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OUTCOMES OF ISOLATED TRICUSPID AORTIC VALVE REPAIR FOR CUSP PROLAPSE: THE ROLE OF FENESTRATIONS

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Abbreviations and Acronyms

A

AR	Aortic regurgitation
ASD	Atrial septal defect
AV	Aortic valve
AVR	Aortic valve replacement
AVr	Aortic valve repair

B

BAV	Bicuspid aortic valve

C

CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
cH	Commissural height
CI	Confidence interval
COVID-19	Coronavirus Disease 2019

E

EACTS	European Association for Cardio-Thoracic Surgery
ECC	Extracorporeal circulation
EF	Ejection fraction
eH	Effective height
ESC	European Society of Cardiology

G

gH	Geometric height

H

HOCM	Hypertrophic obstructive cardiomyopathy
HR	Hazard ratio

I

IQR	Interquartile range

L

LCC	Left coronary cusp
LCS	Left coronary sinus
L/R com	Left/right commissure
LVEDD	Left ventricular end-diastolic diameter
LVESD	Left ventricular end-systolic diameter

M

mm	Millimetres
MVR	Mitral valve regurgitation

N

NCC	Non-coronary cusp
NCS	Non-coronary sinus
N/L com	Non/left commissure
No.	Number
NYHA	New York Heart Association

P

PCI	Percutaneous coronary intervention
PFO	Patent foramen ovale
Pre-op	Preoperatively
PTFE	Polytetrafluoroethylene

R

RCC	Right coronary cusp
RCS	Right coronary sinus
Reop	Reoperation
R/N com	Right/non commissure

S

SAS	Subaortic stenosis
SD	Standard deviation
STJ	Sinotubular junction

T

TAV	Tricuspid aortic valve
TEE	Transoesophageal echocardiography
TIA	Transient ischaemic attack
TVR	Tricuspid valve regurgitation

1 Abstract

Objective. The long-term outcomes of tricuspid aortic valve repair are not yet well-defined, and durability data are scarce. This study sought to investigate the long-term outcomes of tricuspid aortic valve repair in patients with preserved aortic root dimensions and moderate to severe aortic regurgitation secondary to cusp prolapse. Cusp prolapse was caused by cusp fenestration (group I) or myxomatous degeneration (group II). Differences in survival, repair durability, and freedom from post-operative complications between the two groups were analysed. Among patients with cusp fenestration (group I), the influence of different types of fenestration repair, different annuloplasty techniques, and the number of fenestrations requiring repair was investigated.

Methods. Between October 2000 and December 2020, 237 patients (mean age 62 ± 11 years, 93% male) underwent tricuspid aortic valve repair for aortic regurgitation secondary to cusp prolapse (fenestration n=94; myxomatous degeneration n=143). Patch repair was performed in 75 patients with cusp fenestration (autologous patch n=54; heterologous patch n=21). An annuloplasty was added in 82 patients in group I (subcommissural plication n=33, suture annuloplasty n=49). Follow-up data were analysed using time-to-event analyses; predictors of death, reoperation and recurrent regurgitation were identified using Cox regression. Follow-up was 97.1% complete (cumulative follow-up 1530 patient-years, median 69.0 months).

Results. Overall 10-year survival was 77.8%. Survival was better among patients with cusp fenestration ($p = 0.037$) and patients without cardiac comorbidities ($p = 0.002$). Freedom from reoperation was 86.1% after 10 years; reoperation-free survival was 66.9%. Overall 10-year freedom from aortic regurgitation ≥ grade 2 or reoperation was 52.7%, and it was significantly better in group I ($p = 0.033$). Different techniques of repair or annuloplasty, and the number of fenestrations did not influence survival or repair durability in group I. Aortic regurgitation at discharge was a significant predictor of reoperation, while involvement of the left coronary cusp was a significant predictor of recurrent aortic regurgitation or reoperation.

Conclusion. Tricuspid aortic valve repair of cusp prolapse with isolated aortic regurgitation is a safe procedure with acceptable long-term durability, even if prolapse is caused by cusp fenestration. Addition of a circumferential annuloplasty did not improve repair durability in this cohort. However, a low threshold for immediate reintervention after detection of more than mild residual aortic regurgitation (AR > 1) during the initial procedure may help improve the long-term durability of repair.

Zusammenfassung

Hintergrund. Die langfristigen Ergebnisse der Rekonstruktion trikuspider Aortenklappen bei moderater bis schwerer Aortenklappeninsuffizienz und erhaltenen Dimensionen der Aortenwurzel sind nicht umfassend beschrieben. Ziel dieser Arbeit war die Untersuchung langfristiger Ergebnisse der isolierten trikuspiden Aortenklappenrekonstruktion bei Aortenklappeninsuffizienz als Folge eines Taschenprolapses. Ein Prolaps war bedingt durch eine Fenestration (Gruppe I) oder eine myxomatöse Degeneration des Taschengewebes (Gruppe II). Gruppenunterschiede hinsichtlich des Überlebens, der Stabilität des Rekonstruktionsergebnisses und der Freiheit von post-operativen Komplikationen wurden analysiert. Bei Patienten mit Fenestration (Gruppe I) wurde außerdem der Einfluss verschiedener Techniken der Rekonstruktion und Annuloplastie sowie der Anzahl interventionsbedürftiger Fenestrationen untersucht.

Methodik. Zwischen Oktober 2000 und Dezember 2020 erhielten 237 Patienten (mittleres Alter 62 ± 11 Jahre, 93% männlich) eine isolierte trikuspide Aortenklappenrekonstruktion bei prolapsbedingter Klappeninsuffizienz (Fenestration n=94; myxomatöse Degeneration n=143). Eine Rekonstruktion mittels Perikardpatch wurde bei 75 Patienten mit Fenestration durchgeführt (autologer Patch n=54; heterologer Patch n=21). Zudem erhielten 82 Patienten der Gruppe I eine Annuloplastie (subkommissurale Plikation n=33, Naht-Annuloplastie n=49). Die Follow-up-Daten wurden mittels Ereigniszeitanalysen ausgewertet. Prädiktoren von Tod, Reoperation und erneuter Aortenklappeninsuffizienz wurden mittels Cox-Regression ermittelt. Das Follow-up war zu 97,1% vollständig und umfasst 1530 Patientenjahre (Median 69.0 Monate).

Ergebnisse. Das allgemeine 10-Jahres-Überleben lag bei 77.8%. Patienten mit Fenestration (p = 0.037) und Patienten ohne kardiale Komorbiditäten (p = 0.002) zeigten ein besseres Gesamtüberleben. Nach 10 Jahren lag die Freiheit von Reoperation bei 86.1%, das reoperationsfreie Überleben betrug 66.9%. Die Freiheit von erneuter Aortenklappeninsuffizienz ≥ 2 oder Reoperation betrug 52.7% nach 10 Jahren und war überlegen in Gruppe I (p = 0.033). Die verschiedenen Techniken der Rekonstruktion und Annuloplastie in Gruppe I hatten keinen Einfluss auf das Überleben oder die Stabilität des Rekonstruktionsergebnisses. In der Prädiktorenanalyse zeigte sich eine residuelle Insuffizienz bei Entlassung als Prädiktor für Reoperation und die Beteiligung der linkskoronaren Tasche als Prädiktor einer erneuten Aortenklappeninsuffizienz ≥ 2 oder Reoperation.

Schlussfolgerung. Die Rekonstruktion trikuspider Aortenklappen mit Taschenprolaps und isolierter Aortenklappeninsuffizienz ist ein sicheres Verfahren mit einer akzeptablen Langzeitstabilität, auch wenn der Taschenprolaps durch eine Fenestration verursacht wird. Die zusätzliche Anlage einer Naht-Annuloplastie hatte keinen Einfluss auf die Stabilität der Rekonstruktion. Eine großzügige Indikationsstellung zur Reintervention bei persistierender, mehr als milder Aortenklappeninsuffizienz (> Grad 1) nach Abschluss der initialen Rekonstruktion könnte dazu beitragen, die Freiheit von Reoperation weiter zu verbessern.

2 Introduction

2.1 Anatomy of the Aortic Valve

The aortic valve (AV) is one of the human heart's four valves. It has a primary function of ensuring an intermittent, unidirectional flow of blood from the left ventricle to the ascending aorta [118]. Anatomically, the AV lies within the aortic root, which serves as a bridge between the left ventricle and the ascending aorta. The aortic root extends from the basal ring to the sinotubular junction (Figure 1, Panel a) [39]. The terms "basal ring" and "aortic annulus" are synonyms commonly used to refer to a virtual ring passing through the nadir of each aortic cusp (Figure 1, Panel b; Figure 2) [124].

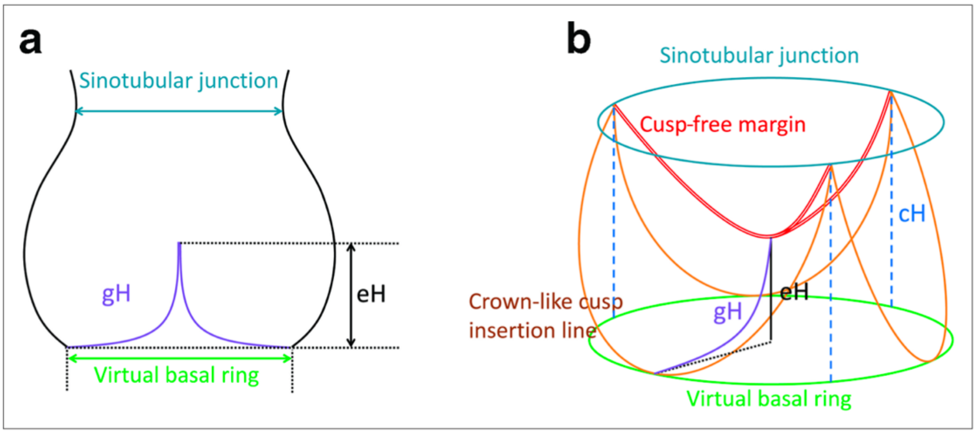


Figure 1. *Schematic Drawing of the Aortic Root (Panel a) and the Tricuspid Aortic Valve (Panel b) [105]. cH*, commissural height; *eH*, effective height; *gH*, geometric height.[1]

The ventriculoaortic junction is defined as the zone where the aortic wall attaches to the left ventricle [39]. It is a curvilinear three-dimensional structure due to the aortic root's asymmetrical external aspect (Figure 2) [39]. As a result, the ventriculoaortic junction lies above the basal ring between the left/right commissure and the right/non commissure. It corresponds to the level of the basal ring at the non/left commissure and in parts of the non-coronary and left coronary sinuses (Figure 2) [39].

[1] Reprinted from Schäfers [105] with permission from SAGE Publications.

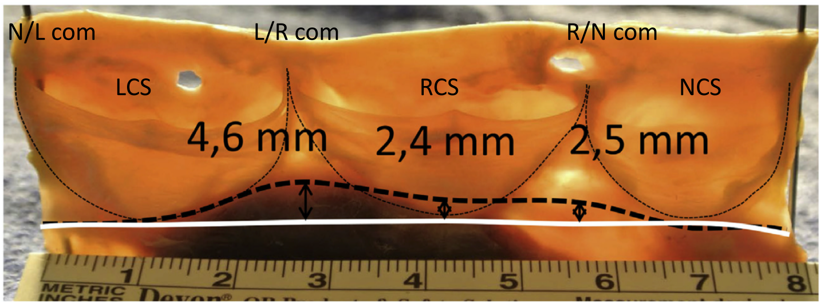


Figure 2. *Intraluminal View of the Aortic Root, Opened Longitudinally [39]. White Line = Basal Ring; Dashed Black Line = Ventriculoaortic Junction.*
LCS, left coronary sinus; *L/R com*, left/right commissure; *NCS*, non-coronary sinus; *N/L com*, non/left commissure; *RCS*, right coronary sinus; *R/N com*, right/non commissure.[2,3]

The AV consists of the aortic valve cusps, the sinuses of Valsalva, and the interleaflet triangles [11, 78]. It has a number of morphologic subtypes, including the unicuspid, bicuspid, tricuspid and quadricuspid aortic valve. Each of these subtypes is characterised by distinctive geometric features [105]. The tricuspid aortic valve (TAV) is the most frequent morphologic subtype [118], and the focus of this study. Figure 1 shows a schematic drawing of the aortic root (Panel a) and the TAV (Panel b). The TAV features three equally sized valve cusps [42], which attach to the aortic wall and coalesce to form three equally distributed commissures at the level of the sinotubular junction [42]. The cusp nadirs define the level of the basal ring [39, 105].

Important geometrical parameters that influence TAV function include free margin length [42], coaptation surface [42], geometric height [gH; 104] and effective height [eH; 101]. In morphologically normal TAVs, average free margin length and coaptation surface are similar across all three cusps [42]. Free margin length averages around 34 mm in adults, while the coaptation surface accounts for about 40% of the cusp surface [42].
The cusps' gH is defined as the longest distance between the cusp nadir and the free margin at the centre of the cusp (Figure 1) [104]. It is a measure of tissue quantity and should be at least 17mm in adults [104]. eH is defined as the distance between the basal ring and the free margin at the centre of the cusp (Figure 1) [101]. It is used to identify cusp prolapse and should be approximately 9 to 10mm in adults [13]. Both eH and gH can be measured intraoperatively and have become integral parameters in aortic valve repair [13, 74, 103].

[2] Numbers (in mm) indicate distance between basal ring and ventriculoaortic junction at the left/right commissure (4.6mm), the right coronary sinus (2.4mm), and the right/non commissure (2.5mm).
[3] Adapted from de Kerchove et al. [39] with permission from Elsevier.

2.2 Valvular Diseases of the Aortic Valve

2.2.1 Aortic Stenosis

Aortic stenosis is defined as an abnormal narrowing of the aortic valve orifice. It is the most prevalent valvular heart disease requiring surgical or catheter intervention in Europe and North America [121]. The most common causes of aortic stenosis include calcific degeneration, rheumatic heart disease and congenital aortic stenosis [26, 64].

2.2.2 Aortic Regurgitation

Aortic regurgitation (AR) is the diastolic reflux of blood from the aorta into the left ventricle. It is the third most common valvular heart disease in western countries behind aortic stenosis and mitral regurgitation [10, 64, 65]. According to recent estimates, AR accounts for up to 20% of valvular heart disease diagnoses [10]. Furthermore, AR affects a significant proportion of the population, with the Framingham Offspring population-based cohort study estimating prevalence at 13.0% in men and 8.5% in women in the United States. Moderate to severe AR was found in 0.5% of the study cohort [111]. Similar results were reported by Nkomo and colleagues [88], who summarised echocardiographic data for over 11,900 participants enrolled in three large, population-based epidemiological studies. National prevalence of moderate to severe AR in the United States adult population was estimated at 0.5%. Additionally, its prevalence was shown to increase with age: 1% of participants aged 65 to 74 and 2% of participants over 75 were found to have moderate to severe AR [88]. In summary, moderate to severe AR represents an important public health concern [88].

AR develops as a result of pathology of the valve cusps and/or dilatation of the aortic root and ascending aorta [83, 121]. More specifically, the mechanisms leading to AR caused by valvular pathology are cusp prolapse, cusp retraction or cusp perforation [18, 105].

Possible aetiologies of AR caused by valvular pathology include age-related degeneration, congenital causes (e.g., bicuspid valve morphology), rheumatic heart valve disease, and endocarditis; traumatic injuries are rare [83, 121]. Furthermore, the leading aetiologies of AR differ significantly between developing countries, where AR is mostly attributed to rheumatic heart disease [83], and Western Europe and North America, where AR is predominantly caused by degenerative or congenital diseases [65].

2.2.3 Natural History of Severe Aortic Regurgitation

Severe AR is a serious condition with a limited prognosis. It leads to development of left ventricular dilatation and dysfunction, debilitating clinical symptoms (e.g., dyspnoea, fatigue, chest pain, palpitations), heart failure, and ultimately death, especially if managed conservatively [15, 45, 56, 63].

A number of prognostic factors associated with poor patient outcomes have been identified. These include symptom severity [45], a reduced ejection fraction (EF; <55%) [45], and AR severity [44]. Severely symptomatic patients (NYHA III – IV) have a yearly death rate of up to 25% [45]. Even mild symptoms (NYHA II) are associated with a significant increase in mortality compared to the general population [45].

In asymptomatic patients, a reduced EF has been associated with a significant increase in mortality [45]. Moreover, more severe AR has been associated with an increased risk of cardiac death, congestive heart failure and new onset of atrial fibrillation [44]. In addition, a reduced EF, an enlarged left ventricular end-systolic diameter (LVESD), and high symptom severity (NYHA III – IV) have been identified as risk factors for poorer survival even after surgical aortic valve replacement [16, 28, 49, 58, 120].

In summary, chronic severe AR is associated with high rates of morbidity and mortality if left untreated. Surgical treatment is associated with decreased cardiac mortality, however post-operative outcomes are significantly better if patients undergo surgery before they become symptomatic or develop severe left ventricular dysfunction [16, 28, 90, 120, 121, 122].

2.3 Surgical Treatment of Aortic Regurgitation: Aortic Valve Replacement

Surgical management of severe AR significantly reduces cardiac mortality, morbidity, left ventricular dimensions and symptom severity, while improving left ventricular function [28, 45, 116, 120, 122]. Current European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines [121] recommend surgical intervention in:

- symptomatic patients with chronic severe AR (unless the operative risk is prohibitive),
- asymptomatic patients with impaired left ventricular function (resting EF ≤ 50%) or left ventricular enlargement (LVESD > 50 mm or LVESD > 25 mm/m^2 body surface area in patients with small body size), and
- symptomatic or asymptomatic patients undergoing heart surgery for another indication (surgery of the ascending aorta or another valve, coronary artery bypass grafting).

Aortic valve replacement (AVR) has long been the predominant approach to surgical management of severe AR [83]. It is “the standard procedure in the majority of patients with aortic regurgitation” (p. 579) according to the current ESC/EACTS guidelines [121].

