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# AVNeo improves early haemodynamics in regurgitant bicuspid aortic valves compared to aortic valve repair

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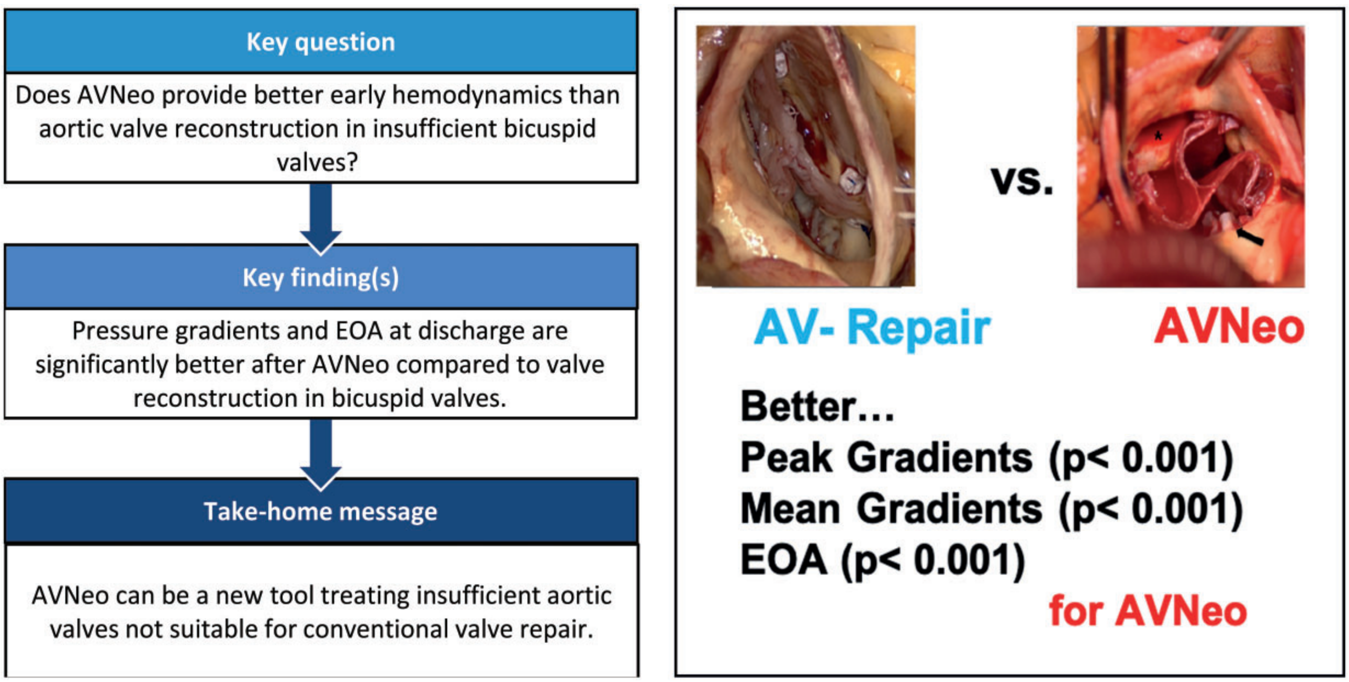


## Abstract

**OBJECTIVES:** Calcified or fibrotic cusps in patients with bicuspid aortic valves and aortic regurgitation complicate successful aortic valve (AV)-repair. Aortic valve neocuspidization (AVNeo) with autologous pericardium offers an alternative treatment to prosthetic valve replacement. We compared patients with regurgitant bicuspid valves undergoing AV-repair or AVNeo.

**METHODS:** We retrospectively analysed patients with regurgitant bicuspid valves undergoing AV-repair or AVNeo. We focused on residual regurgitation, pressure gradients and effective orifice area, determined preoperatively and at discharge.

