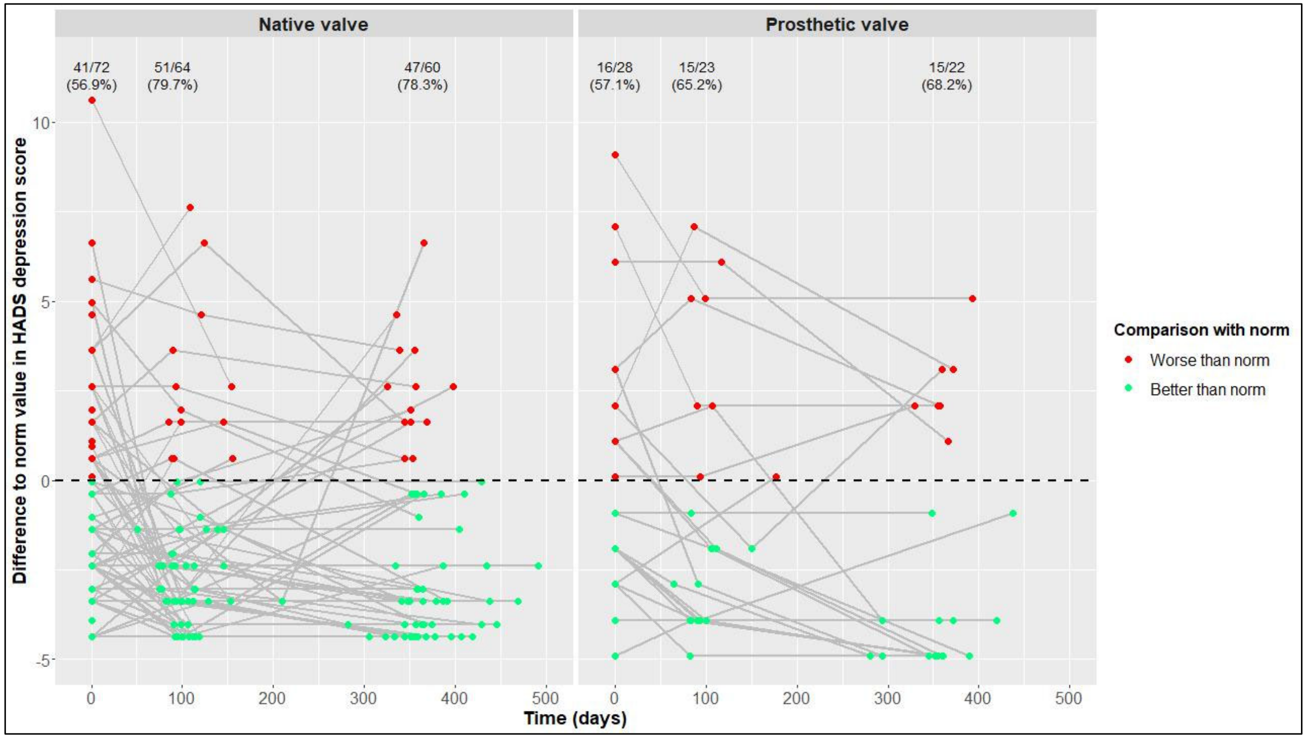


Figure S9. Difference between our values and reference values of self-reported depression on Hospital Anxiety and Depression Scale (HADS) (2) in native valve patients vs. prosthetic valve patients; measurements of individual patients are represented by separate dots and connected to show time trend; absolute and relative frequencies of patients reaching reference values are displayed (raw data).



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2. Summary and Description of the Study

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AIPW	augmented inverse probability weighting
ATT	average treatment effect for the treated
AR	aortic regurgitation
AS	aortic stenosis
AV	aortic valve
AVR	aortic valve replacement
CPET	cardiopulmonary exercise testing
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Association of Cardiology
HADS	Hospital Anxiety and Depression Scale
IPW	inverse probability of treatment weighting
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
NV	native valve
PV	prosthetic valve
peak VO_2	peak oxygen consumption
QoL	quality of life
SF-12	12-Item Short Form Health Survey
6MWT	six-minute walk test

Introduction

Isolated aortic valve (AV) disease is the most prevalent form of native valvular heart disease in Europe as reported by the recently conducted EURObservational Research Programme Valvular Heart Disease II Survey (Iung et al., 2019).

Among patients requiring valvular intervention for severe aortic stenosis (AS) or regurgitation (AR), conventional biological or mechanical prosthetic AV replacement (AVR) is the most frequently performed treatment, making it the standard of care even in younger patients requiring AV surgery (Iung et al., 2019). However, various investigations have established that long-term survival and freedom from cardiovascular events following prosthetic AVR are heavily impacted by an increased risk of anticoagulation-related thromboembolic or bleeding complications, infective endocarditis and structural valve deterioration (Vahanian et al., 2022, Bouhout et al., 2014, Puskas et al., 2014, Rahimtoola, 2010, Etnel et al., 2019).