There are two types of prostheses that are commonly used for valve replacement: mechanical and biological prosthetic valves. These protheses differ markedly in their respective strengths and drawbacks. Mechanical aortic valves require life-long anticoagulation. Consequently, they are associated with an increased incidence of bleeding events [30, 57, 91]. Indeed, the annual risk of serious haemorrhage after implantation of a mechanical aortic valve is approximately 1 to 2% [66, 91, 93, 113]. On the other hand, risk of reoperation is comparatively low [30, 57, 91, 113] and can be estimated at around 1% per year [57, 60, 66, 91].

Biological valve prostheses do not require anticoagulation, resulting in a reduced risk of bleeding [30, 91, 93]. However, structural valve degeneration (e.g., calcification, leaflet flail) and reoperation are significantly more common following implantation of a biological valve [30, 57, 91, 113]. Structural valve degeneration is estimated at 1.5% per year in patients under 65 [57] and reoperation can generally be estimated at around 2% per year [57, 91, 93, 113].
Additionally, the temporal patterns of these complications are important: first, progression of structural valve degeneration is age-dependent. Consequently, freedom from reoperation is significantly lower among patients under 60 years at implantation than in older people [12, 29, 48, 67]. In fact, some studies have reported 15-year reoperation rates of up to 20 to 40% in patients under 60 [29, 48, 67]. Second, primary valve failure in biological valves begins around 7 years after implantation, and failure rates increase noticeably thereafter [57, 91]. This increase in rates of valve failure has been used to explain the rise in long-term excess deaths observed in patients with biological valves after approximately 10 years of follow-up [57].

Mechanical and biological prostheses differ in their association with specific complications, as outlined above. However, long-term survival and overall freedom from valve-related complications are similar following implantation of either prosthesis [30, 57, 91, 93, 113]. As a result, the choice of prosthesis should be based on individual patient characteristics as well as patient preference [121]. Mechanical aortic valves should be considered in patients with long life expectancies, such as patients under the age of 60 to 65, without contraindications to anticoagulation [90, 121]. Biological valves should primarily be considered in patients over 65, in patients with a limited life expectancy, and in patients in whom anticoagulation is contraindicated [90, 121].
In summary, AVR is associated with improved survival, improved left-ventricular function, reduced morbidity, and reduced symptom severity in patients with severe aortic regurgitation [28, 45, 116, 120]. Nevertheless, AVR is also associated with valve-related excess mortality compared to the general population [53, 72]. In addition, patients face a significant cumulative long-term risk of enduring valve-related complications [57, 66, 91, 93, 113]. Essentially, an ideal substrate for prosthetic valves, which would ensure durability and obviate the need for life-long anticoagulation, does not yet exist. As a result, possible alternatives to AVR, such as aortic valve repair, have been explored and developed over the last two decades [2, 18].

2.4 Surgical Treatment of Aortic Regurgitation: Aortic Valve Repair

Over the last 20 years, a number of expert centres have specialised in aortic valve repair (AVr) to develop an attractive alternative to valve replacement [2, 95]. It is not a new approach, with case reports of successful interventions dating back to the early 1960s [e.g., 52]. However, it has since been reintroduced and refined in an attempt to circumvent some of the problems associated with prosthetic valves [2, 95].

AVr involves preserving the original cusp tissue and reconstructing the valve in a way that re-establishes its competence. The goal is to emulate the success of mitral valve repair, which has long been considered the gold standard for treating mitral regurgitation [121]. Mitral valve repair provides excellent long-term results with low rates of reoperation or complications [22, 77], while obviating the need for anticoagulation. Similarly, AVr has shown superior freedom from valve-related complications compared to valve replacement [2, 115]. Specifically, it is associated with low rates of thromboembolic events, serious bleeding events, and a low incidence of endocarditis [2, 9, 95, 115]. Thus, it is not surprising that the proportion of regurgitant aortic valves now being repaired, rather than replaced, has increased significantly over the last 20 years [64, 65].

Nevertheless, approaches to AVr often remain piecemeal. They still largely lack standardized techniques with reproducible outcomes for specific pathologies [105]. A notable exception is the subgroup of patients with bicuspid aortic valves, for whom indications for surgical repair, appropriate repair strategies, and risk factors for poor outcomes are already well-defined [41, 46].

2.4.1 Aortic Valve Repair of the Bicuspid Aortic Valve

The bicuspid aortic valve (BAV) is a common congenital abnormality found in 0.5 to 2% of adults [23]. Approximately 13 to 30% of individuals with a BAV will develop moderate to severe AR throughout their life [81]. Repair of the BAV was introduced in the early 1990s [34, 50] and has undergone continuous refinement. Notable improvements include the development of methods for a standardized assessment of BAV geometry [101, 104], the identification of risk factors for repair failure [3, 17, 69, 86, 106], and the development of evidence-based strategies to address these risk factors [3, 38, 75, 107, 108].

Additionally, de Kerchove and colleagues recently put forward a new repair-oriented classification of BAVs [41]. This classification provides practical guidance to aid decision-making in specific repair scenarios. Unfortunately, a similarly structured, evidence-based approach to tricuspid aortic valve repair does not yet exist.

2.4.2 Aortic Valve Repair of the Tricuspid Aortic Valve

Empirical evidence regarding AVr of the TAV is less compelling than for BAVs. There is a particular paucity of evidence concerning long-term repair outcomes in patients with isolated AR [43, 115]. Isolated AR is defined as AR in patients with normal morphology of the ascending aorta. One reason for the lack of data is that isolated AR in TAVs is relatively rare: it is only present in approximately 10% of patients undergoing AVr [102, 115]. As a result, even high-volume centres may struggle to accumulate a sample that is big enough to allow for meaningful conclusions to be drawn [43].

Furthermore, repair of a TAV is more challenging than repairing a BAV, because it involves three coaptation surfaces instead of a single coaptation line. As a result, valve competence is more difficult to achieve [115]. Thus, some surgeons might be less inclined to attempt a repair, and might choose to replace these valves instead.

Nevertheless, two recent studies have shown that TAV repair for isolated AR is a safe procedure with low hospital mortality and acceptable long-term survival [109, 115]. In fact, patients' survival normalized following surgery, so that post-operative survival did not differ significantly from that of the age- and sex-matched general population [109, 115]. Freedom from reoperation at 15 years was lower than following BAV repair [106], but comparable to aortic valve replacement using a biological valve in a similar age group [20, 109, 115]. Predictors of late reoperation were severe preoperative AR [109], more than mild AR at discharge [109], and left coronary cusp repair [115], which was interpreted as an indicator of more diffuse disease. Valve-related events were rare [109, 115]. Younger age, need for pericardial patch repair and greater left ventricular end-diastolic diameter were identified as predictors of recurrent severe AR [115].

However, a methodological weakness of both studies is that their cohorts were not homogenous with regards to the causal mechanism of AR. The most common mechanism in both cohorts was cusp prolapse. Nevertheless, both studies also included patients with other valvular pathologies, such as perforation, fenestration or retraction. Some of these pathologies required patch repair, which has been postulated as a risk factor for repair failure [69, 106, 115]. As a result, drawing conclusions about the appropriateness and success of AVr in the context of specific cusp pathologies in TAVs remains difficult.

2.5 Cusp Prolapse as a Cause of Isolated Aortic Regurgitation in Tricuspid Aortic Valves

Cusp prolapse appears to be the most common cause of isolated AR in TAVs [9, 74, 109, 115]. Prolapse can be defined as an eH of less than 9mm, or a free margin height that falls below that of adjacent cusps [74, 105]. Common causes of cusp prolapse include myxomatous degeneration and cusp fenestration [74, 102].

2.5.1 Myxomatous Degeneration as a Cause of Cusp Prolapse in Tricuspid Aortic Valves

Myxomatous degeneration is a histological diagnosis of extensive acid mucopolysaccharide deposition in the heart valves [119]. The deposition of acid mucopolysaccharides causes structural changes to the zona fibrosa and zona spongiosa: it alters the cusps' normal histological anatomy and predisposes them to prolapse [119]. Myxomatous degeneration is a common cause of severe isolated AR [1, 102, 119].

The most common technique for repairing cusp prolapse is central plication (Figure 3) [102]. Alternatively, cusp resuspension can be used, for which a running polytetrafluoroethylene (PTFE) suture is placed in the free margin [74]. Additionally, triangular resection of cusp tissue can be used in cusps with significant amounts of excess tissue.

The repair goal is to increase the prolapsing cusp's eH and to achieve a uniform free margin height for all three cusps [74]. Previous studies have shown that these repair techniques are principally safe and stable in the mid- to long term [102, 109, 115]. In this study, we aim to analyse the long-term outcomes of prolapse repair in a homogenous cohort of patients with isolated AR caused by cusp prolapse secondary to myxomatous degeneration.

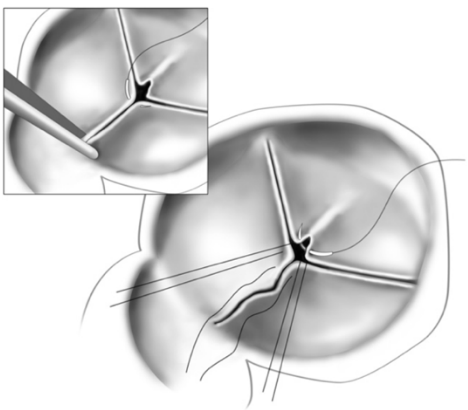


Figure 3. *Drawing of a TAV Illustrating Cusp Plication as a Technique of Prolapse Repair* [102]. *Interrupted Plicating Sutures Are Added to Reduce the Free Margin Length of the Prolapsing Cusp. TAV*, tricuspid aortic valve.[4]

[4] Reprinted from Schäfers et al. [102] with permission from Elsevier.

2.5.2 Fenestrations as a Cause of Cusp Prolapse in Tricuspid Aortic Valves

Fenestrations are tissue defects near the valves' commissures, which are located just below the cusp's free margin (Figure 4). They typically lie within the cusps' coaptation zone and as such do not normally cause AR [74]. Nevertheless, two mechanisms can cause fenestration-derived cusp prolapse and subsequent AR: first, a large tissue defect that extends below the line of coaptation can alter cusp geometry and result in compromised valve competence [27, 51, 68]. Second, elongation or rupture of the free margin above a fenestration can also lead to cusp prolapse (Figure 4) [14, 19, 36, 51, 79, 80, 82, 87, 96]. In these cases, fenestration repair (or valve replacement) is indicated [74, 105].

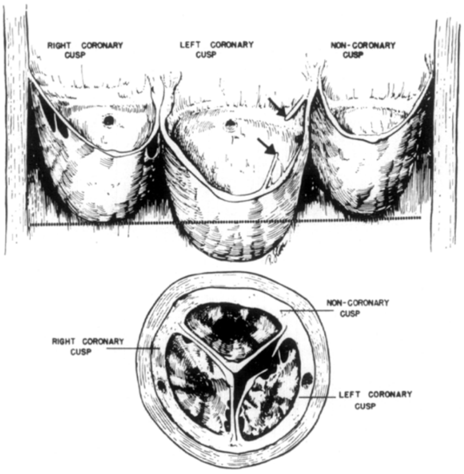


Figure 4. *Drawing of a TAV Illustrating the Typical Location of Cusp Fenestrations. The LCC Prolapsed Following Rupture of the Fibrous Strand Covering the Fenestration, Causing AR [80]. AR*, aortic regurgitation; *LCC*, left coronary cusp; *TAV*, tricuspid aortic valve.[5]

Fenestrations can either be closed directly with sutures, or using a patch (e.g., autologous or heterologous pericardium) [102, 105]. Previous investigations have shown that autologous and heterologous pericardium have similar, acceptable long-term durability in patch repair [8]. However, only a single case series examining the specific outcomes of fenestration repair has been published to date [102]. Other publications focusing specifically on the surgical treatment of fenestrations tend to be case reports, have very limited follow-up, and commonly describe valve replacement rather than repair [6, 61, 62, 79, 84, 85, 89, 99, 114, 123].

Schäfers et al. [102] reported acceptable mid-term durability of fenestration repair in a sample of 39 patients with TAVs. Fenestrations were closed using a pericardial patch. Their results suggest that fenestrations per se might not be a risk factor for repair failure in TAVs. Similarly,

[5] Reprinted from Marcus et al. [80] with permission from Elsevier.

patch repair may not inevitably lead to poor repair outcomes; for example, Karliova and colleagues [69] showed that the durability of patch repair appears to be superior in TAVs compared to BAVs. Furthermore, repair durability seems to vary depending on the underlying cusp pathology [69]. In fact, the most durable repair results were achieved when a patch was used to close a fenestration in a TAV.

Thus, this study aims to compare the repair outcomes of patients with isolated AR caused by cusp prolapse secondary to either fenestration or myxomatous degeneration. In doing so, it aims to evaluate whether fenestrations are a risk factor for repair failure in TAVs. Additionally, this study aims to compare the outcomes of different types of fenestration repair in a homogenous sample of patients with isolated AR caused by cusp prolapse secondary to cusp fenestration.

2.6 The Role of Annuloplasty in Tricuspid Aortic Valve Repair

Annuloplasty techniques are routinely used for additional stabilisation of AVr, even in isolated AR [74]. A number of different techniques have been used and developed over the last decades. Cabrol's [25] subcommissural plication was initially widely adopted, however some data suggest that the annuloplasty effect might not persist [38]. Today it has mostly been replaced by circumferential annuloplasty techniques, which are known to improve durability in BAVs [75, 107].

Nevertheless, a similar benefit of circumferential annuloplasty techniques has not yet been shown in TAVs. A recent investigation by Tamer and colleagues [115] failed to demonstrate an improvement in TAV repair durability among patients who had received a circumferential annuloplasty instead of Cabrol's subcommissural plication. This study seeks to analyse the impact of annuloplasty techniques on repair stability in patients with TAVs undergoing aortic valve repair for isolated AR secondary to cusp fenestration.

2.7 Research Objective

In summary, repair is an attractive alternative to valve replacement in the treatment of AR in TAVs due to the low incidence of valve-related complications. However, appropriate surgical techniques for TAV repair and risk factors for poor repair outcomes are not yet well defined. Additionally, results differ depending on the underlying valvular pathology [9]. Thus, it is critical to analyse the outcomes of well-defined surgical techniques in cohorts featuring the same underlying pathology to allow for a more nuanced, evidence-based repair approach in the future.

The objective of the current study was to evaluate the long-term durability of AVr in patients with TAVs and isolated AR caused by cusp prolapse secondary to either myxomatous degeneration or cusp fenestration. Specifically, this study sought to answer the following questions:

1. What are the long-term outcomes of aortic valve repair for cusp prolapse secondary to myxomatous degeneration or cusp fenestration in terms of (a) survival, (b) freedom from AV reoperation, (c) freedom from post-operative complications or (d) freedom from recurrent AR ≥ 2 or AV reoperation?

2. Are fenestrations requiring repair a risk factor for (a) shorter survival, (b) lower freedom from AV reoperation, (c) lower freedom from post-operative complications or (d) lower freedom from recurrent AR ≥ 2 or AV reoperation following aortic valve repair?

3. Does the type of fenestration repair (autologous patch, heterologous patch, direct suture) influence (a) survival, (b) freedom from AV reoperation, (c) freedom from post-operative complications or (d) freedom from recurrent AR ≥ 2 or AV reoperation following aortic valve repair?

4. Does the type of annuloplasty (subcommissural plication, circular suture annuloplasty) influence (a) survival, (b) freedom from AV reoperation, (c) freedom from post-operative complications or (d) freedom from recurrent AR ≥ 2 or AV reoperation following aortic valve repair in fenestrated aortic valves?

3 Method and Materials

3.1 Study Population

Between October 2000 and December 2020, 441 consecutive patients underwent isolated aortic valve repair of a tricuspid aortic valve at Saarland University Medical Centre (Figure 5). Careful review of the operative reports identified cusp prolapse as the primary cause of aortic regurgitation in 266 patients (60.3%). The remaining 175 patients (39.7%) were excluded from this study.

A further 28 patients were excluded because preoperative aortic regurgitation was not sufficiently severe (n=15), because they were younger than 15 at the time of operation (n=7), because they suffered from a severe congenital cardiac comorbidity (n=5), or because they had previously undergone aortic valve repair (n=1; Figure 5). One patient declined to participate. The eligibility criteria for this study are summarised in Figure 5.

In total, 237 patients fulfilled the eligibility criteria and were selected to take part in this study. Surgical treatment of AR was indicated in all 237 patients in accordance with the current ESC/EACTS guidelines for the management of valvular heart disease [121].

Age at operation ranged from 15 to 83 years and mean age at operation was 62 ± 11 years (median 63, interquartile range (IQR) 14); 221 patients (93.2%) were male (Table 1).

Following inclusion, patients were divided into two groups based on the mechanism of cusp prolapse:

- In 94 patients, cusp prolapse was caused by cusp fenestration. This group will be referred to as 'group I' or 'group fenestration + prolapse'.
- In the remaining 143 patients, cusp prolapse was caused by myxomatous degeneration. This group will be referred to as 'group II' or 'group prolapse'.

This study was approved by the regional ethics committee, which waived patient consent for the analysis and publication of anonymized patient data (Ethikkommission der Ärztekammer des Saarlandes, 202/19).