**RESULTS:** AV-repair was performed in 61 patients (mean age: 43.2 ± 11.3 years) and AVNeo in 22 (45.7 ± 14.1). Prior to the operation patients of the AV-repair group showed severe regurgitation in 38 cases (62.3%) and moderate in 23 (37.6%); in the AVNeo group, all patients exhibited severe regurgitation. Postoperatively, 57 patients (93.4%) patients had no or mild regurgitation after AV-repair and 21 (95.4%) after AVNeo. In AVNeo-patients, peak (10.6 ± 3.1 mmHg vs 22.7 ± 11 mmHg, $P < 0.001$) and mean pressure gradients (5.9 ± 2 mmHg vs 13.8 ± 7.3 mmHg, $P < 0.001$) were significantly lower and the orifice area significantly larger (2.9 ± 0.8 $cm^2$ vs 1.9 ± 0.7 $cm^2$, $P < 0.001$) compared to repair.

**CONCLUSIONS:** Compared to AV-repair, patients AVNeo showed lower mean pressure gradients and larger orifice areas at discharge. The functional result was not different.

**Keywords:** Bicuspid aortic valves • Aortic valve regurgitation • Aortic valve repair • AVNeo with autologous pericardium

**ABBREVIATIONS**

| | |
|---|---|
| AR | Aortic regurgitation |
| AV | Aortic valve |
| AVNeo | Aortic valve neocuspidization |
| BAV | Bicuspid aortic valve |
| CPB | Cardiopulmonary bypass |
| EOA | Effective orifice area |

## INTRODUCTION

In recent years, aortic valve repair (AV-repair) evolved into a treatment alternative for patients with insufficient aortic valves [1]. Although concerns existed regarding the durability and feasibility of repair procedures, especially in patients with bicuspid aortic valves (BAVs), studies showed that AV-repair in patients with BAV is feasible and safe [2, 3]. However, outcome after AV-repair in BAV is influenced by tissue quality, as BAV often show fibrosis and calcifications, which can lead to early repair failure [2, 4]. A recent study from Schäfers *et al.* showed a significant decline in survival and increase in reoperation rates in patients with fibrotic or calcified cusps, with asymmetric valve configuration and need for pericardial patches. They concluded that these patients should primarily receive aortic valve replacement [5]. Schneider and colleagues [6] demonstrated that the use of patch material for partial cusp replacement and cusp calcification beyond the raphe are important predictors for repair failure, respectively.

In this setting, an alternative treatment may be the tricuspid aortic valve neocuspidization (AVNeo) with autologous pericardium [7, 8].

In this retrospective study, we analysed the early postoperative success after AV-repair and AVNeo in patients with BAV morphology and aortic valve regurgitation to compare AV-repair and AVNeo with regards to the early haemodynamic performance.

## PATIENTS AND METHODS

### Ethical statement

The Ethics Committee of the TU Munich approved this study and waived the need for patients' consent (Number: 706/21 S).

In the present study, we included patients with aortic regurgitation (AR) and BAV undergoing either trileaflet reconstruction of the aortic valve with autologous pericardium (AVNeo) or repair of the aortic valve (AV-repair) and evaluated echocardiographic parameters prior to the operation and at discharge. In our department, AVNeo procedures have been conducted since November 2016. The inclusion of AV-repair patients began in 2007. Patients to be included in our study were identified using our institutional database.

The policy in our institution is to preserve a native valve whenever possible. If patients present with regurgitant aortic valves, intraoperative analysis of the valve is performed and, based on these findings, the decision to repair or replace the valve is left on the surgeons' discretion. After introduction of the AVNeo technique in our department, we decided to offer the procedure to younger patients with regurgitant valves, which were not repairable and would have been otherwise replaced.

Each valve was accurately defined as BAV on the basis of our intraoperative findings. Pre- and postoperative transthoracic echocardiography included assessment of the severity of AR (graded as none, mild, moderate and severe), peak and mean pressure gradient over the aortic valve, effective orifice area (EOA), left ventricular ejection fraction and left ventricular end-diastolic diameters [9]. Every patient underwent intraoperative transoesophageal echocardiography before and after cardiopulmonary bypass (CPB). Institutional policy is to not accept more than mild AR after CPB, as detected by transoesophageal echocardiography.