In an effort to mitigate these disadvantages, alternative treatment strategies for the management of AV disease in non-elderly patients (i.e., age < 65 years) have evolved in recent decades at dedicated centers, including AV repair and the Ross procedure. Similar to mitral valve repair, AV repair includes aortic annuloplasty and repair of cusp pathology (Vojacek et al., 2018). The Ross procedure is a more complex operation that involves the replacement of the diseased AV with the patient's own pulmonary valve along with coronary reimplantation and combined with a simultaneous homograft replacement of the pulmonary outflow tract and root (El-Hamamsy, 2018). Both procedures are aimed at overcoming the inherent drawbacks of artificial valve substitutes by preserving as much native valvular/living tissue in aortic position as possible and hence consequently by preserving native aortic valve and root geometry. Currently, the Ross procedure is considered the only AV intervention that allows for restoration of survival comparable to that of the general population (El-Hamamsy et al., 2022). Moreover, due to the absence of a rigid sewing ring, native valve-preserving procedures offer the potential benefit of preserved transvalvular flow characteristics and postoperative hemodynamics similar to those of well-functioning AVs in healthy subjects (El-Hamamsy et al., 2021, Romeo et al., 2021, Unai et al., 2023). Additionally, when performed at experienced centers, AV repair and the Ross procedure are both associated with a reduced risk of valve-related complications compared to prosthetic

AVR, however at the expense of an increased risk of valve-related reoperation (El-Hamamsy et al., 2022, Vahanian et al., 2022, Buratto et al., 2018, Mazine et al., 2017, Aicher et al., 2010, Gökalp et al., 2019).

Nevertheless, even in the most recent joint guidelines for the management of valvular heart disease of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (ESC/EACTS), AV repair is only afforded a IIb indication as an intervention for AR (i.e., "aortic valve repair may be considered in selected patients at experienced centers when durable results are expected"). In the same guidelines, the Ross procedure is not mentioned at all as a treatment option for AR or for AS (Vahanian et al., 2022). This is in contrast to the most recent clinical practice guidelines by the American College of Cardiology and the American Heart Association (ACC/AHA) that attribute a IIb indication to the Ross procedure for the management of non-elderly patients with severe AS (i.e., "in patients <50 years of age who prefer a bioprosthetic AVR and have appropriate anatomy, replacement of the aortic valve by a pulmonic autograft (the Ross procedure) may be considered at a Comprehensive Valve Center") (Otto et al., 2021, Lee et al., 2023).

Postoperative recovery of exercise capacity as well as quality of life (QoL), anxiety and depression obtained by patient self-report (i.e., patient-reported outcomes) have so far not been well investigated in young patients undergoing AV surgery, despite being increasingly considered crucial outcome determinants besides morbidity and mortality which could aid in confirming the believed superiority of native valve-preserving procedures. To date, a few retrospective cross-sectional studies addressing differences between surgical strategies as well as a few prospective reports evaluating postoperative longitudinal changes irrespective of surgical technique have been published (Takajo et al., 2021, Aicher et al., 2011, Zacek et al., 2016, Beacher et al., 2021, Nötzold et al., 2001, Tamás et al., 2009, Petersen et al., 2016). Prospective data on postoperative longitudinal changes with regards to the effect of native valve-preserving procedures vs. conventional prosthetic AVR are currently insufficiently available.

Thus, the primary aim of this study was to prospectively observe and evaluate the effects of living or native valve-preserving surgery (NV group) vs. conventional prosthetic valve replacement (PV group) in non-elderly patients undergoing AV surgery on exercise capacity and patient-reported outcomes at 1 year postoperatively. Secondly, the study aimed to assess postoperative longitudinal changes in physical performance and mental well-being within both groups (i.e., NV or PV group).

Patients and Methods

Study population

This prospective observational study was approved by the ethics committee of the General Medical Council for Hamburg, Germany (PV5723). Written informed consent was obtained from all individual subjects prior to inclusion. Patient enrollment started in October 2017 and ended in August 2020. During that period, all patients referred to the University Heart and Vascular Center Hamburg for elective AV surgery were considered eligible for participation if one of the inclusion criteria was met and none of the exclusion criteria was applicable (see **Table P1** for further details).

Inclusion criteria	**Exclusion criteria**
Aged 18 - 65 years with severe isolated or predominant AR	Only mild to moderate AV dysfunction
Or: Aged < 60 years with severe mixed unicuspid or bicuspid AV disease or severe isolated unicuspid or bicuspid AS	Severe isolated tricuspid AS
	Syndromic congenital heart disease or previous cardiac surgery or intervention in childhood
	Concomitant mitral or tricuspid valve surgery, coronary artery bypass grafting, treatment for active endocarditis
	Impaired mobility due to musculoskeletal disorders or severe obesity (i.e., body weight >150 kg)

	Insufficient knowledge of the German language to participate in self-reporting

Table P1: Inclusion and exclusion criteria for enrollment in study

In total, 100 consecutive patients were prospectively included and observed during postoperative follow-up.