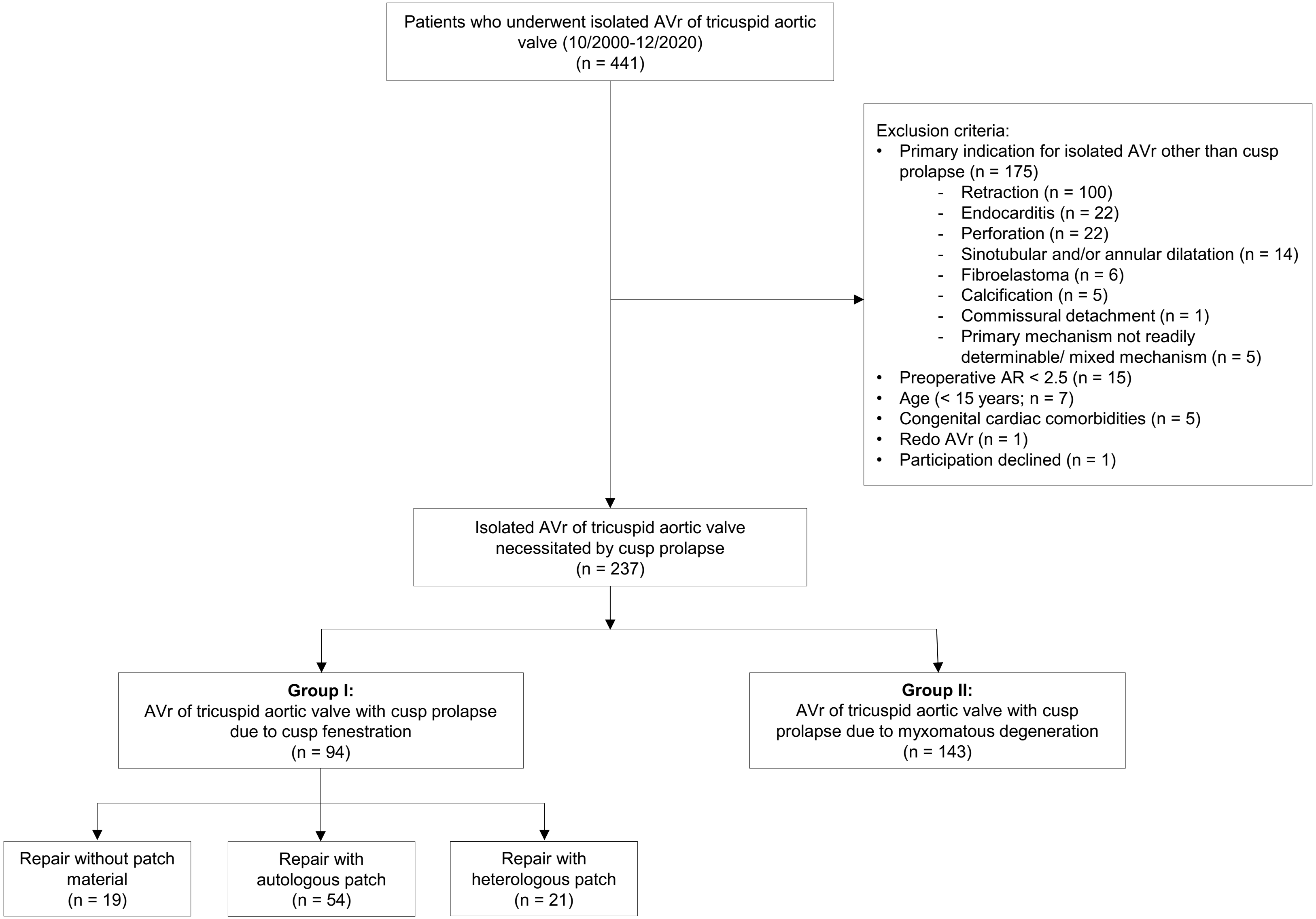


Figure 5. *Eligibility Criteria and Selection of Study Population. AR*, aortic regurgitation; *AVr*, aortic valve repair.

3.1.1 Group I (Fenestration + Prolapse)

Mean age at operation was 58 ± 12 years (median 60, IQR 14); 85 patients (90.4%) were male. Preoperative patient characteristics are summarised in Table 1. Three patients (3.2%) had previously undergone heart surgery (Table 1) and 2 patients (2.1%) had previously undergone percutaneous coronary intervention (PCI) for coronary artery disease (CAD). Preoperative AR was severe in 89 patients (94.7%) and moderate-to-severe in 5 patients (5.3%).

Cardiac comorbidities requiring concomitant surgical intervention were present in 33 patients (35.1%). They are summarised in Table 2. The most common comorbidity requiring intervention was CAD (23.4%), and patients with CAD underwent concurrent coronary artery bypass graft surgery (CABG).

3.1.2 Group II (Prolapse)

Mean age at operation was 64 ± 9 years (median 65, IQR 12); 136 patients (95.1%) were male. Preoperative patient characteristics are summarised in Table 1. Eight patients (5.6%) had previously undergone heart surgery (Table 1) and 2 patients (1.4%) had previously undergone PCI for CAD. Preoperative AR was severe in 132 patients (92.3%) and moderate-to-severe in 11 patients (7.7%).

Cardiac comorbidities requiring concomitant surgical intervention were present in 78 patients (54.5%); they are summarised in Table 2. Common comorbidities were CAD requiring CABG (18.9%), atrial fibrillation requiring surgical ablation (25.2%), mitral valve regurgitation requiring mitral valve repair (28.0%), and tricuspid valve regurgitation requiring tricuspid valve repair (20.3%).

Characteristic	Value			
	Fenestration + Prolapse (n=94)	Prolapse (n=143)	All (n=237)	*p*-value
Age (years)	58 ± 12	64 ± 9	62 ± 11	**< 0.001**
Sex				0.160
male	85 (90.4)	136 (95.1)	221 (93.2)	
female	9 (9.6)	7 (4.9)	16 (6.8)	
Previous cardiac surgery	3 (3.2)	8 (5.6)	11 (4.6)	0.534
CABG	2 (2.1)	3 (2.1)	5 (2.1)	1.000
Mitral valve repair	-	1 (0.7)	1 (0.4)	1.000
CABG + mitral valve repair	-	1 (0.7)	1 (0.4)	1.000
ASD closure	-	1 (0.7)	1 (0.4)	1.000
Septal myectomy	1 (1.1)	1 (0.7)	2 (0.8)	1.000
SAS resection	-	1 (0.7)	1 (0.4)	1.000
Degree of preoperative AR				
2 - 3	5 (5.3)	11 (7.7)	16 (6.8)	0.601
3	68 (72.3)	106 (74.1)	174 (73.4)	0.761
3 - 4	11 (11.7)	8 (5.6)	19 (8.0)	0.090
4	10 (10.6)	18 (12.6)	28 (11.8)	0.649
LVEDD (mm)	63.9 ± 7.7	62.2 ± 7.5	62.8 ± 7.7	0.120

Table 1. *Preoperative Patient Data.*

Values are n (%) or mean ± SD. Percentages may not total 100 because of rounding. The *p*-value relates to statistical differences between groups I (Fenestration + Prolapse) and II (Prolapse). *AR*, aortic regurgitation; *ASD*, atrial septal defect; *CABG*, coronary artery bypass graft surgery; *LVEDD*, left ventricular end-diastolic diameter; *SAS*, subaortic stenosis.

3.2 Comparison of Group Characteristics

Patients with myxomatous degeneration (group II) were significantly older than patients with cusp fenestration (group I; $p < 0.001$), and had significantly more cardiac comorbidities requiring concomitant surgical intervention ($p = 0.003$). Atrial fibrillation ($p = 0.006$), mitral valve regurgitation ($p < 0.001$), and tricuspid valve regurgitation ($p = 0.001$) were more common in patients with myxomatous degeneration.

The two groups did not differ in terms of frequency and type of previous cardiac interventions or the distribution of preoperative AR.

Cardiac Comorbidity	Concomitant Surgical Intervention	Value			
		Fenestration + Prolapse (n=94)	Prolapse (n=143)	All (n=237)	*p*-value
CAD	CABG	23 (24.5)	27 (18.9)	50 (21.1)	0.302
Atrial fibrillation	Surgical ablation	10 (10.6)	36 (25.2)	46 (19.4)	**0.006**
Mitral valve regurgitation	Mitral valve repair	8 (8.5)	40 (28.0)	48 (20.3)	**< 0.001**
Tricuspid valve regurgitation	Tricuspid valve repair	5 (5.3)	29 (20.3)	34 (14.3)	**0.001**
ASD/PFO	Surgical closure	1 (1.1)	7 (4.9)	8 (3.4)	0.151
HOCM	Septal myectomy	1 (1.1)	2 (1.4)	3 (1.3)	1.000
Subaortic stenosis	Resection of subaortic stenosis	-	1 (0.7)	1 (0.4)	1.000

Table 2. *Cardiac Comorbidities Requiring Concomitant Surgical Intervention.*
Values are n (%). Percentages may not total 100 because of rounding. The *p*-value relates to statistical differences between groups I (Fenestration + Prolapse) and II (Prolapse). *ASD*, atrial septal defect; *CABG*, coronary artery bypass graft surgery; *CAD*, coronary artery disease; *HOCM*, hypertrophic obstructive cardiomyopathy; *PFO*, patent foramen ovale.

3.3 Surgical Technique

Transoesophageal echocardiography (TEE; Vivid E9, General Electric Company, Fairfield, Connecticut, USA; Sequoia, Siemens, Erlangen, Germany) was used to measure aortic root dimensions and the degree of AR before the procedure. Measurements of the sinotubular junction and sinus diameter were taken in diastole; the annular diameter was measured in systole. An isolated valve repair strategy without concomitant root repair was pursued if the sinus diameter was ≤ 43 mm.
The degree of AR (grade 1 – 4) was determined pre- and post-operatively according to current recommendations [125].

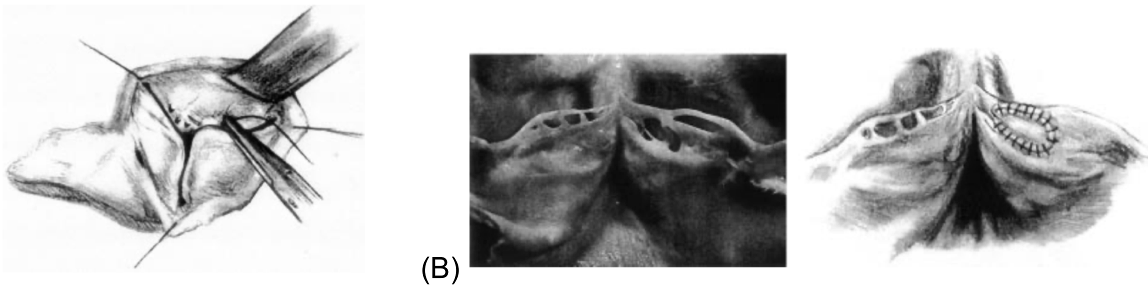
All patients underwent operation via median sternotomy and were placed on extracorporeal circulation. The aorta was cross-clamped and opened using a transverse incision. The incision was made approximately 1 centimetre above the sinotubular junction. Cardioplegia was given directly into the coronary ostia. Stay sutures were placed into the commissures and kept under tension, while carefully maintaining their circumferential orientation. The annular diameter was measured using direct intubation with Hegar dilators.
The aortic valve was carefully inspected and cusp geometry was assessed for each cusp by measuring its geometric and effective height. A minimum geometric height of 18mm was used as a prerequisite for aortic valve repair [105]. The effective height was considered to lie within the normal range if it was 9 – 10 mm, or 45% of the geometric height in small cusps [101]. Prolapse was defined as an effective height of 8 mm or less, or a free margin height at a level of ≥ 2 mm below that of adjacent cusps [9, 105]. If all 3 cusps were affected by prolapse, 1 or 2 cusps were corrected to an effective height of 9 mm and used as reference for the remaining cusps.

The techniques used for correction of cusp prolapse have been described before [4]. Prolapse was routinely corrected using central cusp plication: interrupted sutures were placed centrally in the affected cusps to reduce tissue redundancy until an effective height of 9 – 10 mm was reached (Figure 6, Panel A).
Triangular resection of cusp tissue in the central cusp area was performed in instances of marked tissue redundancy. Correction of cusp prolapse was considered adequate once the 3 free margins were at an identical height and an effective height of at least 9 mm was achieved.

In fenestrated cusps, the surgical approach was modified. In general, fenestrations were only addressed if they contributed to prolapse. Stay sutures were placed in the central portion of the affected and adjacent cusps, and the fenestrated portion of the cusp was kept under tension.

Small fenestrations were closed directly using interrupted polypropylene sutures (6-0). Large fenestrations (>1cm in largest dimension) were closed using patch material. A glutaraldehyde-fixed patch of autologous pericardium was used in 54 patients. A heterologous decellularized pericardial patch (Autotissue, Berlin, Germany) was used in 21 patients.

The patch was made 10-20% larger than the fenestration to avoid cusp restriction. It was sutured into the fenestration using a circumferential 6-0 polypropylene suture with the stay sutures kept under tension (Figure 6, Panel B). The suture was locked intermittently to avoid restriction from excessive tension on the suture line. Cusp configuration was carefully assessed following implantation of the patch. Any residual prolapse was corrected through placement of individual plicating sutures, as described above.



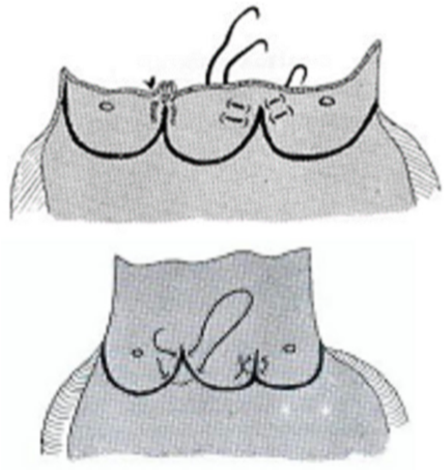
(A) (B)

Figure 6. *Schematic Drawing of Repair Techniques Used in This Cohort: Central Cusp Plication (Panel A; [73]) and Patch Repair (Panel B; [73]).*[6]

Annular dilatation was defined as a basal ring diameter of more than 26mm. The technique for correction of annular dilatation was adapted over the course of this series. Before 2009, annular dilatation was corrected by subcommissural plication (n=70, 29.5%) [25]. Braided sutures with Teflon pledgets (3-0 Ethibond, Ethicon) were used and stitches were placed under the commissures of the affected cusp(s) (Figure 7, Panel A).

Since 2009 (n=147, 62.0%), a circumferential suture annuloplasty has been used to correct annular dilatation (Figure 7, Panel B) [5]. The suture annuloplasty was tied around a Hegar dilator. The patient’s body surface area was used to choose an appropriately sized Hegar dilator and determined the annuloplasty’s final circumference (< 1.8m^2: 21 mm; 1.8m^2 – 2m^2: 23mm; > 2m^2: 25mm).

[6] Reprinted from Langer et al. [73] with permission from Elsevier.

(A) 

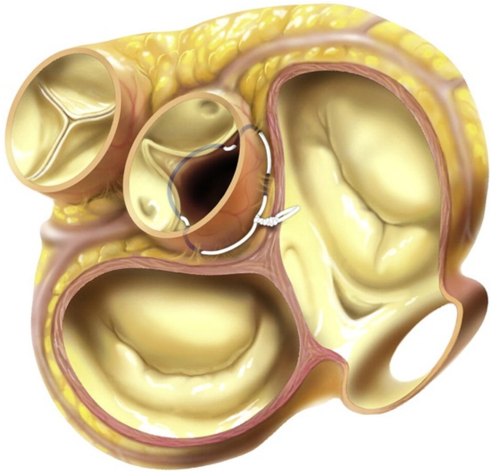
(B) 

Figure 7. *Schematic Drawing of Annuloplasty Techniques Used in This Cohort: Subcommissural Plication (Panel A; [25]) and Circular Suture Annuloplasty (Panel B; [5]).*[7]

If concomitant surgical interventions were necessary (Table 2), they were generally performed first, and followed by repair of the aortic valve.

All patients were studied with TEE (Vivid E9, General Electric Company, Fairfield, Connecticut, USA; Sequoia, Siemens, Erlangen, Germany) throughout the surgery. Additionally, intraoperative TEE was repeated immediately after the repair to assess the aortic valve for any residual AR, and to measure its eH. Detection of mild residual AR or more (≥ AR 1-2) triggered an immediate reintervention on the aortic valve to improve the repair result. Post-operatively, all patients received aspirin (100mg/day) for two months.

3.4 Follow-up

Patients were followed up with regular clinical and echocardiographic assessments by their cardiologist or the outpatient clinic of the Department of Thoracic and Cardiovascular Surgery at Saarland University Medical Centre. A final cross-sectional follow-up was completed between May 2020 and December 2020.

Clinical and echocardiographic follow-up data were obtained through direct contact with the patient and/or their treating physician (primarily their cardiologist, or their general practitioner). A careful history was taken with regards to valve-related post-operative complications (stroke or transient ischaemic attack (TIA), bleeding, endocarditis) and patients' anticoagulation status. Surgical reports were requested and reviewed for both patients who underwent reoperation on the aortic valve (AV reoperation) at a different institution.

[7] Reprinted from Youssefi et al. [124] with permission from the AME Publishing Company.

Follow-up was considered complete if a detailed clinical history and a recent echocardiographic report (no older than 2 years) could be obtained. A cut-off of 2 years was chosen as long-term cardiological follow-up appointments are typically scheduled every 12-18 months, and many patients cancelled their 2020 appointments due to the COVID-19 pandemic. Follow-up was complete in 97.1% of patients (group I: 96.8%; group II: 97.2%).

Early survival was defined as survival at 30, 60 and 90 days after surgery [7]. Similarly, early reoperation or complications were defined as events occurring within the first 30, 60, or 90 days after surgery. Late survival, reoperations or complications will be used to refer to long-term outcomes beyond the initial 90 days.

The first post-operative occurrence of AR grade 1 – 4 was defined as the date of the echocardiographic study in which the respective AR grade was first diagnosed.

Post-operative complications were defined as any major bleeding event, stroke or TIA, operated valve endocarditis, any AV reoperation, and any reoperation necessitated by a complication of the initial operation (e.g., re-exploration for post-operative bleeding). Major bleeding was defined as any bleeding event resulting in death, hospitalisation, permanent injury, or requiring transfusion [7]. Bleeding events associated with major trauma or a major operation were not considered in this category [7].

Stability of aortic valve repair was assessed using freedom from AV reoperation, and using a composite outcome variable including freedom from recurrent AR of grade 2 or greater (AR ≥ 2) or AV reoperation. Patients' functional status following AR recurrence was assessed using the New York Heart Association's (NYHA) functional classification of heart failure [117].

Cumulative follow-up time was 18 368 patient-months (1 530.7 patient-years; Table 3). The average follow-up period was 77.5 months (6.5 years; median 69.0 months, IQR 86.0 months) for the entire cohort. The average follow-up period was 88.2 months (7.4 years; median 86.5 months, IQR 82.0 months) in group I and 70.5 months (5.9 years; median 61.0 months, IQR 83.0 months) in group II (Table 3).