The surgical principle of the AV Neo procedure is the replacement of the diseased native valve with new cusps made of autologous pericardium. The technique was introduced in 2011 [7] and we apply the technique as described by Ozaki and colleagues. In brief, after median sternotomy, a pericardial patch is harvested, fixed in glutaraldehyde for 10 min and rinsed in saline 3 times for 6 min. Meanwhile, the cusps of the native aortic valve were excised and, in case of calcification, the annulus thoroughly debrided. With commercially available cusp sizers each cusp was measured individually and the corresponding size cut from the pericardium with templates. The neo-cusps were then sewn to the annulus with 4–0 monofilament sutures, starting at the nadir with defined distances between each stitch, as described by Ozaki and our group: for the first 4 stitches on each side of the nadir, a distance ratio of 1:3 is kept and afterwards, stitches are placed in a ratio of 1:1 [8, 10]. Once each commissure was reached, the neo-cusps were secured with additional sutures. Every valve was reconstructed with 3 cusps and if measurements displayed a difference of more than 2 sizes for the neo-cusp, the sizes of the neo-cusps were adjusted by creating a neocommissure. All AVNeo procedures were primary surgical procedures.

In case of classic AV-repair, principles of treatment were published by Boodhwani and colleagues [11] and can be applied to the majority of patients presenting with AR. After initiation of CPB and transverse aortotomy, the native valve was assessed. According to the intraoperative findings, repair strategies consisted of restoration of adequate coaptation of the cusps and treatment of cusp mobility: in case of cusp prolapse, plication or triangular resection of the prolapsing segment was performed. In case of restrictive cusp mobility, i.e. through calcified raphe, the raphe was resected by triangular excision and the defect either closed directly or with a patch. For better comparison of the 2 techniques, only patients without procedures of the aortic root were included. To stabilize the repair or to reduce annular diameter, subcommissural annuloplasty was performed.

Statistical analysis was performed using IBM SPSS Version 23 (IBM, Armonk, NY, USA). Continuous variables are presented as mean values and standard deviation, categorical variables as numbers and percentage. We assessed the data for normality and analysed continuous variables with either Mann–Whitney U or Wilcoxon tests. For comparison of categorial variables, we used either chi-square or Fishers' exact test. To assess pre- and postoperative variables, paired *t*-tests were performed. Statistical significance was considered for $P < 0.05$.

## RESULTS

### Patient characteristics

A total of 22 patients with BAV and AR underwent AV Neo procedures between November 2016 and January 2020 for AR. Mean age was 45.7 (34.7, 57.3) years and 18 patients were male (81.8%). All patients had severe AR. The detailed preoperative echocardiographic data are depicted in Table 1.

AV-repair was performed in 61 patients with BAV and AR between July 2007 and March 2016. Mean age was 43.2 (36.5, 50.9) years and 58 patients were male (95.1%). Severe AR was found in 38 cases (62.3%) and moderate AR in 23 cases (37.6%). In 23 patients with moderate AR, replacement of the ascending aorta was performed, prompting aortic valve repair. The detailed echocardiographic data are given in Table 1.

### Perioperative outcome

In AVNeo patients, valves were classified intraoperatively as Sievers type 0 in 1 (4.5%), Sievers type 1 in 18 (81.8%) and Sievers type 2 in 3 patients (13.6%). Of the Sievers type 1, 16 (88.9%) had a fused left–right coronary cusp and 2 (11.1%) a fused right non-coronary cusp. All valves were tricuspidalized by implantation of 3 neo-cusps. In 12 patients (54.5%), we implanted 3 equally sized cusps and in 10 patients (45.5%), the size of the cusps differed by one size. Mean size of the neo-cusps measured by the cusp sizer was 31.2 for the right coronary cusp and 31.1 for the left and non-coronary cusp. In 16 cases (72.7%), a neo-commissure had to be constructed. Before correction of the cusp size, the left coronary cusp was the smallest (29) and the mean size of the right and non-coronary cusp were 31 and 33, respectively. Mean CPB time was 164.4 (144.5, 177.5) min with a mean aortic cross-clamp time of 132.3 (120, 140) min. Concomitant procedures were carried out in 6 cases (27.3%) and are depicted in detail in Table 2. Intraoperative transoesophageal echocardiography revealed a mean coaptation length of $16.2 \pm 1.9$ mm in the AVNeo patients. Transthoracic echocardiography at discharge showed no or mild AR in 21 patients (95.4%). One patient (4.5%) had to undergo reoperation within the initial hospital stay. Reason for reoperation was recurrent severe AR, caused by a tear in the left coronary neo-cusp. In this case, the valve was replaced by a mechanical prosthesis. More echocardiographic parameters are provided in Table 1.