Surgical procedure

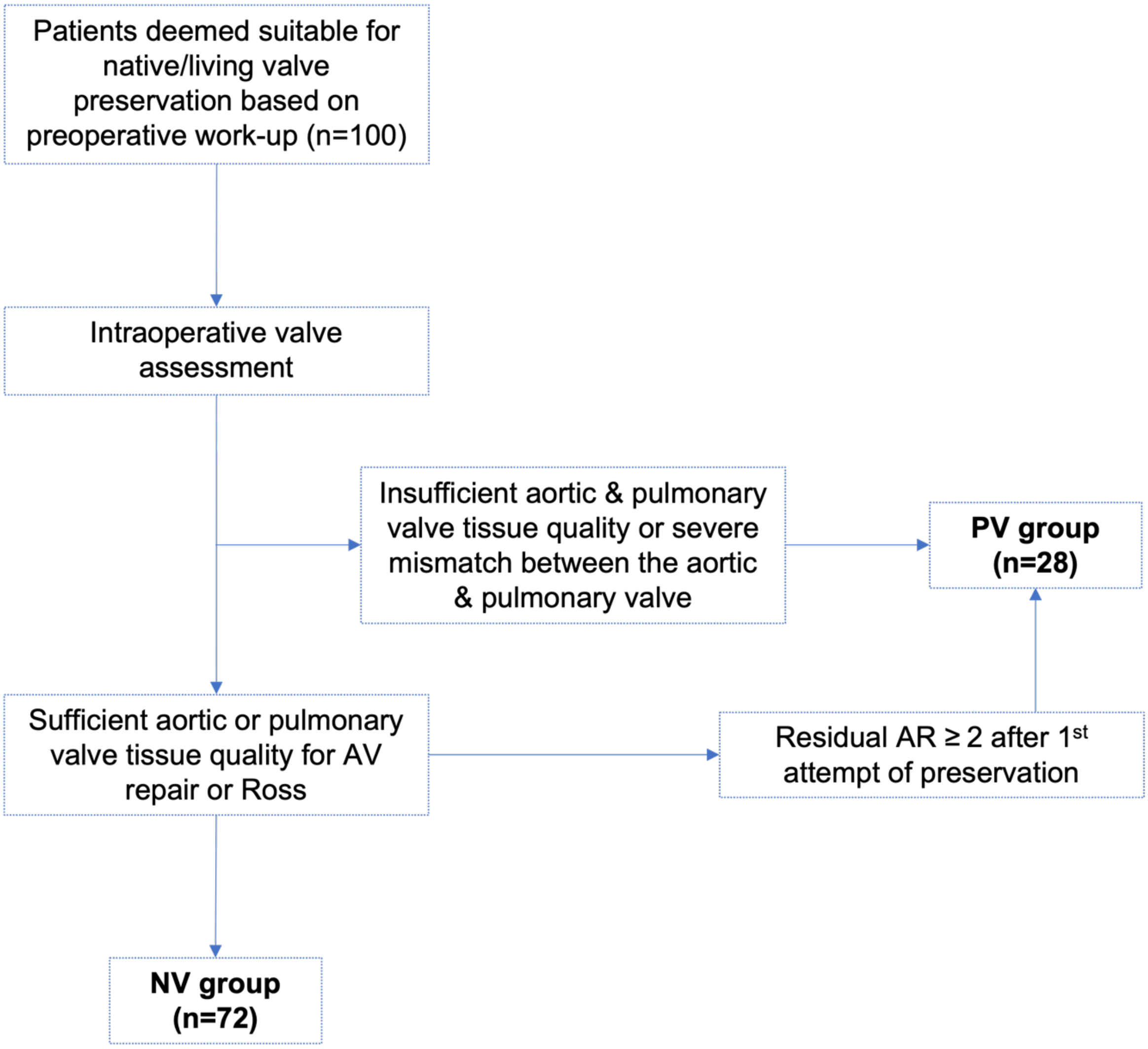
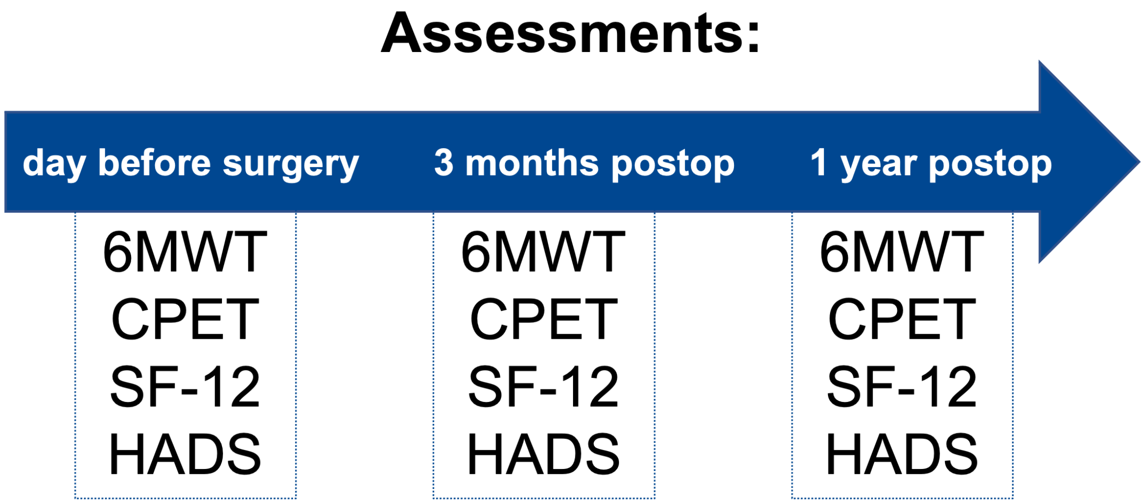