Follow-Up	Fenestration + Prolapse (n=94)	Prolapse (n=143)	All (n=237)
Total (months)	8 287	10 081	18 368
Mean (months)	88.2 ± 58.7	70.5 ± 51.1	77.5 ± 54.8
Median (months)	86.5	61.0	69.0
IQR (months)	82.0	83.0	86.0
Range (months)	0 – 235	0 – 217	0 – 235
Minimum	6 days	4 days	4 days

Table 3. *Summary of Follow-Up.*
Values are mean ± SD unless otherwise indicated. *IQR*, interquartile range.

3.5 Statistical Analysis

Descriptive statistics are presented as mean ± standard deviation (SD) and median plus IQR for continuous variables, or frequencies and percentages for categorical and dichotomous variables. Differences in continuous variables were analysed using an independent samples *t*-test, or a Mann-Whitney U test if the assumption of normality was violated. Normality was assessed using the Shapiro-Wilk test. Categorical and nominal data were analysed using the chi-square test, or Fisher's exact test if more than 20% of the expected values were between 1 and 5 [32].

Freedom from death, AV reoperation, post-operative complications and recurrence of AR ≥ 2 were calculated in time-to-event analyses using the Kaplan-Meier method. Group differences were analysed using the log-rank test. A competing risks analysis involving AV reoperation and death was performed to determine patients' reoperation-free survival. Kaplan Meier curves were curtailed once the number of patients at risk fell below 10% of the original cohort size, thus becoming too small to provide reliable visual estimates of survival rates [94].

Univariable and multivariable risk factor analysis was performed using Cox regression. Hazard ratios (HR) with 95% confidence intervals (CIs) are reported for statistically significant predictors only. For statistically significant categorical predictor variables, the assumption of proportional hazards was assessed visually using Kaplan Meier curves [126]. Predictor variables that did not meet the assumption of proportional hazards were not analysed further.

A two-tailed alpha level of 0.05 was adopted for all statistical tests. All analyses were performed using SPSS 25 (IBM, Armonk, NY) [59], R (Version 4.1.0) [97] and RStudio (Version 1.4.1717) [100].

4 Results

4.1 Perioperative Data

Frequency and Distribution of Cusp Pathology

The number of prolapsed cusps requiring repair differed significantly between the two groups ($p = 0.001$). In total, 368 prolapsed cusps were treated (I: 130 cusps; II: 238 cusps).

In group I, a fenestration was involved in the mechanism of prolapse in 102 of the 130 treated cusps (78.5%). Furthermore, in this group, a total of 112 fenestrations were treated in 94 patients (Figure 8): 77 patients (81.9%) required treatment of a prolapsing cusp with 1 fenestration repair, 16 patients (17.0%) required treatment of 2 fenestrations, and in 1 patient (1.1%) 3 fenestrations were treated.

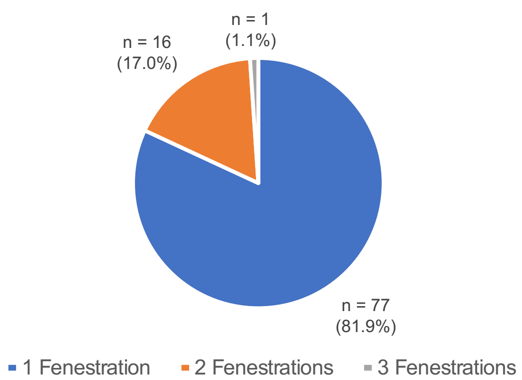


Figure 8. *Number of Fenestrations Treated Per Patient (Group I).*

In both groups, cusp prolapse was commonly present in 1 cusp (I: n=59, 62.8%; II: n=58, 40.6%) or 2 cusps (I: n=34, 36.2%; II: n=75, 52.4%; Figure 9). Repair of a single cusp was more common in group I ($p < 0.001$), while repair of 2 cusps was required more frequently in group II ($p = 0.014$). Cusp prolapse in all 3 cusps was less common (I: n=1; 1.1%; II: n=10; 7.0%; $p = 0.054$).

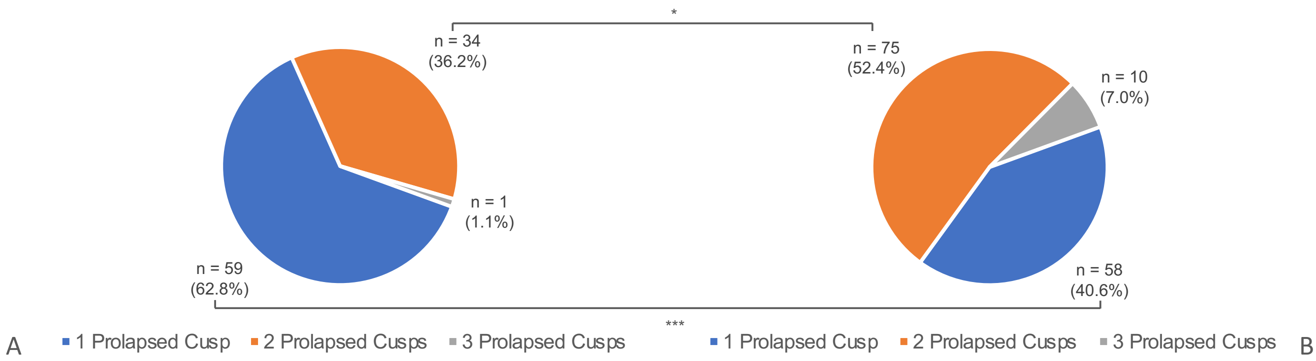


Figure 9. *Number of Prolapsed Cusps Treated Per Patient in Group I (Panel A) and Group II (Panel B). Statistically Significant Group Differences Are Marked Using Asterisks (* indicates p < 0.05, *** indicates p < 0.001).*

In addition, the distribution of cusp pathology (fenestration + prolapse vs. 'isolated' prolapse) differed significantly between the two groups ($p < 0.001$; Figure 10). The right coronary cusp (RCC) was involved in the majority of cases (I: n=89, 79.5%; II: n=134, 56.3%), although RCC involvement was more common in group I ($p < 0.001$). Conversely, a higher incidence of non-coronary cusp (NCC) involvement was found in group II (I: n=13, 11.6%; II: n=72, 30.3%; $p < 0.001$). Prolapse of the left coronary cusp (LCC) was seen least frequently in both groups (I: n=10, 8.9%; II: n=32, 13.4%; $p = 0.225$).

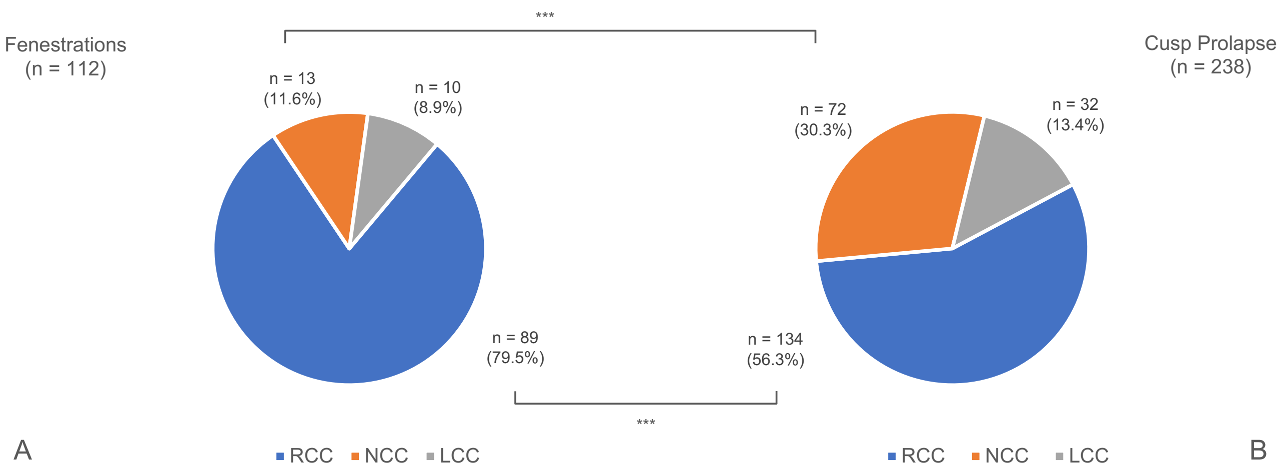


Figure 10. *Distribution of Cusp Pathology in Group I (Panel A) and Group II (Panel B). Statistically Significant Group Differences Are Marked Using Asterisks (*** indicates p < 0.001).*
LCC, left coronary cusp; *NCC*, non-coronary cusp; *RCC*, right coronary cusp.

Repair Techniques

Three different repair techniques were used to address cusp fenestration in group I (Table 4). In the majority of patients (n=54, 57.5%), fenestrations were closed using an autologous pericardial patch; they were closed with a heterologous pericardial patch in 21 patients (22.3%), and in 19 patients (20.2%) fenestrations were closed directly.

Characteristic	Value			*p*-value
	Fenestration + Prolapse (n=94)	Prolapse (n=143)	All (n=237)	
Repair techniques – Fenestration				
autologous pericardial patch	54 (57.4)			
heterologous pericardial patch	21 (22.3)			
no patch	19 (20.2)			
Repair techniques – Cusp Prolapse				
cusp plication		132 (92.3)		
resection of cusp tissue		11 (7.7)		
Annuloplasty technique				**0.023**
none	12 (12.8)	8 (5.6)	20 (8.4)	0.052
subcommissural plication	33 (35.1)	37 (25.9)	70 (29.5)	0.127
suture annuloplasty	49 (52.1)	98 (68.5)	147 (62.0)	**0.011**
Annular diameter (mm)	29.4 ± 2.7	29.2 ± 3.0	29.7 ± 2.3	0.372
Extracorporeal circulation (min)	65.9 ± 22.1	69.4 ± 30.2	68.0 ± 27.3	0.909
Cross-clamp time (min)	45.5 ± 15.8	42.1 ± 19.3	43.4 ± 18.0	**0.015**

Table 4. *Perioperative Patient Data.*

Numeric variables are presented as mean ± SD, dichotomous variables are n (%). Percentages may not total 100 because of rounding. The *p*-value relates to statistical differences between groups I (Fenestration + Prolapse) and II (Prolapse).

In group I, any aortic annuloplasty was added in the majority of cases (n=82, 87.2%; Table 4). Before 2009, 26/32 patients (81.3%) underwent subcommissural plication; in the remaining 6 patients (18.7%) no annuloplasty was added (Figure 11, Panel A). After 2009, a suture annuloplasty was added in 49/62 patients (79.0%), 7/62 patients (11.3%) underwent subcommissural plication, and in 6/62 patients (9.7%) no annuloplasty was added (Figure 11, Panel B).

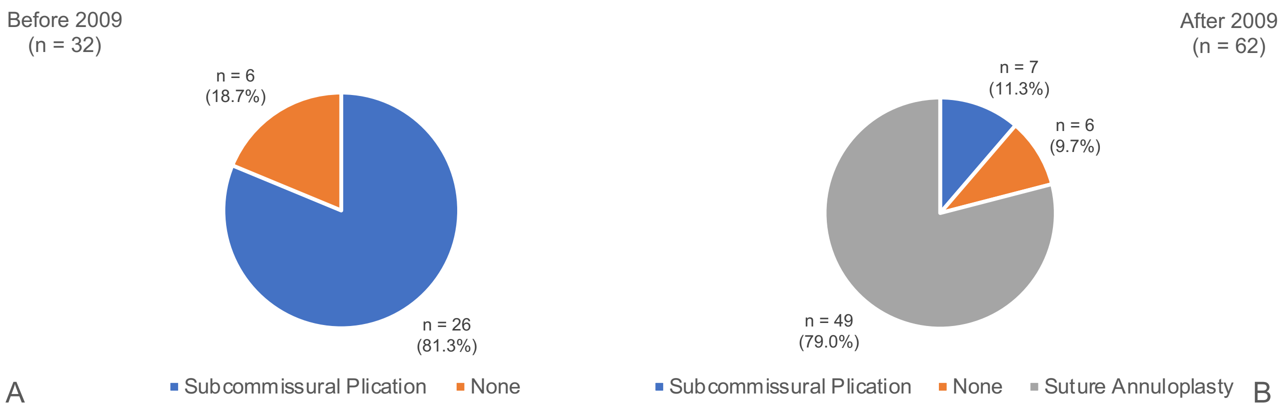


Figure 11. *Frequency Distribution of Annuloplasty Techniques in Group I Before 2009 (Panel A) and After 2009 (Panel B).*

In group II, cusp prolapse was addressed primarily by cusp plication (n=132; 92.3%). In 11 cases (7.7%), triangular resection of cusp tissue with subsequent cusp adaptation was chosen (Table 4).

Any aortic annuloplasty was added in the vast majority of patients (n=135, 94.4%; Table 4). Before 2009, 29/31 patients (93.5%) underwent subcommissural plication; in the remaining 2 patients no annuloplasty was added (6.5%; Figure 12, Panel A). After 2009, a suture annuloplasty was added in 98/112 patients (87.5%), 8/112 patients underwent subcommissural plication (7.1%), and in 6/112 patients (5.4%) no annuloplasty was added (Figure 12, Panel B).

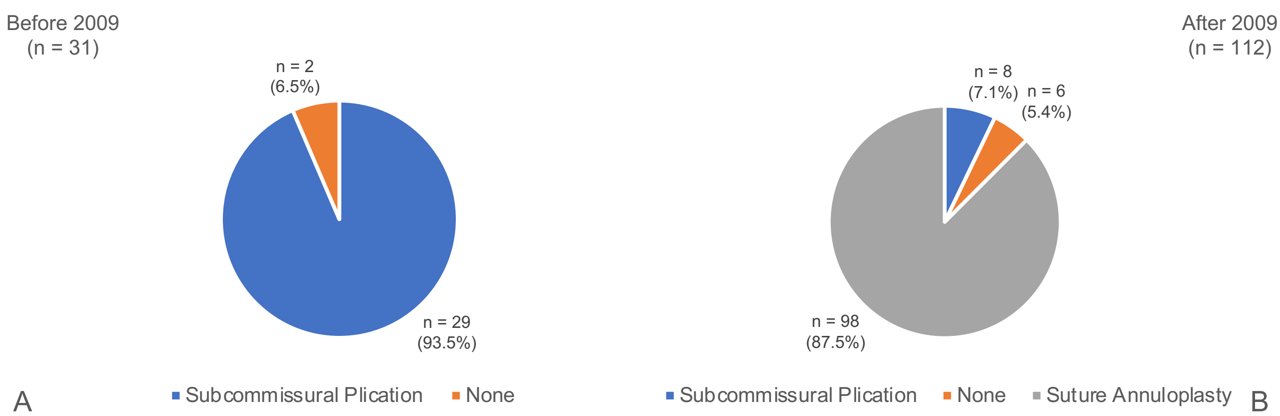


Figure 12. *Frequency Distribution of Annuloplasty Techniques in Group II Before 2009 (Panel A) and After 2009 (Panel B).*

Furthermore, the frequency of the respective annuloplasty techniques differed between the two groups (p = 0.023; Table 4). The number of patients who underwent suture annuloplasty was significantly higher in group II (I: 52.1%; II: 68.5%; p = 0.011, Figure 13).

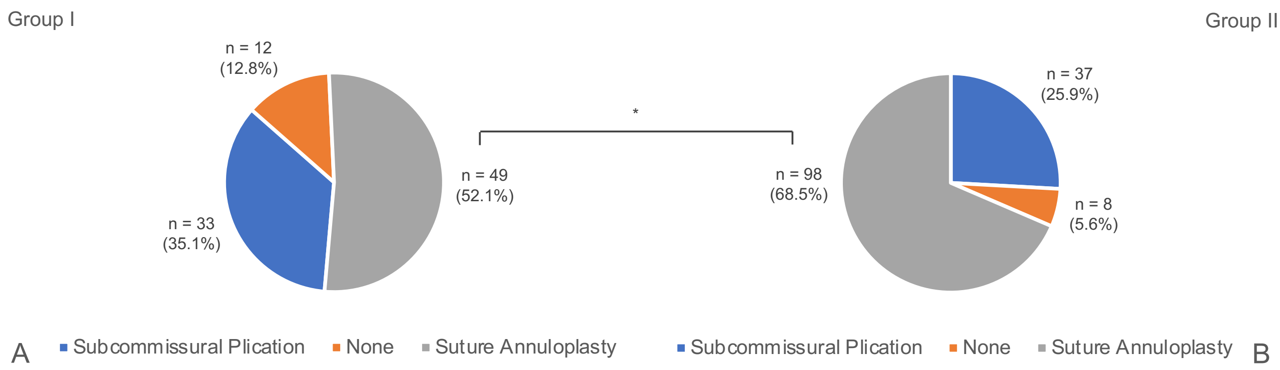


Figure 13. *Frequency Distribution of Annuloplasty Techniques in Groups I (Panel A) and II (Panel B). Statistically Significant Group Differences Are Marked Using an Asterisk (* indicates p < 0.05).*

Extracorporeal Circulation and Cross-Clamp Time

Time on cardiopulmonary bypass ranged from 31 – 157 minutes. There was no difference in cardiopulmonary bypass time between the two groups (I: 65.9 ± 22.1 minutes; II: 69.4 ± 30.2 minutes; p = 0.909; Table 4).

Cross-clamp time ranged from 18 – 109 minutes; the average cross-clamp time was longer in group I (I: 45.5 ± 15.8 minutes; II: 42.1 ± 19.3 minutes; p = 0.015; Table 4).

Aortic Regurgitation at Discharge

In the majority of cases, minimal or less AR was seen at discharge. Specifically, 77 patients (81.9%) in group I and 114 patients (79.7%) in group II were discharged with no to minimal AR (AR grades 0 – 1; Table 5). Mild AR (AR 1 – 2) was seen in 15 patients (16.0%) in group I and 23 patients (16.1%) in group II. In 2 group I patients (2.1%) and 6 group II patients (4.2%) moderate AR (AR 2) was found (Table 5).