In patients undergoing AV-repair, intraoperative valve analysis showed 59 Sievers type 1 (96.7%) and 2 Sievers type 0 (3.3%) aortic valves. Of the Sievers type 1 BAV, 55 (93.2%) had a fused left–right coronary cusp and 4 (6.8%) a fused right non-coronary cusp. Techniques for treatment of AR were subcommissural annuloplasty in 53 (86.9%) cases, plication in 47 (77%), triangular resection in 39 (63.9%), patch implantation in 11 (18%) and

**Table 1:** Echocardiographic parameters

| Parameter | AV-repair (*n* = 61) | AVNeo (*n* = 22) | *P*-value |
|---|---|---|---|
| Preoperative | | | |
| AR | | | |
| None | 0 | 0 | |
| Mild | 0 | 0 | |
| Moderate | 23 (37.6) | 0 | |
| Severe | 38 (62.3) | 22 (100) | |
| Peak gradient (mmHg) | 15.4 (9, 20) | 21 (13, 33) | 0.073 |
| Mean gradient (mmHg) | 8.5 (5, 11) | 13 (8, 20) | 0.074 |
| EOA ($cm^2$) | 2.9 (2, 4,1) | 2.9 (1.7, 3.9) | 0.877 |
| LVEF (%) | 57.7 (55, 60) | 57.8 (53.8, 62.8) | 0.928 |
| LVEDD (mm) | 60.3 (22.3, 29) | 59.2 (53, 67) | 0.718 |
| Annulus (mm) | 27.2 (25.3, 29) | 28.2 (27.5, 31) | 0.326 |
| Aortic root (mm) | 38.7 (35, 39.3) | 36.4 (31.8, 39.3) | 0.506 |
| Ascending aorta (mm) | 42.7 (36, 50) | 39.7 (34.8, 44) | 0.056 |
| Discharge | | | |
| AR | | | |
| None | 39 (63.9) | 16 (76.2) | |
| Mild | 19 (31.1) | 5 (23.8) | |
| Moderate | 1 (1.6) | 0 | |
| Severe | 2 (3.3) | 0 | |
| Peak gradient (mmHg) | 22.7 (14, 28) | 10.6 (8.3, 13) | **<0.001** |
| Mean gradient (mmHg) | 13.8 (8, 19) | 5.9 (4.3, 7.8) | **<0.001** |
| EOA ($cm^2$) | 1.9 (1.5, 2.3) | 2.9 (2.2, 3.3) | **<0.001** |
| LVEF (%) | 51.9 (50, 60) | 52.1 (43.5, 60) | 0.684 |
| LVEDD (mm) | 52.3 (49, 57) | 51.7 (50, 60) | 0.665 |
| Aortic root (mm) | 36.7 (35, 43) | 35.7 (32.5, 40) | 0.197 |
| Ascending aorta (mm) | 32.7 (33, 40) | 34.7 (31.5, 38) | 0.120 |

Continuous variables: mean ± standard deviation. Categorical variables: absolute and relative frequencies. Statistical significant values are presented as bold numbers.

AR: aortic regurgitation; EOA: effective orifice area; LVEF: left ventricular ejection fraction (%); LVEDD: left ventricular end-diastolic diameter (mm).

**Table 2:** Concomitant procedures and MACCE

| Parameter | AV-repair (*n* = 61) | AVNeo (*n* = 22) |
|---|---|---|
| Concomitant procedures | 37 (60.7) | 6 (27.3) |
| Mitral valve | 7 (11.5) | 2 (9.1) |
| Tricuspid valve | 1 (1.6) | 0 |
| CABG | 4 (6.6) | 0 |
| Ascending aortic replacement | 27 (44.3) | 6 (27.3) |
| MACCE | | |
| Stroke | 0 | 0 |
| Bleeding | 4 (6) | 0 |
| Reoperation | 3 (4.9) | 1 (4.5) |
| Death | 0 | 0 |

Categorial variables: absolute and relative frequencies.