Figure P1: Flow chart for choice of surgical procedure

Based on preoperative work-up including transthoracic and transesophageal echocardiography for detailed assessment of the underlying AV pathology and pulmonary valve function, at least one attempt to preserve the native valvular tissue was decided on in all study participants. Yet, bioprosthetic and mechanical AVR as back-up plan was also discussed in advance with the patients if intraoperative conversion from native valve preservation to prosthetic AVR would be necessary. For choice of artificial valve substitute shared decision-making was performed. However due to substantial progress of bioprosthetic valve substitutes in design and function in recent years, bioprosthetic AVR was deliberately advocated even in younger patients, combined with simultaneous annulus enlargement in small aortic annuli to enable the implantation of bioprostheses with an internal diameter of ≥ 25 mm hence preventing postoperative patient-prosthesis mismatch and allowing for future transcatheter valve-in-valve procedures.

In all patients with isolated or predominant AR in whom the tissue quality intraoperatively appeared sufficient for a successful and durable repair, AV repair was pursued. In patients aged < 60 years with unicuspid or bicuspid AV morphology and a severely restrictive raphe resulting in isolated AS or mixed AV disease in whom pulmonary valve tissue quality seemed adequate, the Ross procedure was performed. If aortic and pulmonary valve tissue both appeared insufficient for a successful repair or Ross procedure upon intraoperative valve assessment, if there was severe mismatch between the native aortic and native pulmonary valve or if moderate-to-severe residual AR was present on intraoperative transesophageal echocardiography after a first attempt of native valve preservation, conversion to conventional bioprosthetic or mechanical AVR was decided on (see **Figure P1**). Moreover, if the aortic root appeared dilated, valve-sparing root replacement (i.e., David/reimplantation or Yacoub/remodeling procedure) or composite graft replacement of the aortic root and valve (i.e., Bentall procedure) was carried out.

Study protocol



6MWT: six-minute walk test, CPET: cardiopulmonary exercise testing, SF-12: 12-Item Short Form Health Survey, HADS: Hospital Anxiety and Depression Scale

Figure P2: Study protocol including all visits and assessments

The study protocol included three visits: upon admission (i.e., usually the day before surgery), at 3 months postoperatively and at 1 year postoperatively during routine follow-up assessments. In addition to routine blood work and transthoracic echocardiography for assessment of AV, pulmonary valve and left ventricular function, each visit involved a six-minute walk test (6MWT) and cardiopulmonary exercise testing (CPET) on a bicycle ergometer (Vyntus CPX, Vyaire Medical, Hoechberg, Germany) as measures of cardiopulmonary functional capacity as well as the 12-Item Short Form Health Survey (SF-12) for evaluation of physical and mental QoL (Bullinger, 1998) and the Hospital Anxiety and Depression Scale (HADS) for assessment of anxiety and depression (Herrmann-Lingen, 2011) as measures of patient-reported outcomes (see **Figure P2**). Patients who missed their follow-up appointments were contacted via telephone and received the questionnaires via mail. All available information from outpatient follow-up assessments from other institutions or providers (i.e., echocardiography, CPET) were gathered for further systematic analysis by contacting the referring cardiologists.

Statistical analysis

As described in the original publication, statistical analysis consisted of three parts: (1) estimation of the average treatment effect for the treated (ATT) (i.e., NV patients) at 1-year follow-up using augmented inverse probability weighting (AIPW) (i.e., a propensity score-based method combining calculation of the treated weights – a special form of inverse probability of treatment weighting (IPW) – to correct for baseline differences and an augmentation of the estimator with a regression model for the outcome variable) as well as assessment of longitudinal changes from baseline to 1-year follow-up within the (2) NV group and (3) PV group using the Wilcoxon sign-ranked test. The Bonferroni method was selected to adjust for multiple comparisons. Within each part of the analysis, a hierarchical test procedure was applied that included three parameters in fixed sequence: (1) 6MWT distance → (2) self-reported SF-12 physical QoL → self-reported SF-12 mental QoL. Statistical testing was performed until first non-rejection of the respective null hypothesis. Covariate balance after IPW was assessed by calculating the standardized mean differences (i.e., difference in means divided by the standard deviation). Additionally, differences at 1-year follow-up to gender- and age-specific published data on healthy individuals (Bullinger, 1998, Troosters et al., 1999, Wasserman et al., 2005, Hinz and Brahler, 2011) within both groups were descriptively evaluated and the remaining parameters (i.e., peak oxygen consumption (peak VO_2) and peak work rate assessed by CPET, anxiety and depression assessed using the HADS questionnaire) were also descriptively analyzed and summarized. Peak VO_2 measurements collected until November 2018 were considered invalid and excluded due to a defective gas concentration sensor. Hence, only patients with baseline assessment after November 2018 (n=65) were included in the sub-analysis of peak VO_2 values. Follow-up of patients ended prematurely at the time of treatment failure defined as need for AV reoperation or death. Consequently, statistical analysis was only performed until treatment failure occurred. A weighted Cox regression model incorporating the ATT IPW weights was used to analyze confounder-adjusted time to treatment failure.