There was no significant difference in the frequency distribution of post-operative AR grades at discharge between the two groups (p = 0.930).

AR Grade	Post-Operative Assessment		
	Fenestration + Prolapse (n=94)	Prolapse (n=143)	All (n=237)
0	16 (17.0)	27 (18.9)	43 (18.1)
0 – 1	25 (26.6)	35 (24.5)	60 (25.3)
1	36 (38.3)	52 (36.4)	88 (37.1)
1 – 2	15 (16.0)	23 (16.1)	38 (16.0)
2	2 (2.1)	6 (4.2)	8 (3.4)

Table 5. *Post-Operative Echocardiographic Assessment of Aortic Regurgitation at Discharge.*

Values are n (%). Percentages may not total 100 because of rounding. *AR*, aortic regurgitation.

4.2 Survival

4.2.1 Early Survival

All patients survived the post-operative hospital stay. One patient died of ventricular arrhythmia 22 days after the surgery. Thus, all-cause mortality at 30, 60, and 90 days post-surgery was 0.4%. It was 0% in group I and 0.7% in group II.

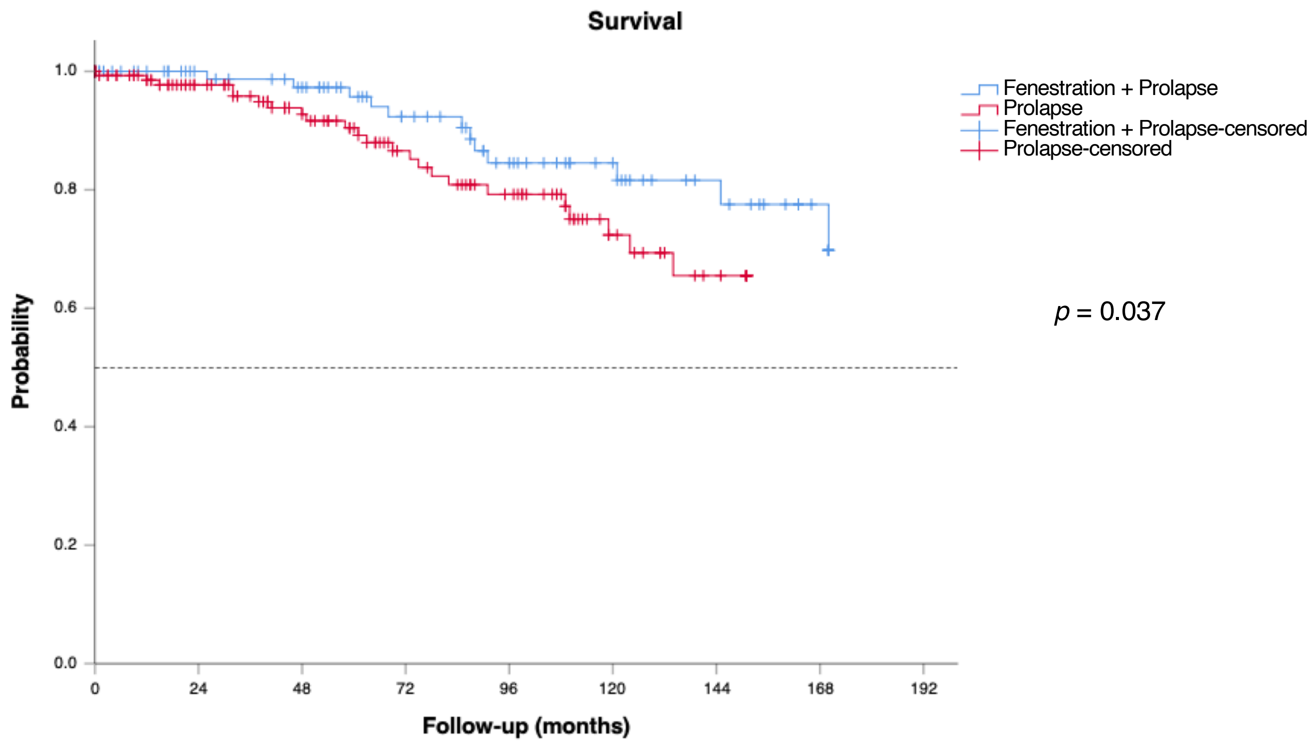
4.2.2 Late Survival

Forty patients died during the follow-up period: of these, 23 patients (57.5%) died of cardiac causes. Overall all-cause mortality was 16.9% (Table 6); it was 13.8% in group I and 18.9% in group II.

Classification of Causes of Death	Fenestration + Prolapse (n=94)	Prolapse (n=143)	All (n=237)
Total	13 (13.8)	27 (18.9)	40 (16.9)
Cardiac deaths	8 (61.5)	15 (55.6)	23 (57.5)
Non-cardiac deaths	5 (38.5)	12 (44.4)	17 (42.5)

Table 6. *Classification of Causes of Death.*

Values are n (%). Percentages may not total 100 because of rounding.



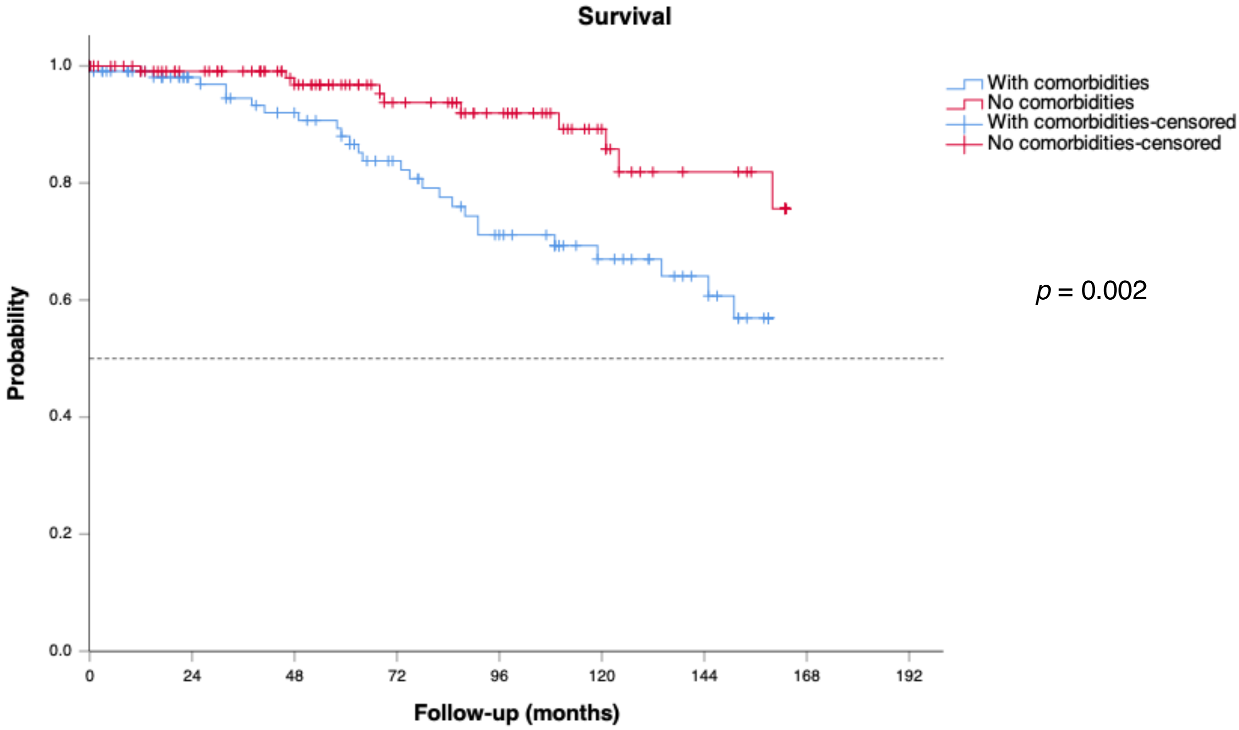
No. at Risk									
Fenestration + Prolapse	94	76	68	53	39	29	20	10	-
Prolapse	143	109	84	61	48	25	15	-	-

Figure 14. *Long-Term Survival After Aortic Valve Repair.*

Five-year survival was 92.6% (I: 95.7%; II: 90.5%), 10-year survival was 77.8% (I: 84.5%; II: 72.4%). There was a significant difference in survival between the two groups (p = 0.037), with patients in group I showing better long-term survival than patients in group II (Figure 14).

4.2.2.1 Influence of Concomitant Cardiac Comorbidities on Survival

The influence of concomitant cardiac comorbidities on survival was investigated because of the unequal distribution of cardiac comorbidities between group I and group II (Table 2). Five-year survival was 96.8% in patients without comorbidities and 88.0% in patients with comorbidities. After 10 years, survival was 89.2% in patients without comorbidities and 67.0% in patients with comorbidities. There was a difference in survival between these two groups; patients without comorbidities showed significantly better long-term survival than patients with comorbidities (p = 0.002; Figure 15).

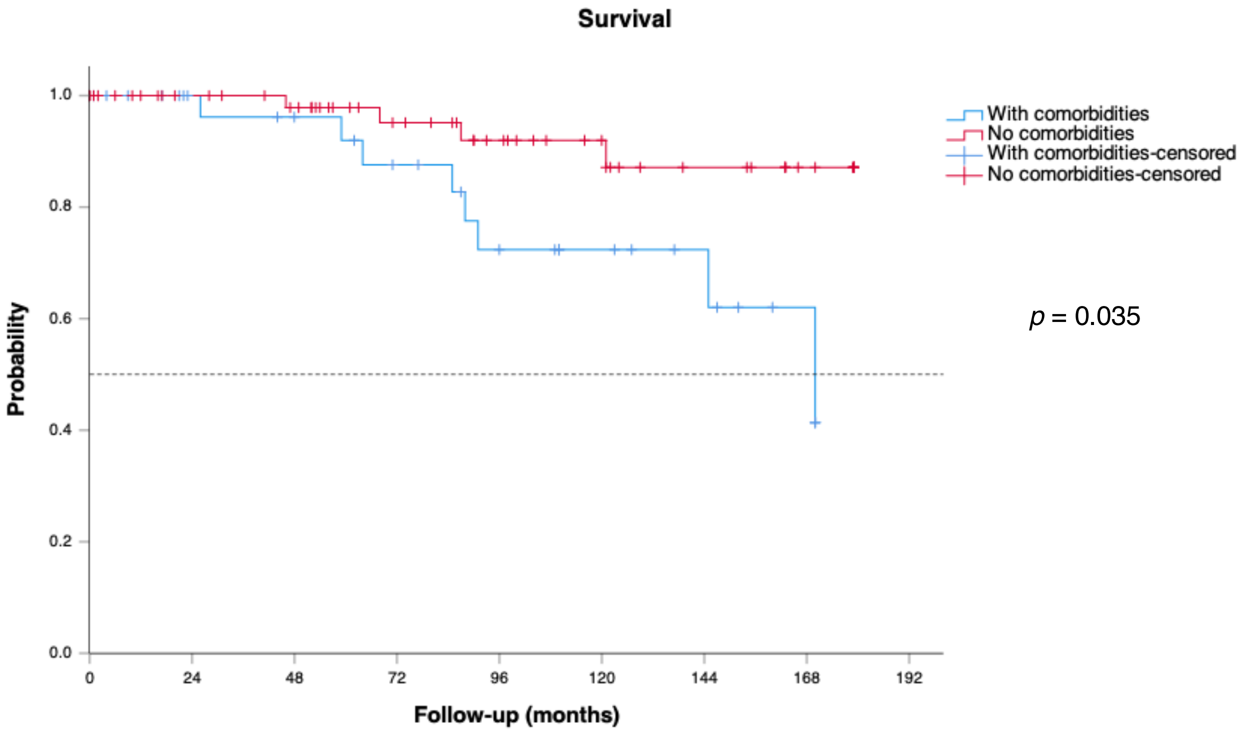


No. at Risk									
With comorbidities	111	83	70	55	42	28	19	-	-
No comorbidities	126	102	82	59	45	26	16	-	-

Figure 15. *Long-Term Survival After Aortic Valve Repair With and Without Concomitant Cardiac Comorbidities.*

Additional subgroup analyses of the four most common cardiac comorbidities in this sample showed reduced 10-year survival in all four groups. Ten-year survival was 74.7% in patients with concomitant coronary artery disease (n=50), 62.1% in patients with concomitant tricuspid valve regurgitation (n=34), 59.9% in patients with concomitant mitral valve regurgitation (n=48), and 58.7% in patients with concomitant atrial fibrillation (n=46).

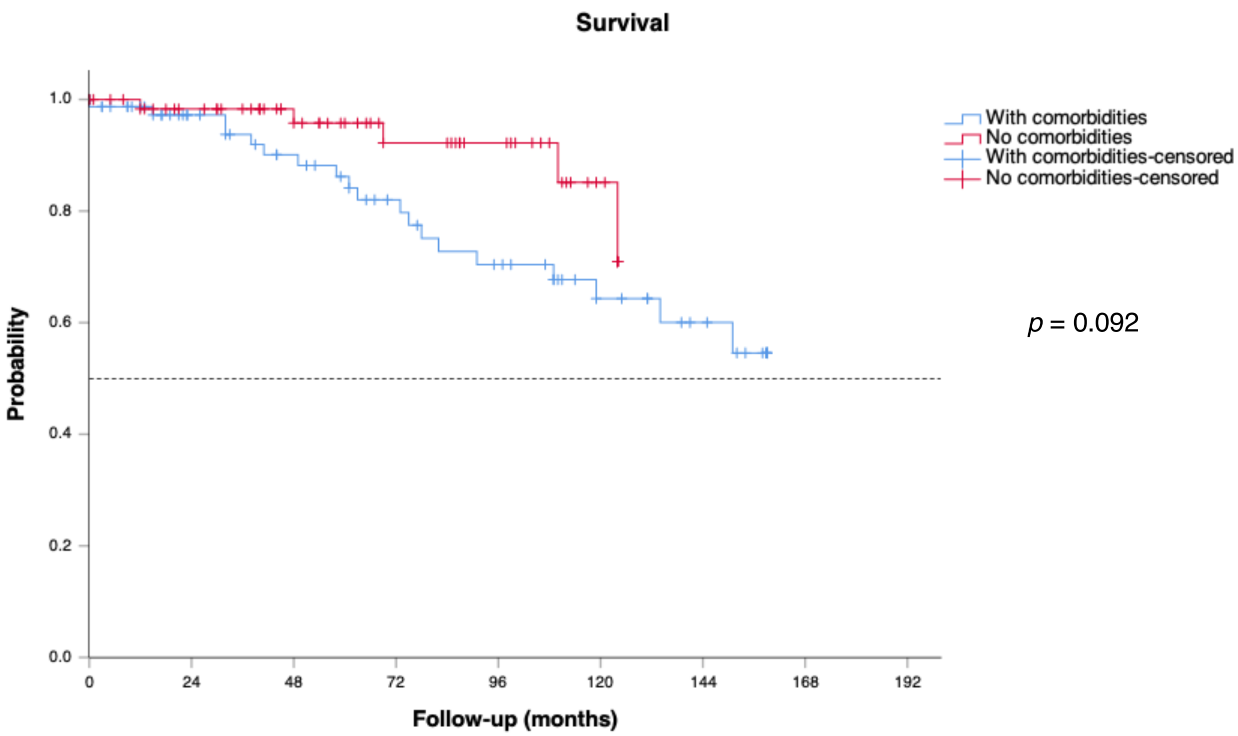
In group I, 5-year survival was 97.9% in patients without comorbidities, and 92.0% in patients with comorbidities. After 10 years, survival was 92.0% and 72.4%, respectively. In this group, long-term survival was significantly better in patients without comorbidities (p = 0.035; Figure 16).



No. at Risk									
With comorbidities	33	26	23	19	13	10	7	3	-
No comorbidities	61	50	45	34	26	19	13	7	-

Figure 16. *Long-Term Survival After Aortic Valve Repair With and Without Concomitant Cardiac Comorbidities in Group I.*

In group II, 5-year survival was 95.8% in patients without comorbidities, and 86.2% in patients with comorbidities. After 10 years, survival was 85.1% and 64.3%, respectively. In this group, there was no statistically significant difference in long-term survival between the two subgroups (p = 0.092; Figure 17), but the data suggest a trend towards improved survival in patients without comorbidities.