CABG: coronary aortic bypass graft; MACCE: major adverse cardiac and cerebral events.

commissural stitches in 8 (13.1%) cases. Mean CPB and aortic cross-clamp time was 100.3 (72, 115.5) and 75.3 (53.5, 86) min with concomitant procedures carried out in 37 cases (60.7%) (Table 2). Transthoracic echocardiography at discharge showed no or mild AR in 58 patients (95.1%). Moderate AR was found in 1 patient (1.6%) and severe in 2 (3.3%). More detailed echocardiographic data are provided in Table 1. Three patients had to undergo redo surgery within the initial hospital stay. Indication was recurrent high-grade AR in 2 patients and aortic stenosis in one. Treatment was redo AV-repair in 1 patient and prosthetic valve replacement in 2 patients.

## Haemodynamic analysis

To analyse our data, we compared echocardiographic data before operation and at discharge.

For AV Neo, significant differences between preoperative and discharge measurements were found for the following parameters: peak and mean gradients decreased significantly (21 [13, 33] mmHg to 10.6 [8.3, 13] mmHg; $P < 0.001$ and 13 [8, 20] mmHg to 5.9 [4.3, 7.8] mmHg; $P < 0.001$), as well as left ventricular ejection fraction (57.8 [53.8, 62.8] % to 52.1 [43.5, 60]; $P = 0.003$) and left ventricular end-diastolic diameter (59.2 [53, 67] mm to 51.7 [50, 60]; $P < 0.001$). The only parameter remaining constant was the EOA (2.9 [1.7, 3.9] $cm^2$ and 2.9 [2.2, 3.3] $cm^2$; $P = 0.914$).

For AV-repair, the following parameters differed significantly between preoperative and discharge: peak and mean gradients increased (15.4 [9, 20] mmHg to 22.7 [14, 28] mmHg; $P = 0.03$ and 8.5 [5, 11] mmHg to 13.8 [8, 19] mmHg; $P = 0.003$), while left ventricular ejection fraction (57.7 [55, 60] % to 51.9 [50, 60] %; $P < 0.001$) and left ventricular end-diastolic diameter (60.3 [22.3, 29] mm to 52.3 [49, 57] mm; $P < 0.001$) decreased. The mean EOA significantly decreased (2.9 [2, 4,1] $cm^2$ and 1.9 [1.5, 2.3] $cm^2$; $P = 0.035$).

## Intergroup statistical analysis

Preoperative inter-group comparison showed no statistically significant differences between AVNeo and AV-repair. At discharge, peak (10.6 [8.3, 13] mmHg vs 22.7 [14, 28] mmHg, $P < 0.001$) and mean pressure gradients (5.9 [4.3, 7.8] mmHg vs 13.8 [8, 19] mmHg, $P < 0.001$) were significantly lower and mean EOA (2.9 [2.2, 3.3] $cm^2$ vs 1.9 [1.5, 2.3] $cm^2$, $P < 0.001$) was significantly larger in the AVNeo group (Table 1). Graphic visualization as box plots can be found in Figs 1–3.

# DISCUSSION

To treat AR, aortic valve repair is considered in selected patients [12]. AV-repair leads to a low incidence of valve-related complications such as thromboembolic events, bleeding, endocarditis, reoperations [13, 14] and an improved postoperative outcome compared to conventional surgical valve replacement [15]. Results and durability of repair of BAV are comparable with repair of tricuspid aortic valves [3, 11, 16]. However, 3 main factors are known to influence outcome after AV-repair in patients with BAV: quality of the native tissue of the leaflets, geometric orientation of the commissures and dimensions of the aortic annulus. Each of these factors may favour the decision whether to replace the valve with a prosthesis or perform a repair procedure.