Results

Patient characteristics

15/72 (21%) NV patients underwent valve-sparing root replacement with simultaneous cusp repair including 13 David/reimplantation procedures and 2 Yacoub/remodeling procedures. The remaining NV patients underwent isolated valve repair without replacement of the sinuses or the Ross procedure. 2/28 (7%) PV patients received composite graft replacement of the aortic valve and root (i.e., Bentall procedure). The remaining 26/28 PV patients underwent isolated valve replacement without replacement of the sinuses. As outlined in **Table 1** of the original publication, the dominant indication for surgery was isolated AR in both groups, followed by isolated AS in NV patients and mixed AV disease in PV patients. NV patients mostly presented with unicuspid or bicuspid AV disease while the proportion of patients presenting with unicuspid/bicuspid and tricuspid AV disease were more evenly distributed amongst the PV group. Additionally, there were marked differences between both cohorts with respect to age, sex, sum of cardiac risk factors, severity of symptoms and overall perioperative risk profiles. After IPW, most baseline characteristics were more homogenously distributed in both groups as indicated by standardized mean differences ≤ 0.2 (e.g. age, sex, AV morphology, New York Heart Association class, preoperative pro B type natriuretic peptide level, preoperative left ventricular ejection fraction (LVEF), preoperative indexed left ventricular end-systolic diameter (LVESD), predicted risk of mortality and the presence of none or just one cardiac risk factor).

Information on perioperative patient characteristics and in-hospital outcomes are summarized in **Supplementary Table 1** of the original publication. Cardiopulmonary bypass duration and aortic cross-clamp time was slightly longer in the NV group, while PV patients tended to stay longer in the intensive care unit. With respect to peri- and postoperative (severe) adverse events, 4 patients of each group required permanent pacemaker implantation for persistent postoperative total atrioventricular block. In addition, 8% of NV and 11% of PV patients needed surgical reintervention for complication other than heart rhythm disorder (e.g. residual or recurring severe AR, superficial sternal wound infection and sternal instability, lung injury with consecutive pneumothorax and subcutaneous emphysema, pericardial effusion/tamponade) before discharge.

Time to treatment failure

In total, two deaths occurred during postoperative follow-up: 1 NV patient died from small-cell lung carcinoma and 1 PV patient from sudden cardiac death. In the NV group 9 patients required reoperation for residual or recurrent severe AR during early postoperative follow-up, all of them having received AV repair as the initial procedure. No Ross patient required re-do surgery. Moreover, no reoperation following AVR was observed until 1 year postoperatively. Consequently, weighted Cox regression analysis revealed an increased confounder-adjusted risk for treatment failure in NV patients (weighted hazard ratio: 10.57 [95% CI: 1.24-90.01], p=0.031) (see **Supplementary Figure 1**).

Treatment effect as differences at 1 year postoperatively

At 1 year postoperatively, a positive, although not significant, estimated average treatment effect for the treated (i.e., NV patients) with respect to the 6MWT distance was observed (ATT: 35.64 meters [95% CI: -17.03-88.30], adj. p=0.554) (see **Figure 1**). In line with the hierarchical test procedure, no further ATT estimation was performed for physical and mental QoL. However, **Figures 2-3** show that physical and mental QoL scores were comparable in both groups at 1 year postoperatively (median physical QoL score: 55 (6) in NV vs. 54 (7) in PV patients; median mental QoL score: 56 (7) in NV vs. 56 (13) in 182 PV patients).

Longitudinal changes from baseline to 1-year follow-up

As outlined in **Table 2** of the original publication, NV and PV patients both showed significant improvements in 6MWT distance and physical QoL score from baseline to 1-year follow-up. In terms of mental QoL score, significant improvements were observed in the NV cohort and, although not statistically significant, there were also notable improvements in the PV cohort.

Difference to gender and age-specific published data on healthy individuals

As displayed in **Figure 4** of the original publication, the percentage of patients reaching reference values of 6MWT distance derived from published data on healthy individuals was 16.9% in the NV and only 5.3% in the PV group at 1 year postoperatively. In contrast, the percentages of patients reaching reference values of physical and mental QoL at 1-year follow-up were more similar in NV and PV patients (physical QoL: 69.5% vs. 72.7%, respectively; mental QoL 66.1% vs. 63.6%, respectively) (see **Figures 5-6**).