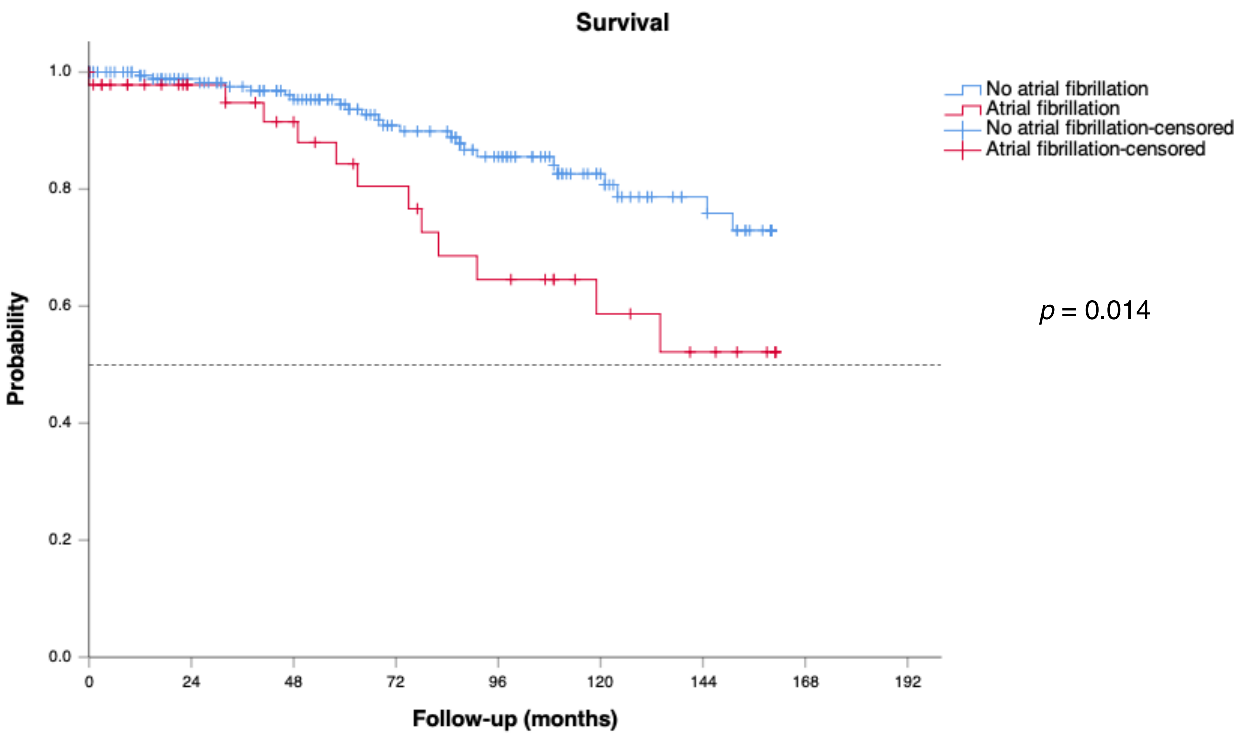
No. at Risk									
With comorbidities	78	57	47	36	29	18	12	-	-
No comorbidities	65	52	37	25	19	7	-	-	-

Figure 17. *Long-Term Survival After Aortic Valve Repair With and Without Concomitant Cardiac Comorbidities in Group II.*

4.2.2.1.1 Influence of Atrial Fibrillation on Survival

The influence of atrial fibrillation on survival was investigated separately because it can occur independently of mitral valve regurgitation [55], and because it is the most common arrhythmia of clinical significance. Atrial fibrillation has an estimated prevalence of 3% in the general adult population [31, 70]; however, it is even more prevalent among older patients and those with cardiac comorbidities [70, 71].

Five-year survival was 94.5% in patients without atrial fibrillation, and 84.3% in patients with atrial fibrillation. Ten-year survival was 82.6% and 58.7%, respectively. There was a significant difference in survival between the two groups (p = 0.014): patients without atrial fibrillation showed significantly better survival than patients with atrial fibrillation (Figure 18).



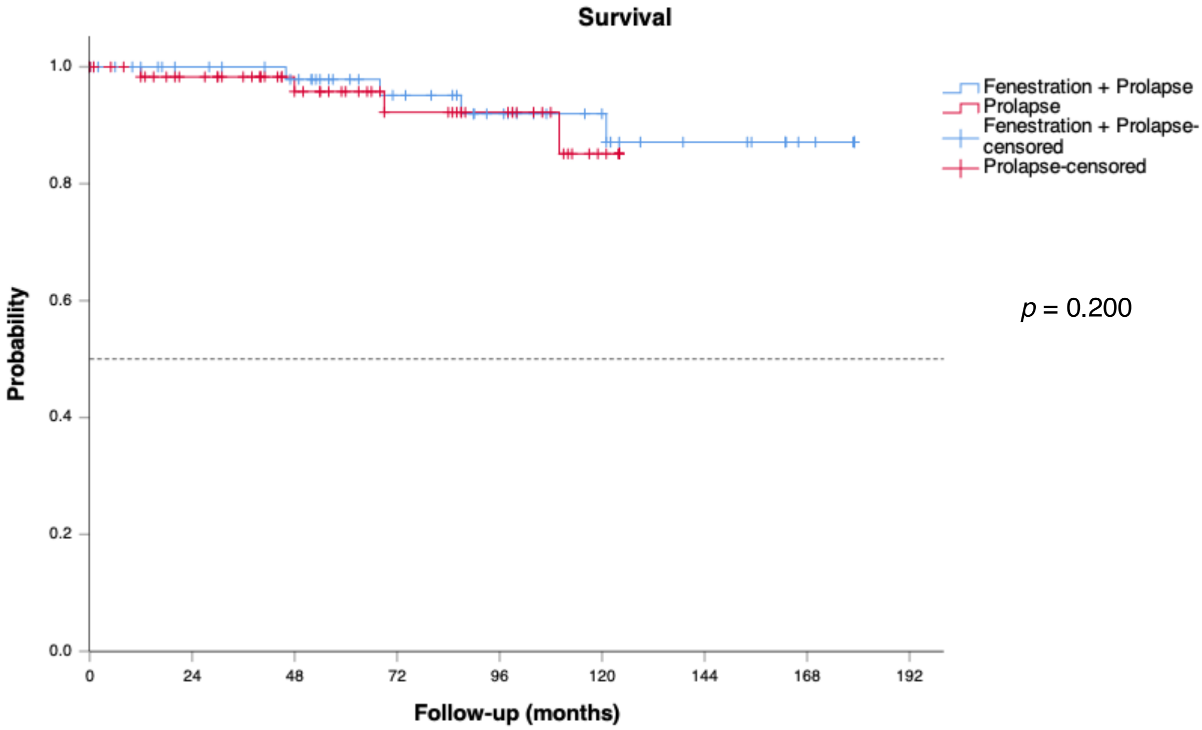
No. at Risk									
No atrial fibrillation	191	153	126	93	71	44	28	-	-
Atrial fibrillation	46	32	26	21	16	10	7	-	-

Figure 18. *Long-Term Survival After Aortic Valve Repair in Patients With and Without Atrial Fibrillation.*

4.2.2.2 Survival in Patients Without Concomitant Cardiac Comorbidities

Among patients without concomitant cardiac comorbidities, 5-year survival was 96.8% (I: 97.9%; II: 95.8%) and 10-year survival was 89.2% (I: 92.0%; II: 85.1%).

There was no significant difference in survival between patients without comorbidities from groups I and II (p = 0.200; Figure 19).



No. at Risk									
Fenestration + Prolapse	61	50	45	34	26	19	13	7	-
Prolapse	65	52	37	25	19	7	-	-	-

Figure 19. *Long-Term Survival After Aortic Valve Repair in Patients Without Concomitant Cardiac Comorbidities, by Group.*

4.2.3 Predictors of Death

4.2.3.1 Univariable Models

In addition to single factors, a compound factor called ‘Comorbidities’ was created and tested as a predictor. ‘Comorbidities’ is a compound variable comprising all cardiac comorbidities that required concomitant cardiac surgery in this sample (see Table 2 for full list). Age at operation, in years, was analysed as a continuous predictor variable.

Univariable Cox regression analysis identified comorbidities (compound; p = 0.003), atrial fibrillation (p = 0.017), mitral valve regurgitation (p = 0.050), tricuspid valve regurgitation (p = 0.003), age (p < 0.001), extracorporeal circulation (ECC) time (p = 0.001), and cross-clamp time (p = 0.012) as significant predictors of death (Table 7). The assumption of proportional hazards was met for comorbidities (compound), atrial fibrillation, and tricuspid valve regurgitation. It was not met for mitral valve regurgitation.

A table summarising the variables tested as univariable predictors of death within groups I and II is included in Appendix 1. In group I, comorbidities (compound; p = 0.045), CAD (p = 0.005) and age (p = 0.005) were identified as significant predictors of death. The type of fenestration repair (direct suture, autologous pericardial patch, heterologous pericardial patch; p = 0.389) and the number of fenestrations requiring intervention (p = 0.192) did not predict death.

In group II, tricuspid valve regurgitation (p = 0.027), age (p < 0.001), ECC time (p = 0.002) and cross-clamp time (p = 0.002) were identified as significant predictors of death. The number of prolapsed cusps requiring repair did not predict death (p = 0.798).

4.2.3.2 Multivariable Model

Only age (p < 0.001) and extracorporeal circulation time (p = 0.031) remained statistically significant predictors of death in the multivariable model (Table 8).

Predictor Variable	Univariable Model	
	p-value	Hazard Ratio [95% CIs]
Comorbidities (compound)	**$p = 0.003$**	2.895 [1.444 – 5.802]
CAD	$p = 0.125$	-
Atrial fibrillation	**$p = 0.017$**	2.246 [1.158 – 4.358]
MVR	**$p = 0.050$**	1.944 [1.001 – 3.776]
TVR	**$p = 0.003$**	3.176 [1.474 – 6.846]
Male sex	$p = 0.523$	-
Age at operation	**$p < 0.001$**	1.096 [1.055 – 1.139]
1^{st} vs. 2^{nd} half of sample	$p = 0.532$	-
Type of annuloplasty	$p = 0.283$	-
AR pre-op	$p = 0.572$	-
AR discharge	$p = 0.882$	-
ECC time	**$p = 0.001$**	1.018 [1.008 – 1.029]
Cross-clamp time	**$p = 0.012$**	1.022 [1.005 – 1.040]
gH	$p = 0.912$	-
No. of prolapsed cusps	$p = 0.461$	-
Operation before vs. after 2004	$p = 0.244$	-
LCC repair	$p = 0.696$	-
RCC repair	$p = 0.963$	-
NCC repair	$p = 0.824$	-

Table 7. *Univariable Predictors of Late Death, All.*

AR, aortic regurgitation; *CAD*, coronary artery disease; *CIs*, confidence intervals; *ECC*, extracorporeal circulation; *gH*, geometric height; *LCC*, left coronary cusp; *MVR*, mitral valve regurgitation; *NCC*, non-coronary cusp; *No.*, number; *pre-op*, preoperatively; *RCC*, right coronary cusp; *TVR*, tricuspid valve regurgitation.

Predictor Variable	Multivariable Model	
	p-value	Hazard Ratio [95% CIs]
Comorbidities (compound)	-	-
CAD	-	-
Atrial fibrillation	-	-
MVR	-	-
TVR	-	-
Male sex	-	-
Age at operation	**$p < 0.001$**	1.104 [1.058 – 1.153]
1st vs. 2nd half of sample	-	-
Type of annuloplasty	-	-
AR pre-op	-	-
AR discharge	-	-
ECC time	**$p = 0.031$**	1.018 [1.002 – 1.034]
Cross-clamp time	-	-
gH	-	-
No. of prolapsed cusps	-	-
Operation before vs. after 2004	-	-
LCC repair	-	-
RCC repair	-	-
NCC repair	-	-

Table 8. *Multivariable Predictors of Late Death, All.*
AR, aortic regurgitation; *CAD*, coronary artery disease; *CIs*, confidence intervals; *ECC*, extracorporeal circulation; *gH*, geometric height; *LCC*, left coronary cusp; *MVR*, mitral valve regurgitation; *NCC*, non-coronary cusp; *No.*, number; *pre-op*, preoperatively; *RCC*, right coronary cusp; *TVR*, tricuspid valve regurgitation.

4.3 Aortic Valve Reoperation

Nineteen patients (8.0%) underwent reoperation on the aortic valve (AV reoperation). Reoperations were performed between 8 days and 177 months after the initial repair (I: 8 days – 118 months; II: 3 months – 177 months). The average interval between operations was 57.4 months (4.8 years; median 57.0 months). The linearized event rate was 1.2% per patient-year. Nine patients in group I (9.6%) and 10 patients in group II (7.0%) required AV reoperation. In group I, the average interval between operations was 56.2 months (4.7 years; median 57.0 months). The linearized event rate was 1.3% per patient-year. In group II, the average interval between operations was 58.4 months (4.9 years; median 53.5 months). The linearized event rate was 1.2% per patient-year.

4.3.1 Indications for AV Reoperation

Structural valve deterioration was the primary indication for AV reoperation in both groups.
In group I, structural valve deterioration was seen in 66.7% of reoperations (n=6). In 2 patients, cusp retraction was found at reoperation after 57 and 104 months, and recurrent cusp prolapse was seen in another 2 patients (reoperation after 14 and 18 months). Additionally, 1 patient required reoperation because of a tear between the implanted pericardial patch and the cusp tissue (reoperation after 13 months), and in another patient the sutures used to close the fenestration were found to have cut through the valve tissue (reoperation after 8 days).
Furthermore, a combination of structural valve deterioration and non-structural valve dysfunction was seen in 22.2% of reoperations (n=2). Recurrent cusp prolapse was found in both patients, either in combination with a dilatation of the aortic root and ascending aorta (reoperation after 92 months), or the basal ring (reoperation after 118 months).
Finally, 11.1% of reoperations (n=1) were required as a result of non-structural valve dysfunction: One patient required reoperation for dilatation of the ascending aorta (reoperation after 90 months).

In group II, structural valve deterioration was seen in 80.0% of reoperations (n=8). Cusp retraction was seen in 4 patients (reoperation after 49, 58, 59, and 67 months), and recurrent cusp prolapse was seen in 2 patients (reoperation after 37 and 177 months). One patient underwent reoperation for cusp calcification after 100 months, while another underwent reoperation after 30 months due to cusp detachment and damage to the cusp tissue.

Non-structural valve dysfunction was seen in 10.0% of reoperations (n=1): in 1 patient, reoperation was required after 3 months because of persistent residual AR. Finally, 1 patient (10.0%) underwent reoperation for aortic valve endocarditis 4 months after the initial repair.
Repair failure was a cause of AV reoperation in the vast majority of cases (n=16; 84.2%). In each group, it was a cause of reoperation in 8 instances (I: 8/9, 88.9%; II: 8/10, 80.0%).

4.3.2 Type of AV Reoperation

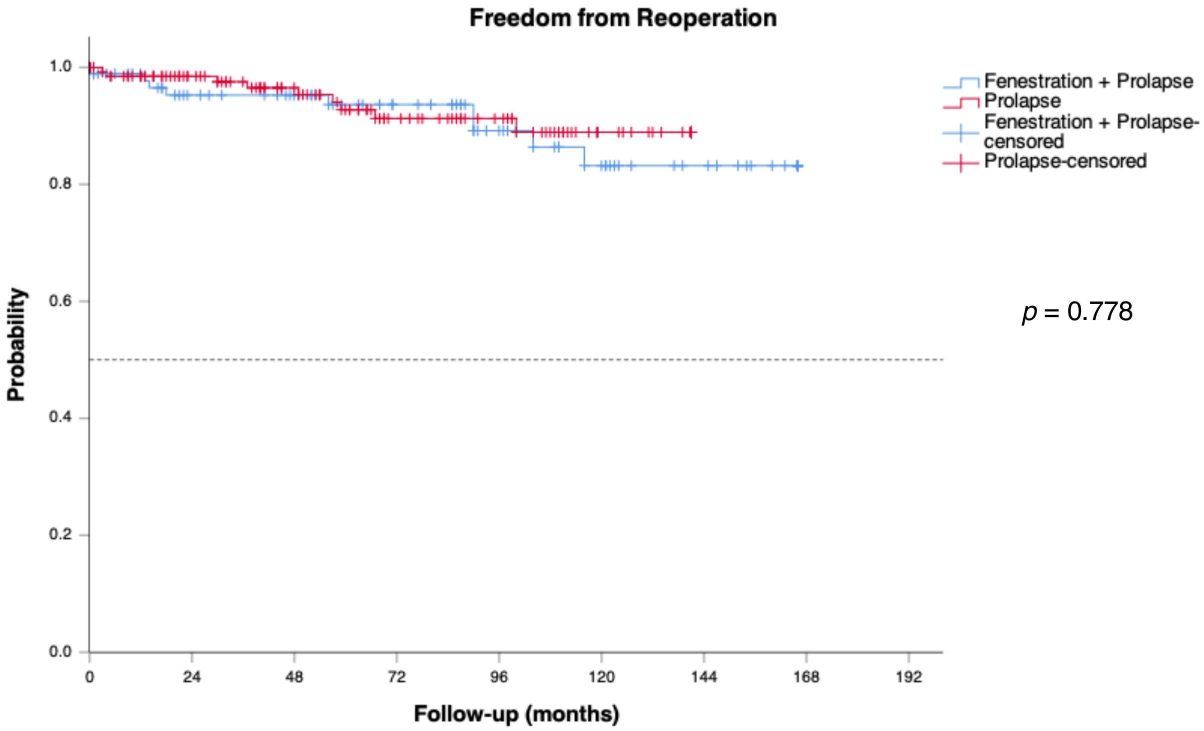
At reoperation, biological aortic valve replacement was the most commonly performed procedure (n=13, 68.5%) in both groups (I: n=5, 55.6%; II: n=8, 80.0%). AV re-repair was chosen in 5 instances (26.4%; I: n=3, 33.3%; II: n=2, 20.0%). A mechanical aortic valve was implanted once (5.3%; I: n=1, 11.1%; II: n=0, 0%).
Replacement of the ascending aorta was required concomitantly in 2 instances (10.6%): In group I, 1 patient underwent AV re-repair and replacement of the ascending aorta (11.1%), while 1 group II patient underwent biological AVR and replacement of the ascending aorta (10.0%).

4.3.3 Early AV Reoperation

Early AV reoperation was rare. One patient underwent reoperation after 8 days; the sutures placed to close a fenestration had cut through the valve tissue. Thus, 30-, 60- and 90-day freedom from AV reoperation was 99.6%. It was 98.9% in group I, and 100% in group II.

4.3.4 Freedom From AV Reoperation

Five-year freedom from AV reoperation was 93.2% (I: 93.7%; II: 92.8%). After 10 years, it was 86.1% (I: 83.2%; II: 88.9%). There was no difference between the two groups (p = 0.778; Figure 20).



No. at Risk									
Fenestration + Prolapse	94	72	64	50	35	24	16	-	-
Prolapse	143	107	82	56	43	21	-	-	-

Figure 20. *Freedom From AV Reoperation After Aortic Valve Repair.*
AV, aortic valve.