Construction of a new valve with autologous pericardium (AVNeo) has been presented as an alternative to prosthetic valve replacement [7]. In 2018, Ozaki *et al.* [17] reported on excellent haemodynamic performance and a low reoperation rate of 4.2% in a cohort of 850 patients 53.7 ± 28.2 months following AVNeo. The same group also described the AVNeo procedure for patients with BAV in whom the authors replaced the bicuspid valve with 3 pericardial leaflets following the construction of neo-commissures [8]. However, it is not known if the AVNeo procedure yields an advantage over conventional reconstruction techniques early after the operation.

## Haemodynamic parameters

In the present investigation, the main difference between the AVNeo procedure and reconstruction of the native valve was found in the postoperative haemodynamic parameters. After AV-repair, peak and mean gradients increased significantly (22.7 [14, 28] and 13.8 [8, 19] mmHg), while the gradients decreased after AVNeo (10.6 [8.3, 13] and 5.9 [4.3, 7.8] mmHg; $P \leq 0.001$ for both). Correspondingly, the EOA increased significantly after AVNeo. In contrast, a major increase in gradients and a decrease of EOA after AV-repair has been described previously and may contribute to failure of AV-repair [16, 18, 19]. In addition, the reconstruction of insufficient BAV with impaired leaflet morphology may require the implementation of complex repair strategies, e.g. large resections and patch implantation [11]. Aicher and colleagues [2] showed that the use of pericardial patches for leaflet augmentation or partial replacement was a predictor for reoperation; Tanaka and colleagues [20] observed recurrent AR in patients undergoing reimplantation procedures with cusp repair techniques as free margin reinforcement or patch repair. Our group showed that in a series of 150 patients undergoing isolated AV-repair, the use of a patch led to early repair failure, caused by patch degeneration, and recurrent prolapse or calcification [16].

## Anatomy of the bicuspid aortic valve

As early as 2011, Aicher and colleagues showed that orientation of the commissures influenced reoperation rates. In asymmetrical valves with a commissural orientation ≤160° repair failure occurs more frequently [2]. In 2019, de Kerchove and colleagues [4] reported higher rates of valve replacement for very asymmetrically oriented valves. Asymmetric commissural orientation does not affect outcome after the AVNeo procedure, as equal size distribution of the neo-cusps can be achieved with the creation of neo-commissures [17]. In the present series, a neo-commissure was created in 16 cases (72.2%) and equally sized cusp were implanted in 12 patients (54.5%). In 10 patients (45.5%), the size of one implanted cusp differed by one size. Before correction with a neo commissure the size between the smallest (left coronary cusp, 29 mm) and the largest cusp (non-coronary cusp, 33 mm), differed by 4 sizes. The benefit of this size distribution is a more symmetric valve opening and closing. This mechanism may contribute to a more equal distribution of mechanical forces on the neo cusps resulting in a significantly improved haemodynamic as shown in this study.