Descriptive analysis of changes in peak VO_2 and work rate

From baseline to 1 year postoperatively, improvements in median peak VO_2 and work rate were +3.7 mL/kg/min and +33.5 Watts in NV vs. +1.4 mL/kg/min and +13.5 Watts in PV patients. Median peak VO_2 at 1-year follow-up was 24.6 (6.4) mL/kg/min in NV and 17.7 (8.7) mL/kg/min in PV patients while median peak work rate was 190 (73) Watts in NV and 127 (87) Watts in PV patients. At all visits including baseline assessment, median peak VO_2 and work rate were better in the NV compared to PV group (see **Supplementary Figures 2-3**). At 1 year postoperatively, the percentages of patients reaching reference values of peak VO_2 and work rate derived from published data on healthy individuals were similar in the NV and PV cohort (peak VO_2: 33.9% vs. 31.6%, respectively; peak work rate: 2.6% vs. 6.7%, respectively) (see **Supplementary Figures 6-7**).

Descriptive analysis of changes in anxiety and depression

From baseline to 1 year postoperatively, median anxiety and depression scores decreased by 3 and 3 points in the NV vs. 2 and 2.5 points in the PV group, respectively. Median anxiety and depression scores were similar in both groups at all visits. At 1-year follow, NV and PV patients both showed a median anxiety score of 4 and a median depression score of 1 (see **Supplementary Figures 4-5**). Moreover, 45.8% of NV and 40.9% of PV patients reached reference values of anxiety at 1 year postoperatively. In terms of depression, reference values were reached by 78.3% of NV and only 68.2% of PV patients (see **Supplementary Figures 8-9**).

Echocardiographic parameters at discharge and 1 year postoperatively

As displayed in **Supplementary Table 2**, mean transvalvular gradients, LVEF and indexed LVESD at discharge were comparable in NV and PV patients (peak AV gradient: 17±10 vs. 18±8 mmHg, respectively; mean AV gradient: 9±6 vs. 10±4 mmHg, respectively; LVEF: 49±7 vs. 46±11 %, respectively; indexed LVESD: 21±3 vs. 23±5 mm/m^2, respectively). Until 1 year postoperatively, mean peak and mean AV gradient dropped to 13±8 and 7±5 mmHg in NV and 17±7 and 9±3 mmHg in PV patients while mean LVEF increased to 54±7 % in the NV and 55±5 % in the PV group. Indexed LVESD also decreased throughout the follow-up equaling 19±3 mm/m^2 in both groups at 1-year follow-up.

Discussion

Irrespective of the specific underlying valvular defect, the treatment of non-elderly patients with AV disease imposes a challenge on cardiac surgeons and cardiologists due to the unique characteristics of this young and relatively healthy patient cohort that sets them apart from older patients suffering from degenerative non-congenital valve disease: (1) a longer anticipated life expectancy and thus a higher cumulative risk of valve-related complications, (2) higher levels of physical activity and increased metabolism and (3) a greater importance and value of physical, mental and social well-being (Lansac et al., 2019). Besides morbidity and mortality, it is therefore also crucial to evaluate postoperative cardiopulmonary capacity and self-reported outcomes when aiming to assess the benefits and risks of different treatment strategies in this patient cohort.

<u>The risk of native valve preservation</u>

In the current study, native valve preservation, more specifically AV repair, was associated with an increased risk of AV reoperation during follow-up compared to conventional prosthetic AVR. This is most likely attributable to a learning curve with a more liberal/aggressive approach at the beginning of the study that included performing AV repair in bicuspid and tricuspid valves with large fenestrations, in bicuspid valves with large calcifications and a severely restrictive raphe and in unicuspid valves necessitating the use of patch material. This is in line with findings from other groups that have linked patch augmentation and the bicuspidization procedure in unicuspid morphology (Schafers et al., 2008) to an increased risk for AV repair failure (Gökalp et al., 2019, Schneider et al., 2017, Igarashi et al., 2020). Based on this experience, there was a change in surgical strategy in the three specific above-mentioned situations throughout the course of the study from primary AV repair towards primary Ross procedure.

<u>The benefit of native valve preservation</u>

Living/native valve-preserving procedures have been developed for non-elderly patients to avoid prosthetic AVR with its concurring lifetime risks of anticoagulation-related complications or structural valve deterioration, thereby aiming to improve postoperative long-term survival and freedom from cardiovascular events (Vojacek et al., 2018, El-Hamamsy, 2018). To what extent non-elderly patients also benefit from native valve preservation at short- and mid-term follow-up, especially with respect to postoperative cardiopulmonary capacity and patient-reported outcomes, has only been insufficiently evaluated so far. Results of all previous studies comparing native valve-preserving procedures and prosthetic AVR with respect to physical and mental performance at short or mid-term follow-up are summarized in the following **Table P3**:

Previous works	Substantial differences	No substantial differences
Nötzold et al., 2001	Postoperative **physical and mental QoL** in adults negatively linked with **mechanical AVR compared to Ross**	
Aicher et al., 2011	Confirmation of Nötzold's results + **extension from Ross to AV repair**	No substantial differences in **HADS subscales** between **AV repair vs. Ross vs. mechanical AVR**
Zacek et al., 2016	Confirmation of Nötzold's results + **extension from Ross to AV repair**	
Beacher et al., 2021		No significant differences in **physical and mental QoL** in children and young adults following **Ross vs. mechanical AVR**
Takajo et al., 2021	Better initial postoperative **exercise capacity** on CPET in children and young adults after **Ross vs. mechanical AVR**	