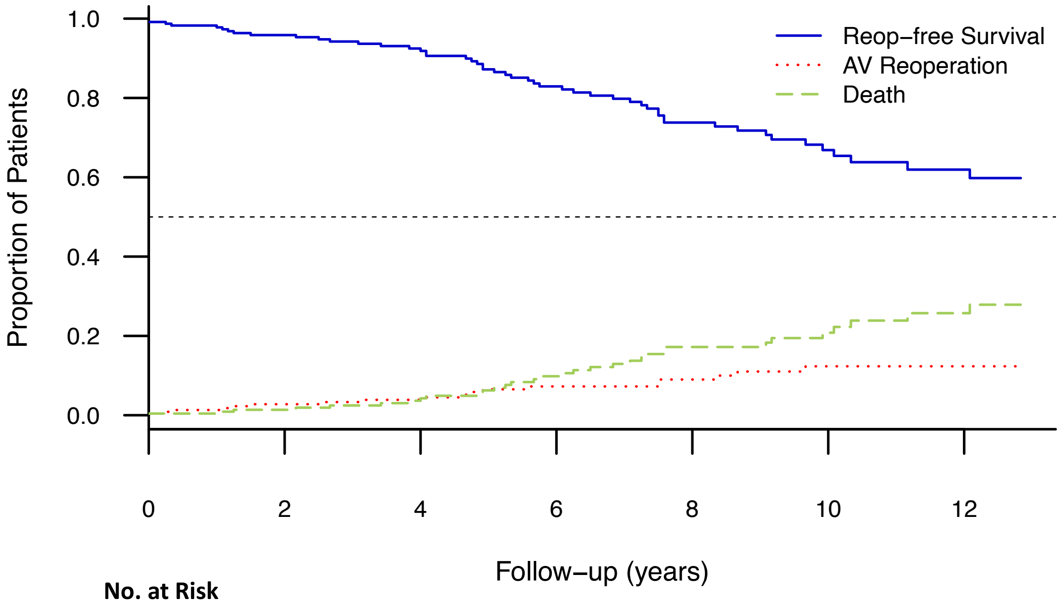
4.3.4.1 Influence of Comorbidity Status and Number of Prolapsed Cusps Requiring Repair on Freedom From AV Reoperation

In patients without concomitant cardiac comorbidities, freedom from AV reoperation was 93.5% and 83.3% after 5 and 10 years, respectively. It was 92.7% and 88.5% in patients with comorbidities. There was no difference between these groups ($p = 0.623$).

Freedom from AV reoperation in patients with 1 prolapsed cusp requiring repair was 91.6% and 86.0% after 5 and 10 years, respectively. It was 95.2% and 90.4% in patients requiring repair of 2 prolapsed cusps. There was no difference between these groups ($p = 0.210$).

4.3.5 Competing Risks Analysis: Death and AV Reoperation

A competing risks analysis including AV reoperation and death showed a reoperation-free survival of 87.2% and 66.9% at 5 and 10 years, respectively (Figure 21).

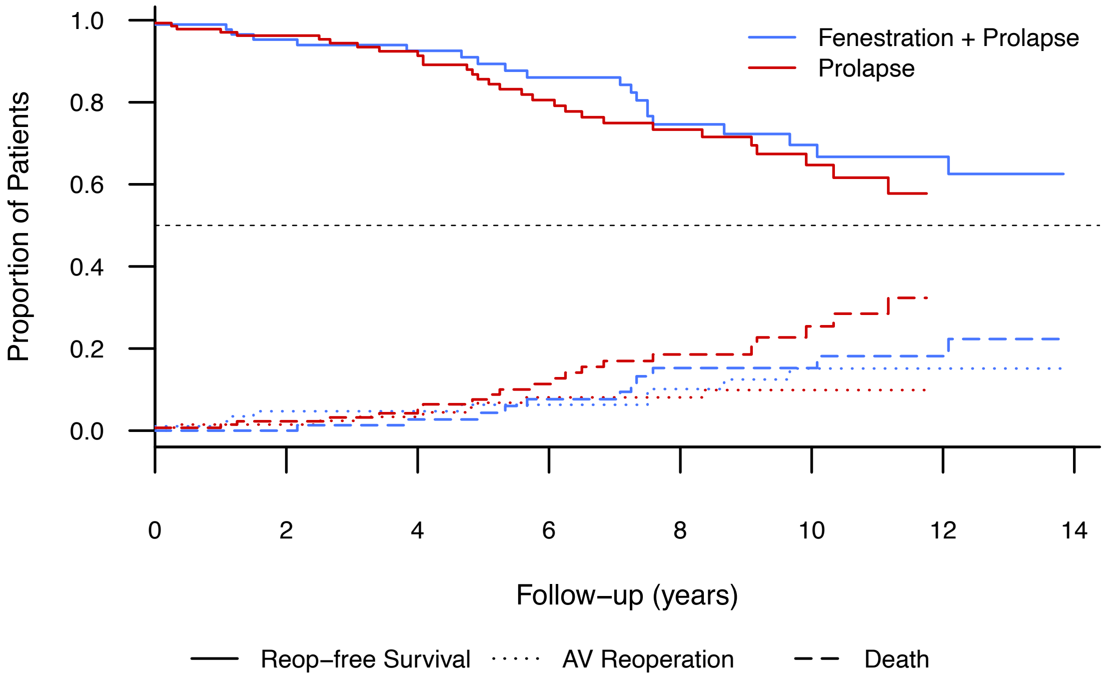


No. at Risk

237	180	150	108	81	47	29

Figure 21. *Competing Risks Analysis Including AV Reoperation and Death.*
AV, aortic valve; *Reop*, reoperation.

Subsequently, reoperation-free survival was analysed separately for groups I and II (Figure 22). After 5 years, reoperation-free survival was 89.4% (group I) and 85.6% (group II). After 10 years, it was 69.6% (group I) and 64.7% (group II).



No. at Risk

F + P	94	72	65	50	36	25	16	-
P	143	108	85	58	45	22	-	-

Figure 22. *Competing Risks Analysis Including AV Reoperation and Death, by Group.* *AV*, aortic valve; *F + P*, Fenestration + Prolapse; *P*, Prolapse; *Reop*, reoperation.

4.3.6 Predictors of Reoperation

Aortic regurgitation at discharge was a significant univariable predictor of AV reoperation (p = 0.042, Table 9).

The type of annuloplasty (p = 0.998), geometric height (< 20 mm vs. ≥ 20mm; p = 0.221), and the systematic measurement of effective height, introduced in 2004 (p = 0.984), did not predict need for AV reoperation.

Predictor Variable	*p*-value	Hazard Ratio [95% CIs]
Comorbidities (compound)	p = 0.624	-
Male sex	p = 0.071	-
Age at operation	p = 0.189	-
1^{st} vs. 2^{nd} half of sample	p = 0.429	-
Type of annuloplasty	p = 0.979	-
AR pre-op	p = 0.909	-
AR discharge	**p = 0.042**	2.536 [1.035 – 6.212]
ECC time	p = 0.405	-
Cross-clamp time	p = 0.629	-
gH	p = 0.221	-
No. of prolapsed cusps	p = 0.074	-
Operation before vs. after 2004	p = 0.984	-
LCC repair	p = 0.160	-
RCC repair	p = 0.515	-
NCC repair	p = 0.389	-

Table 9. *Univariable Predictors of AV Reoperation, All.*
AR, aortic regurgitation; *AV*, aortic valve; *CIs*, confidence intervals; *ECC*, extracorporeal circulation; *gH*, geometric height; *LCC*, left coronary cusp; *NCC*, non-coronary cusp; *No.*, number; *pre-op*, preoperatively; *RCC*, right coronary cusp.

A table summarising the variables tested as univariable predictors of AV reoperation within groups I and II is included in Appendix 2.

In group I, age was identified as a significant protective factor (p = 0.016). The type of repair (direct suture, autologous pericardial patch, heterologous pericardial patch; p = 0.451) and the number of fenestrations requiring intervention (p = 0.866) did not predict AV reoperation.

In group II, no significant predictors of AV reoperation were identified. The number of prolapsed cusps requiring surgical intervention did not predict AV reoperation (p = 0.274).

4.4 Post-Operative Complications

Thirty-four patients (14.3%) experienced 40 post-operative events (Table 10); the most common complication was need for reoperation (I: n=10, 10.6%; II: n=13, 9.1%). Seven patients (3%) experienced a stroke (n=5) or a TIA (n=2). In 6 of these patients, atrial fibrillation had previously been documented.

Seven patients (3%) experienced at least 1 bleeding event. Of these, 5 patients experienced 1 bleeding event, and 2 patients had 2 bleeding events each. Three patients were on anticoagulants when bleeding occurred (1x phenprocoumon, 2x rivaroxaban).

One patient developed aortic valve endocarditis and subsequently underwent AV replacement at a different institution.

In summary, a composite linearized event rate of 2.6% per patient-year was found for the entire cohort (I: 2.3%; II: 2.9%). A table summarising the linearized event rates of individual post-operative complications for both groups is included in Appendix 3.

Type of Complication	Number of Events		
	Fenestration + Prolapse (n=16)	Prolapse (n=24)	All (n=40)
Endocarditis	-	1 (4.2)	1 (2.5)
Stroke/TIA	3 (18.8)	4 (16.7)	7 (17.5)
Bleeding events			
No. of bleeding events	3 (18.8)	6 (25.0)	9 (22.5)
No. of patients affected	2	5	7
Reoperation (total)	10 (62.5)	13 (54.2)	23 (57.5)
AV reoperation	9	10	19
Reoperation for post-operative complications	1	3	4

Table 10. *Frequency of Post-Operative Complications.*
Values are n (%). Percentages may not total 100 because of rounding. *AV*, aortic valve; *No.*, number; *TIA*, transient ischaemic attack.

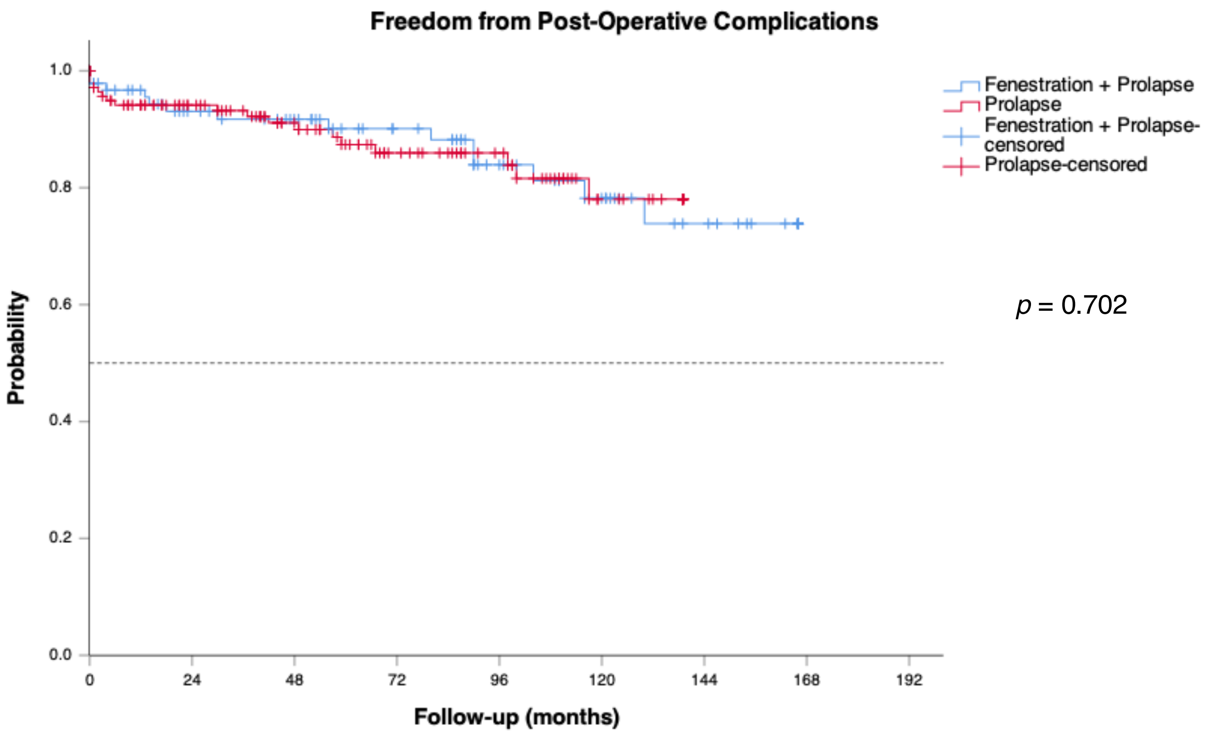
4.4.1 Early Reintervention for Post-Operative Complications

Early reintervention for post-operative complications was rare. In group I, 1 patient underwent replacement of the ascending aorta and partial arch replacement for a type A aortic dissection 7 days after the initial operation. The entry was located at the aortotomy site.

In group II, 2 patients had to be re-explored for post-operative bleeding. The bleeding occurred a few hours after the initial operation in 1 patient, and 4 days after the initial operation in the other patient. A third patient underwent removal of the suture annuloplasty for obstruction of the circumflex artery caused by the suture.
Thus, 30-, 60-, and 90-day freedom from post-operative complications requiring reintervention was 98.3%. It was 98.9% in group I and 97.9% in group II.

4.4.2 Freedom From Post-Operative Complications

Five-year freedom from post-operative complications was 88.6% (I: 90.1%; II: 87.4%). After 10 years, freedom from post-operative complications was 78.0% (I: 78.2%; 78.1%). There was no difference in freedom from post-operative complications between the two groups (*p* = 0.702; Figure 23).



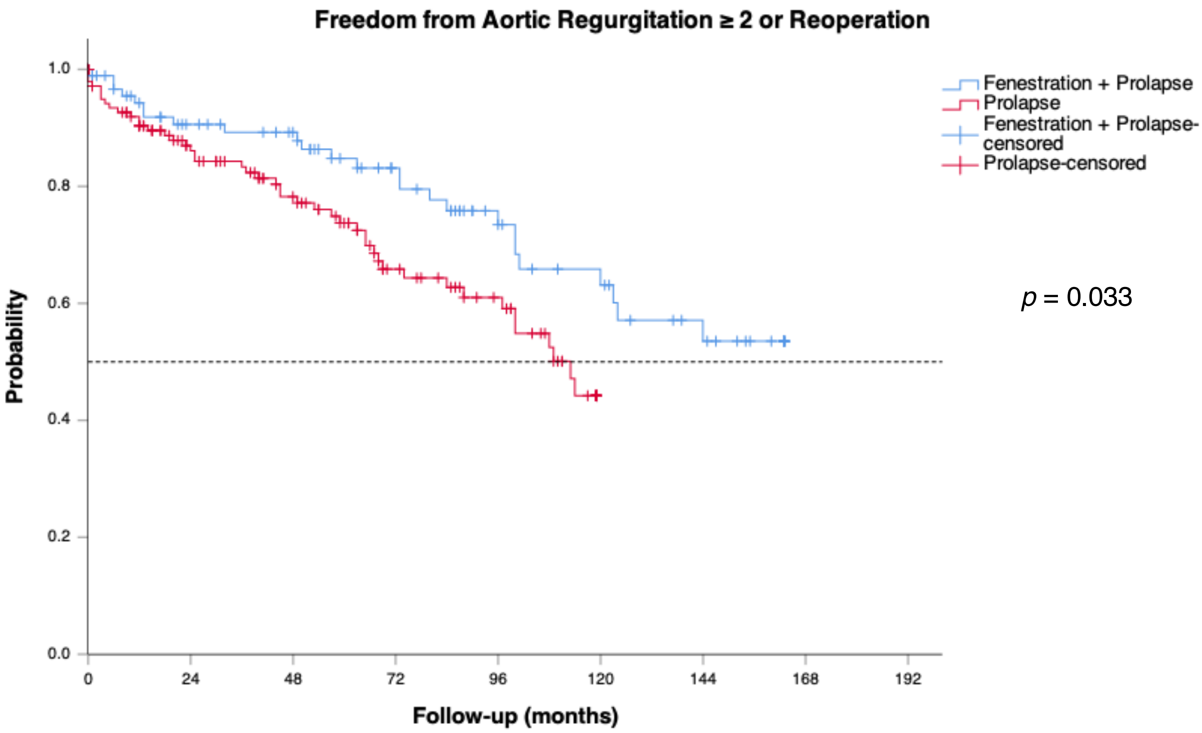
No. at Risk									
Fenestration + Prolapse	94	71	62	49	34	24	15	-	-
Prolapse	143	103	78	55	42	19	-	-	-

Figure 23. *Freedom From Post-Operative Complications Following Aortic Valve Repair.*

4.5 Stability of Aortic Valve Repair: Freedom From Aortic Regurgitation ≥ 2 or Aortic Valve Reoperation

AR ≥ 2 was found in 46 patients who were still alive at the time of follow-up, and who had not yet needed to undergo AV reoperation (I: n=15; II: n=31). Patients' functional status was assessed as NYHA I or II in 82.6% (n=38; I: n=14; II: n=24), and NYHA III in 4.3% (n=2; I: n=1; II: n=1). In the remaining 6 cases (13.0%), patients' NYHA classification was not available.

Freedom from AR ≥ 2 or AV reoperation after 5 years was 78.3% (I: 84.8%; II: 73.7%). After 10 years, freedom from AR ≥ 2 or AV reoperation was 52.7% (I: 63.1%; II: 44.2%). There was a significant difference in freedom from AR ≥ 2 or AV reoperation between the two groups (p = 0.033; Figure 24). Freedom from AR ≥ 2 or AV reoperation was significantly higher in patients with prolapse secondary to fenestration than in patients with prolapse secondary to myxomatous degeneration.



No. at Risk									
Fenestration + Prolapse	94	70	62	46	30	23	15	-	-
Prolapse	143	96	73	45	32	-	-	-	-

Figure 24. *Freedom From Aortic Regurgitation ≥ 2 or AV Reoperation Following Aortic Valve Repair. AV*, aortic valve.

4.5.1 Predictors of Aortic Regurgitation ≥ 2 or AV Reoperation

LCC repair was a statistically significant univariable predictor of recurrent AR ≥ 2 or AV reoperation (p = 0.019; Table 11).

Type of annuloplasty (p = 0.106), geometric height (<20 mm vs. ≥ 20mm; p = 0.244) and the systematic measurement of effective height, introduced in 2004 (p = 0.310), did not predict recurrent AR ≥ 2 or AV reoperation.