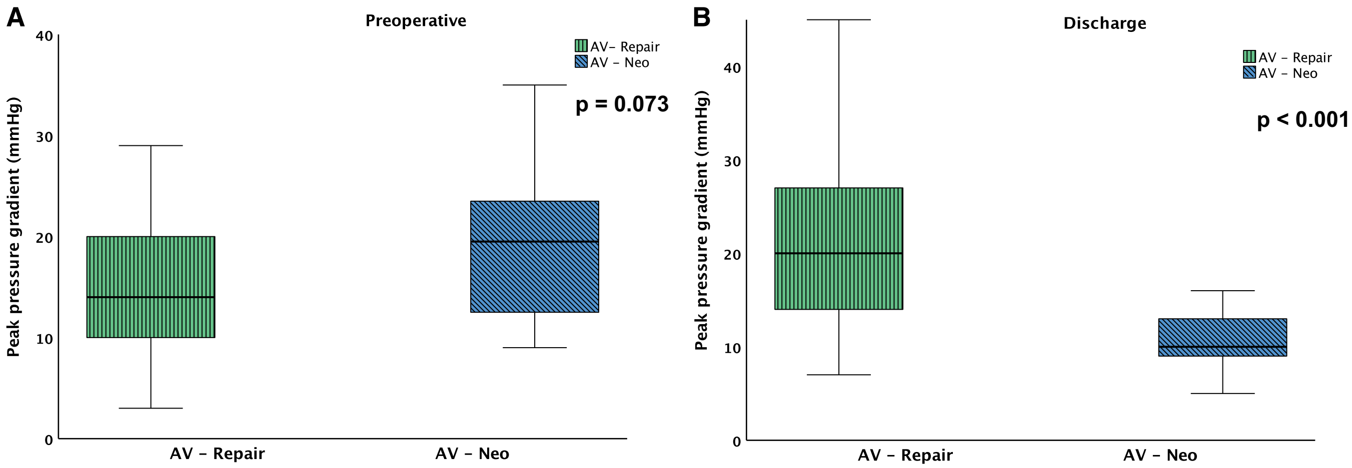


**Figure 1:** (**A**) Preoperative peak pressure gradients; (**B**) discharge peak pressure gradients. AV: aortic valve.

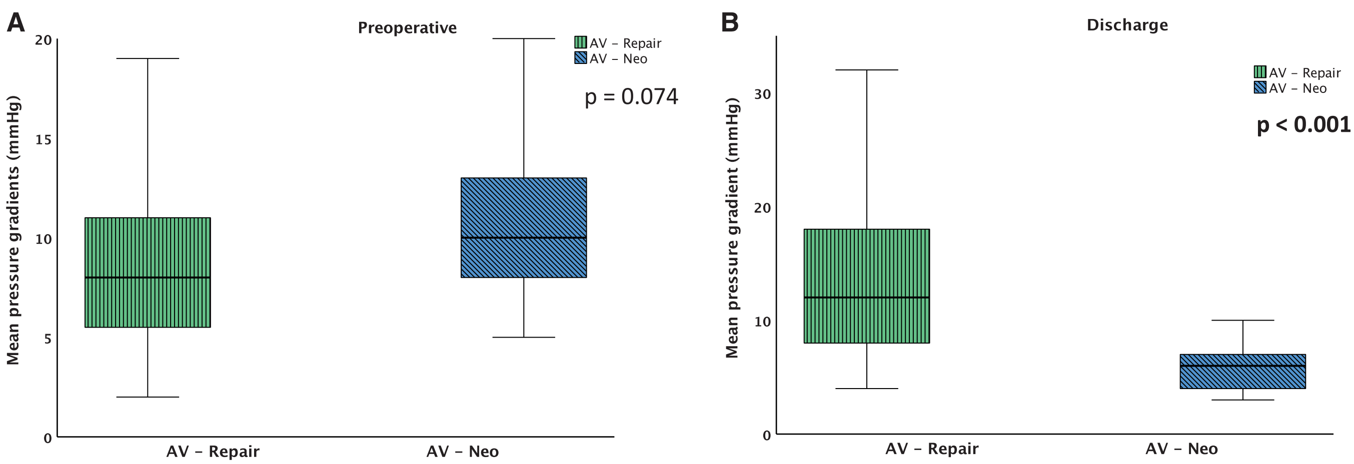


**Figure 2:** (**A**) Preoperative mean pressure gradients; (**B**) discharge mean pressure gradients. AV: aortic valve.

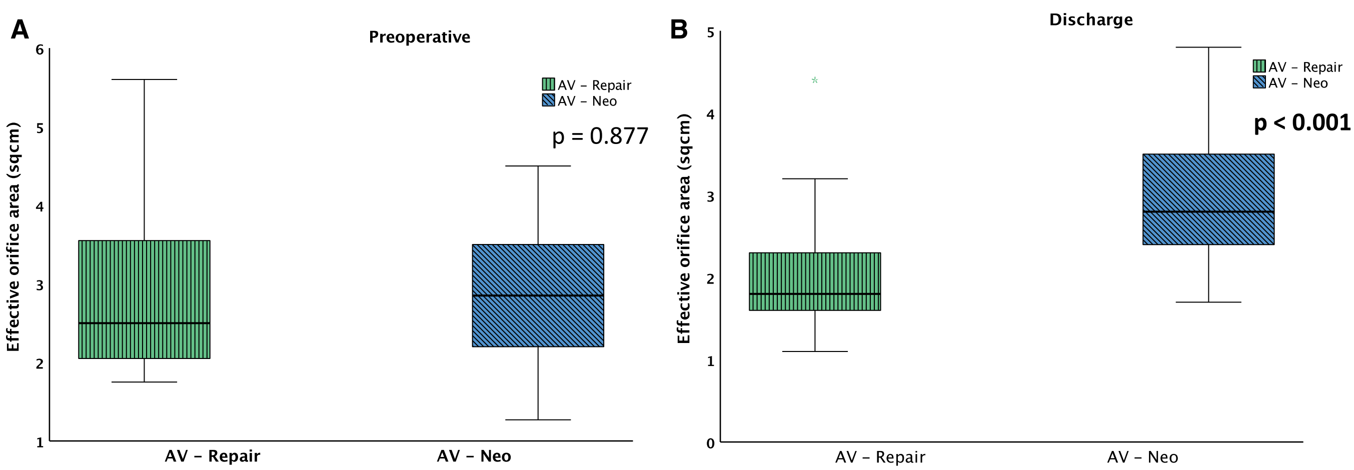


**Figure 3:** (**A**) Preoperative effective orifice area; (**B**) discharge effective orifice area. AV: aortic valve; Sqcm: square centimetre.

## Annulus size

In AV procedures, reduction and/or stabilization of the annular diameter may contribute achieving a sufficient effective height of the native cusp of ≥9 mm, which correlates with freedom from AR after AV-repair [21]. If the annulus surpasses 28 mm, a valve-sparing root replacement using the reimplantation technique prevents recurrent AR compared to subcommissural annuloplasty [22]. In our series, preoperative mean annulus diameter was 27.2 ± 3.4 mm in patients with AV-repair and 28.2 ± 2.3 mm in patients for AVNeo. In the AV-repair group patients were treated in 86.9% of the cases with subcommissural annuloplasty resulting in low reoperation rates during mid-term follow-up [16]. Despite these results, one should keep in mind that recent publications suggest to abandon the technique of subcommissural annuloplasty due to increased rates of reoperations [23]. In patients undergoing AVNeo, we did not perform any kind of annular stabilization. AVNeo cusps were tailored individually to each patients' annular dimension and will thus create a sufficient coaptation length. This is reflected by a mean coaptation length of 16.2 ± 1.9 mm in the present study population. This large coaptation length should allow for valve competence also in cases of progressive aortic annulus dilatation. Long-term results on valve competence and changes in coaptation length over time are needed to finally judge on the necessity of additional annulus treatment during AVNeo.)