Table P3: Previous studies on physical and mental performance after native valve-preserving AV surgery vs. prosthetic AVR

As displayed above, previous findings of other groups are somewhat inconsistent regarding the superiority of native valve-preserving procedures when considering physical and/or mental performance at short-/mid-term follow-up. In the current investigation, native valve preservation translated into a positive, although not significant, estimated average treatment effect of 35.64 meters with respect to 6MWT distance. The results replicated the findings from Beacher and colleagues that self-reported physical and mental QoL scores as measured by the SF-12 were similar in the NV and PV group at 1 year postoperatively – in contrast to the reports from Nötzold et al., Aicher et al. and Zacek et al. (Nötzold et al., 2001, Aicher et al., 2011, Zacek et al., 2016, Beacher et al., 2021). However, anxiety and depression were comparable in both groups at 1-year follow-up confirming the results obtained by Aicher and colleagues with respect to HADS subscales (Aicher et al., 2011). Only peak VO_2 and work rate assessed by CPET were considerably better in the NV compared to PV cohort at 1 year postoperatively which is in agreement with a study conducted by Takajo and colleagues (Takajo et al., 2021). However, these current findings with respect to peak VO_2 and work rate should be interpreted with caution as the observed between-group differences in the NV and PV groups were already present at the time of baseline assessment and potentially linked to differences in age and sex distribution in both groups. Nevertheless, in summary, all previous investigations as well as this current study provide evidence for a comparable and definitely not inferior performance after native/living valve-preserving procedures vs. prosthetic AVR at short and mid-term follow-up.

Longitudinal changes from baseline to 1-year follow-up

From baseline to 1 year postoperatively, notable longitudinal improvements in 6MWT distance and self-reported physical and mental QoL following both native valve-preserving surgery and prosthetic AVR were observed. Additionally, considerable decreases in self-reported anxiety and depression during the first postoperative year were noticed in both groups. This is in line with a previous investigation by Petersen and colleagues (Petersen et al., 2016) who assessed longitudinal changes in physical and mental performance after AV surgery during the first 6 months postoperatively, also using the 6MWT as well as the SF-12 and HADS questionnaires, but without differentiating among surgical strategies. Absolute improvements in physical and mental QoL scores as well as anxiety and depression in their patients were comparable. Absolute improvement in 6MWT distance was, however, markedly greater in their study (Petersen et al., 2016), but could be the result of their patients performing worse on 6MWT at baseline which in turn allows for greater postoperative improvements in walking distance as maximum distance is limited by the fact that subjects are only allowed to walk and must not run even if possible (ATS, 2002). The better baseline 6MWT performance of patients from the current study possibly reflects the impact of earlier indication for AV surgery in asymptomatic patients as recommended by the revised 2017 ESC/EACTS guidelines for the management of valvular heart disease published just prior to inclusion of the first patient (Baumgartner et al., 2017). Of note, these guidelines have just recently been revised again and AV surgery is now recommended even earlier in asymptomatic patients (Vahanian et al., 2022).

In contrast to the above-mentioned report, our current study additionally investigated longitudinal improvements in CPET parameters. Small improvements in peak VO_2 and work rate at 1 year postoperatively were detected and tended to be slightly more pronounced in NV compared to PV patients. The only previous study comparing CPET results in patients before and after AV surgery and including patients with native valve-preserving procedures was performed by Tamás and colleagues who observed a steady peak VO_2 and a small increase in peak work rate of only 12 Watts until 6 months postoperatively (Tamás et al., 2009).

Limitations

This current study reports a single-center experience. Consequently, generalization of findings to other centers and settings is limited. No randomization or preoperative assignment to study groups was performed and samples sizes were not calculated in advance but rather reflect an “as treated” group assignment while the primary surgical strategy was always NV preservation. This method led to uneven sample sizes. Moreover, the correct specification of either the propensity score or the outcome model that served as basis for AIPW were possibly impeded by unmeasured confounders, heterogenous treatment groups and poor small sample properties of causal inference methods in general. This might explain why some patient characteristics, including the sum of cardiac risk factors and reason for surgery, remained heterogeneously distributed even after IPW as indicated by standardized mean differences > 0.2.

Furthermore, anticoagulation-related thromboembolic or bleeding complications and structural valve deterioration more specifically impact long-term survival and freedom from cardiovascular events following prosthetic AVR. Yet, due to the limited follow-up of one year, this study only assessed short-term effects of native valve preservation vs. prosthetic AVR on physical and mental performance. To assess mid- and long-term benefits and risks of native valve-preserving procedures, a longer follow-up would be required. Also, as follow-up of patients was only carried out until treatment failure occurred, conclusions drawn are technically only valid until a patient requires re-do surgery. This might introduce a slightly biased positive view for the NV group. In summary, findings of this study should be confirmed in further prospective, ideally multicentric studies with larger samples sizes, more homogeneous patient cohorts and a longer postoperative follow-up. Also, follow-up of patients should be continued even after AV reoperation to allow for an interpretation of the results independent from the risk for treatment failure. In addition, a valve-specific questionnaire and stress echocardiography should be added to the study protocol to enable more detailed insights into QoL after heart valve surgery in specific as well as a more detailed assessment of transvalvular gradients and left ventricular hemodynamics during exercise.

Conclusion

Physical and mental performance improved during the first year after both native valve-preserving surgery and prosthetic AVR. At 1 year postoperatively, patient-reported outcomes were similar in both cohorts while native valve preservation was associated with a positive, but not significant, treatment effect on postoperative 6MWT distance. Moreover, there was a tendency towards more NV patients reaching reference values of 6MWT at 1-year follow-up as compared to PV patients. It can thus be concluded that despite an increased risk of treatment failure, physical performance and mental well-being after living/native valve-preserving surgery were comparable to performance and well-being after conventional prosthetic AVR in non-elderly adults. Therefore, shared decision-making with each individual patient to choose the appropriate treatment adapted to his or her own specific needs is essential.

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3. Abstract (English Version)

This study aimed to prospectively observe and evaluate the effect of native valve-preserving aortic valve surgery, including aortic valve repair and the Ross procedure, compared to conventional prosthetic aortic valve replacement on postoperative exercise capacity and patient-reported outcomes. 100 consecutive non-elderly patients aged < 65 years with severe aortic valve disease were prospectively included and assessed before surgery and at 3 months and 1 year postoperatively. Marked postoperative longitudinal improvements in physical and mental performance were observed after both native valve-preserving procedures and prosthetic valve replacement. At 1 year postoperatively, patient-reported outcomes, including self-reported physical and mental quality of life, anxiety and depression, were comparable in both cohorts while native valve preservation was associated with a positive, although not significant treatment effect on postoperative six-minute walking distance. Peak oxygen consumption and work rate assessed by cardiopulmonary exercise testing were better at all assessments in native valve patients. At 1 year, there was a tendency towards more native valve patients reaching reference values of six-minute walking distance as compared to prosthetic valve patients. To conclude, physical and mental performance improved after native valve-preserving surgery and was comparable to the performance after conventional prosthetic aortic valve replacement.

4. Abstract (German Version)

Das Ziel dieser Studie war die prospektive Beobachtung und Untersuchung des Effekts des Erhalts des patienteneigenen Herzklappengewebes mittels Aortenklappenrekonstruktion oder Ross-Operation auf die postoperative körperliche Leistungsfähigkeit und subjektiv empfundene Behandlungsergebnisse im Vergleich zum standardmäßigen Aortenklappenersatz mittels biologischer oder mechanischer Prothese. Dafür wurden konsekutiv jüngere Patienten unter 65 Jahren mit hochgradigem Aortenklappenvitium prospektiv in die Studie eingeschlossen und präoperativ sowie 3 Monate und 1 Jahr postoperativ nachuntersucht. Postoperativ wurden deutliche longitudinale Verbesserungen in physischer und mentaler Performance in beiden Gruppen – nach Nativklappen-erhaltender Operation und Aortenklappenersatz – beobachtet. Zum Zeitpunkt der 1-Jahres Untersuchung waren subjektiv empfundene Behandlungsergebnisse (d.h. physische und mentale Lebensqualität, Angst und Depression) in beiden Gruppen vergleichbar während der Erhalt des patienteneigenen Herzklappengewebes zumindest mit einem positiven, jedoch nicht signifikanten Behandlungseffekt in Bezug auf die postoperative 6-Minuten Gehstrecke assoziiert war. Zu allen Untersuchungszeitpunkten zeigten die Nativklappen-Patienten in einer Fahrrad-Spiroergometrie eine bessere maximale Sauerstoffaufnahme und Leistung auf dem Fahrradergometer. Zum Zeitpunkt der 1-Jahres Untersuchung erreichten tendenziell mehr Nativklappen-Patienten als Aortenklappenersatz-Patienten Normwerte der 6-Minuten Gehstrecke. Zusammenfassend verbesserten sich physische und mentale Performance nach Nativklappen-erhaltender Aortenklappenoperation und waren vergleichbar mit der Performance nach konventionellem Aortenklappenersatz.

5. Contributions of the Authors

In the following table, the substantial contributions of each author to the study are listed.

	Author names	Conception and design	Analysis and interpretation	Writing of the original draft	Critical revision of the manuscript	Final approval of the manuscript	Data collection	Provision of materials, patients or resources	Statistical expertise	Obtaining funding	Literature search	Administrative, technical or logistic support
1.	Theresa Holst	✓	✓	✓	✓	✓	✓	✓			✓	
2.	Johannes Petersen	✓	✓		✓	✓		✓			✓	
3.	Sarah Friedrich		✓		✓	✓			✓			✓
4.	Benjamin Waschki				✓	✓		✓				✓
5.	Christoph Sinning				✓	✓		✓				✓
6.	Meike Rybczynski				✓	✓		✓				✓
7.	Hermann Reichenspurner				✓	✓		✓		✓		
8.	Evaldas Girdauskas	✓	✓		✓	✓	✓	✓		✓	✓	

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7. Curriculum vitae

Entfällt aus datenschutzrechtlichen Gründen.

8. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

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Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: ....