## Limitations

Limitations of our study are the relatively small numbers and the limited follow-up time, especially for patients with AVNeo, as well as the retrospective design of this study. In addition, differences are not adjusted by possible confounders, so that the observed differences could be affected by undetected biases. Larger, randomized-controlled trials are necessary to address these points.

In conclusion, AV-repair and AVNeo are alternative treatment modalities for patients with BAVs and regurgitation. AVNeo resulted in a better early haemodynamic performance compared to AV repair in BAV morphology. Long-term data on AVNeo are an indispensable prerequisite to finally judge the value of AVNeo for the treatment of aortic valve pathologies.

**Conflict of interest:** Markus Krane discloses a financial relationship with Japanese Organization fo Medical Devic Development (JOMDD) and A. Duschek GmbH. All other authors have no conflicts of interest to declare.

## Data availability

The data underlying this article will be shared in reasonable request to the corresponding author.

## Author contributions

**Anatol Prinzing:** Conceptualization; Data curation; Formal analysis; Methodology; Validation; Visualization; Writing—original draft. **Johannes Böhm:** Data curation; Writing—review & editing. **Konstantinos Sideris:** Data curation; Writing—review & editing. **Keti Vitanova:** Formal analysis; Writing—review & editing. **Rüdiger Lange:** Supervision; Writing—review & editing. **Markus Krane:** Supervision; Writing—review & editing.

## Reviewer information

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