Predictor Variable	*p*-value	Hazard Ratio [95% CIs]
Comorbidities	p = 0.325	-
Male sex	p = 0.731	-
Age at operation	p = 0.909	-
1^{st} vs. 2^{nd} half of sample	p = 0.061	-
Type of annuloplasty	p = 0.106	-
AR pre-op	p = 0.181	-
AR discharge	p = 0.085	-
ECC time	p = 0.780	-
Cross-clamp time	p = 0.062	-
gH	p = 0.244	-
No. of prolapsed cusps	p = 0.860	-
Operation before vs. after 2004	p = 0.310	-
LCC repair	**p = 0.019**	1.898 [1.110 – 3.246]
RCC repair	p = 0.780	-
NCC repair	p = 0.731	-

Table 11. *Univariable Predictors of AR ≥ 2 or AV Reoperation, All.*
AR, aortic regurgitation; *CIs*, confidence intervals; *ECC*, extracorporeal circulation; *gH*, geometric height; *LCC*, left coronary cusp; *NCC*, non-coronary cusp; *No.*, number; *pre-op*, preoperatively; *RCC*, right coronary cusp.

In groups I and II, no significant univariable predictors of AR ≥ 2 or AV reoperation could be identified. A table summarising the variables tested as univariable predictors of AR ≥ 2 or AV reoperation within groups I and II is provided in Appendix 4.

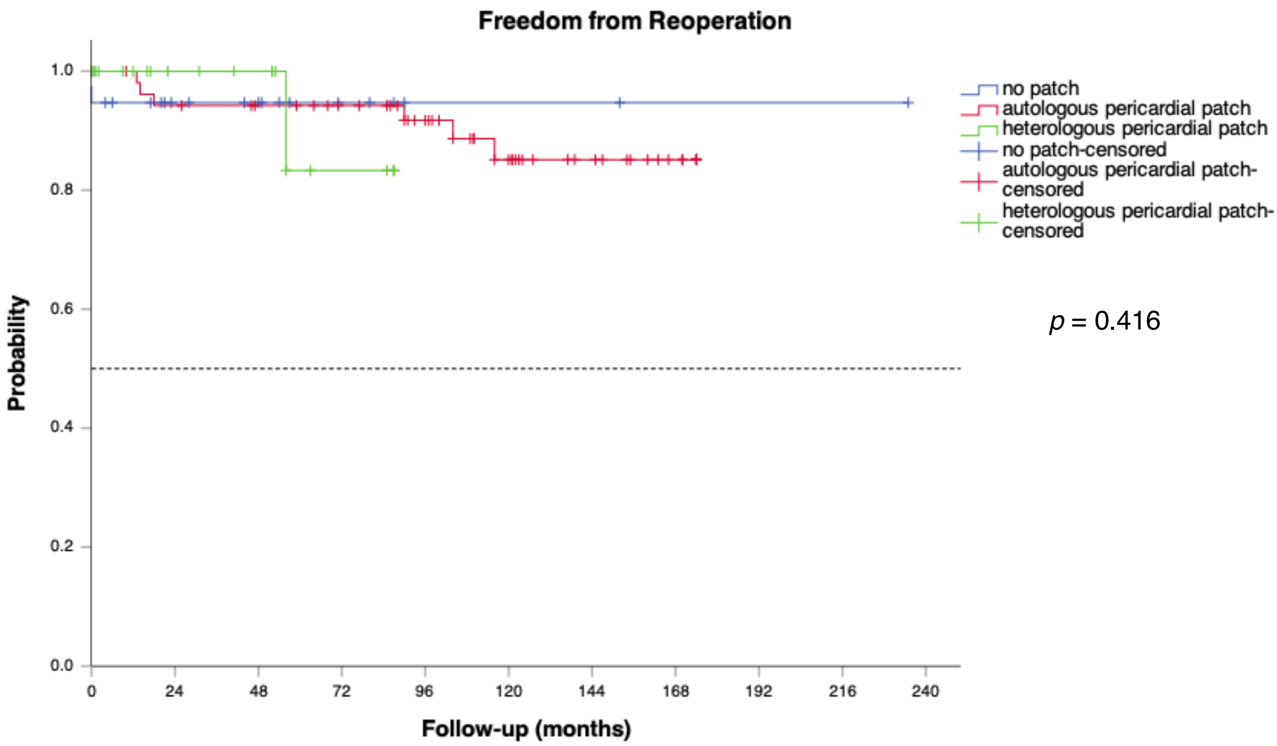
The type of repair (direct suture, autologous pericardial patch, heterologous pericardial patch; p = 0.352) and the number of fenestrations requiring intervention (p = 0.070) did not predict recurrent AR ≥ 2 or AV reoperation in group I. The number of prolapsed cusps requiring surgical intervention did not predict recurrent AR ≥ 2 or AV reoperation in group II (p = 0.921).

4.6 Within-Group Analyses: Fenestration + Prolapse (Group I)

4.6.1 Technique of Repair

There was no statistically significant difference in survival (p = 0.139), freedom from AV reoperation (p = 0.416; Figure 25), freedom from post-operative complications (p = 0.385), or freedom from AR ≥ 2 or AV reoperation (p = 0.330) between patients who had undergone AV repair using an autologous patch (n=54), a heterologous patch (n=21), or a direct suture (n=19).

Kaplan Meier curves illustrating survival, freedom from post-operative complications, and freedom from AR ≥ 2 or AV reoperation for the three groups are included in Appendix 6.



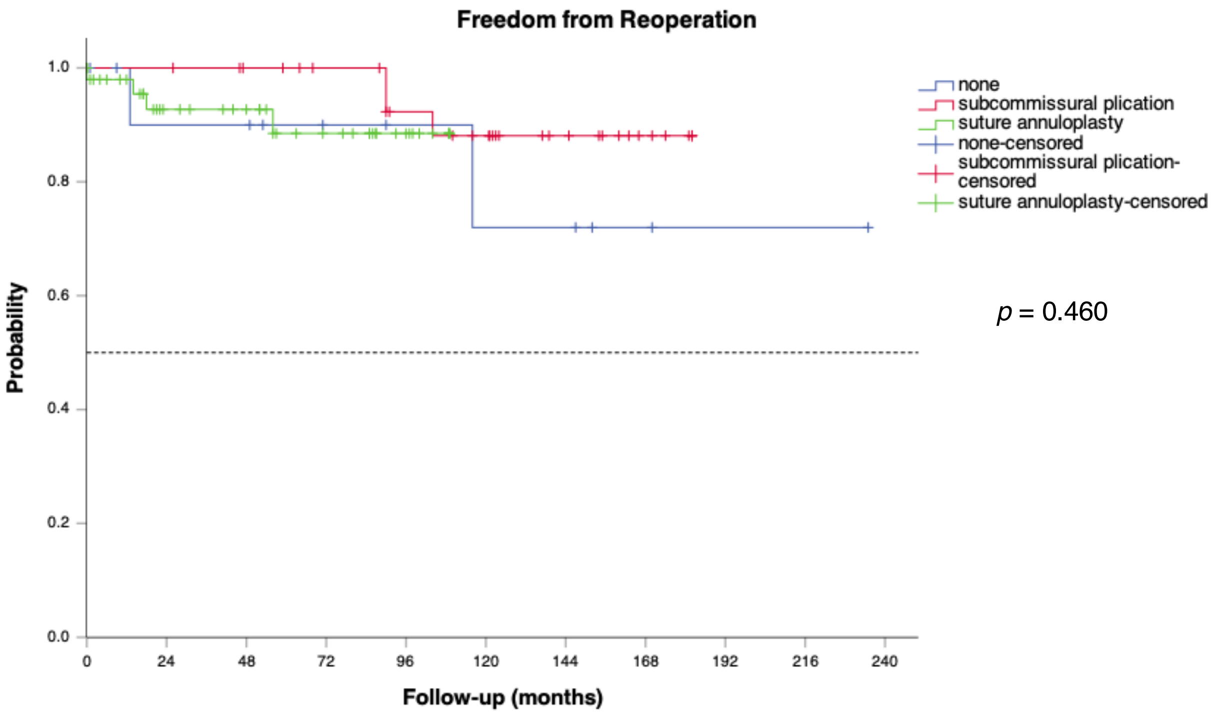
No. at Risk											
No patch	19	12	9	5	2	2	2	1	1	1	-
Autologous patch	54	49	46	42	33	22	14	7	-	-	-
Heterologous patch	21	11	9	3	-	-	-	-	-	-	-

Figure 25. *Group I Freedom From AV Reoperation Following AV Repair, by Technique of Repair. AV*, aortic valve.

4.6.2 Type of Annuloplasty

There was no statistically significant difference in survival (p = 0.433), freedom from AV reoperation (p = 0.460; Figure 26), freedom from post-operative complications (p = 0.343), or freedom from AR ≥ 2 or AV reoperation (p = 0.250) between patients who had undergone annular stabilisation using subcommissural plication (n=33) or suture annuloplasty (n=49), or patients who had not undergone additional stabilisation of the aortic annulus (n=12).

Kaplan Meier curves illustrating survival, freedom from post-operative complications, and freedom from AR ≥ 2 or AV reoperation for the three groups are included in Appendix 7.



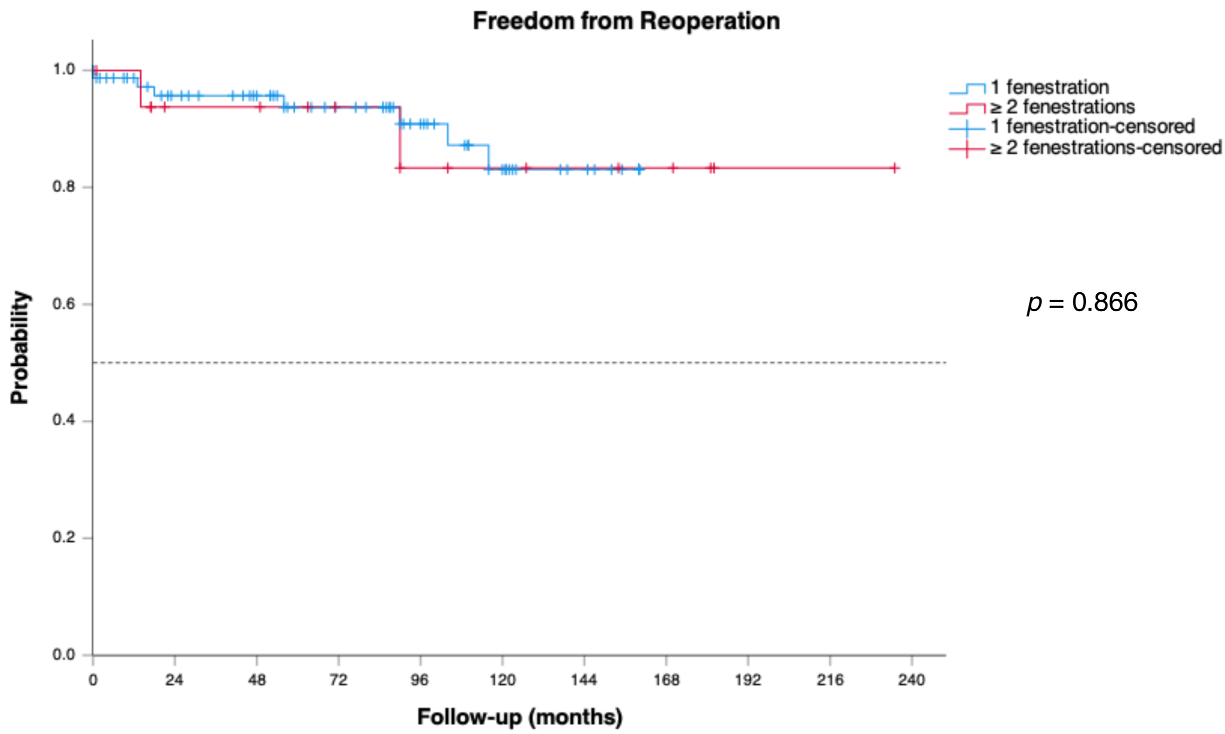
No. at Risk											
None	12	9	9	6	5	4	4	2	1	1	-
Subcommissural plication	33	33	30	27	22	19	12	6	-	-	-
Suture annuloplasty	49	30	25	17	8	-	-	-	-	-	-

Figure 26. *Group I Freedom From AV Reoperation Following AV Repair, by Type of Annuloplasty. AV*, aortic valve.

4.6.3 Number of Fenestrations Requiring Intervention

There was no significant difference in survival (*p* = 0.160), freedom from AV reoperation (*p* = 0.866; Figure 27), freedom from post-operative complications (*p* = 0.374) and freedom from AR ≥ 2 or AV reoperation (*p* = 0.051) between patients who had had 1 (n=77) or ≥ 2 (n=17) fenestrations requiring surgical intervention.

Kaplan Meier curves illustrating survival, freedom from post-operative complications, and freedom from AR ≥ 2 or AV reoperation for both groups are included in Appendix 8.



No. at Risk

1 fenestration	77	60	52	41	28	18	11	-	-	-	-
≥ 2 fenestrations	17	12	12	9	7	6	5	4	1	1	-

Figure 27. *Group I Freedom From AV Reoperation Following AV Repair, by Number of Fenestrations Requiring Intervention. AV*, aortic valve.

5 Discussion

5.1 Background

Over the last two decades, aortic valve repair has undergone continuous refinement in a few expert centres, and it is now an attractive alternative to valve replacement in the treatment of aortic regurgitation [2, 95]. Several studies have been published on the surgical techniques, risk factors, and outcomes of BAV repair [e.g., 69, 86, 106, 108], resulting in evidence-based recommendations for practice [46].

However, relatively little is known about the repair outcomes of TAVs. A few studies have analysed mixed samples of patients with BAVs or TAVs [e.g., 95, 109], but data on carefully selected, homogenous samples of patients with TAVs are scarce. Moreover, those studies that have analysed outcomes of TAV repair often do not differentiate between normal or pathological aortic root dimensions, and usually do not consider the specific mechanisms underlying AR [35, 37, 54]. Thus, the empirical evidence concerning TAV repair outcomes is limited, especially in patients with preserved aortic root dimensions. Furthermore, recent evidence suggests that repair outcomes can differ significantly depending on the underlying pathology, with prolapse repair showing better durability than repair of cusp retraction [9]. As a result, more nuanced information is needed about the outcomes of specific repair techniques used to treat specific underlying cusp pathologies.

The aim of this study was to investigate the long-term outcomes of isolated tricuspid AVr in patients with moderate to severe AR secondary to cusp prolapse. The outcomes of AVr for two specific pathologies, cusp prolapse secondary to myxomatous degeneration or cusp fenestration, were analysed. Furthermore, this study sought to determine whether fenestrations requiring repair are a risk factor for poorer repair outcomes, and whether multiple fenestrations requiring intervention are associated with a poorer prognosis. In patients with cusp fenestration, the influence of different annuloplasty techniques and different types of fenestration repair on long-term outcomes was investigated.

To the best of the author’s knowledge, this study is the first to systematically analyse the outcomes of different repair techniques for cusp prolapse secondary to cusp fenestration. It is also the first to investigate the role of different annuloplasty techniques in the context of fenestration repair. Additionally, it is the first study to explore potential differences in post-operative outcomes following repair of one or multiple fenestrations in TAVs.

5.2 Early Results

In this series, early mortality was low in both groups; no patient died in hospital. All-cause 90-day mortality was 0.4% overall; 0% in patients with a prolapsing cusp requiring fenestration repair and 0.7% in patients with cusp prolapse secondary to myxomatous degeneration. These results are in line with the existing literature. In a recent comparable study, which also investigated outcomes of isolated TAV repair for AR, no in-hospital deaths were reported [115].

Early post-operative morbidity was similarly low. Overall 90-day freedom from reintervention was 98.3%, only one patient had to undergo early re-repair of the AV. In this case, the initial fenestration repair was reinforced using a patch, because the sutures that had originally been used to close the fenestration had cut through the valve tissue. Other indications for early reintervention were post-operative bleeding, circumflex artery stenosis caused by the suture annuloplasty, and type A aortic dissection. Post-operative atrioventricular blocks and in-hospital strokes or TIAs did not occur. The only comparable study did not differentiate between the occurrence of early and late post-operative complications, a direct comparison is therefore not possible. Nevertheless, the results are in line with other studies on AVr, which also reported a low incidence of early post-operative complications [95, 109].

At discharge, 43.4% of patients had trivial or less AR (AR grade 0 or 0 – 1), while 37.1% had mild AR (AR grade 1). Only 3.4% of patients were discharged with AR grade 2. These results compare favourably to the only comparable study in the literature: Tamer et al. [115] discharged 79.5% of patients with AR graded 1+. Only 7.9% were discharged with no AR, and 11.8% of patients were discharged with an AR grade of 2+. In summary, the results of this study suggest that AVr is a safe procedure in patients with TAV regurgitation caused by cusp prolapse, and early post-operative complications are rare.

5.3 Late Results

5.3.1 Survival

Overall 5- and 10-year survival was 92.6% and 77.8%. Furthermore, 10-year survival in patients without and with cardiac comorbidities was 89.2% and 67.0%, respectively, indicating significantly better long-term survival among patients without comorbidities. Similarly, atrial fibrillation at the time of operation resulted in significantly poorer long-term survival compared to patients with a normal sinus rhythm.

The current results are in line with the available literature. In 2014, Sharma and colleagues reported 5- and 10-year survival rates of 91% and 80% in patients who had undergone AVr

for isolated AR at the Mayo Clinic. Furthermore, they found slightly improved 5- and 10-year survival rates of 92% and 85% in patients who did not require any “major” (p. 103) concomitant cardiac procedures. However, Sharma et al. included a heterogeneous group of patients, of whom 40% had undergone BAV repair. Thus, this study’s informational value regarding the long-term outcomes of TAV repair, specifically, is somewhat limited.
In a more comparable sample, Tamer et al. [115] recently reported 5- and 10-year survival rates of 95% and 81%. However, they did not specifically investigate the influence of comorbidities on survival in their cohort. In summary, AVr of TAVs in patients with moderate to severe AR secondary to cusp prolapse is associated with acceptable long-term survival.

In our study, univariable Cox regression identified age, extracorporeal circulation time, cross-clamp time, cardiac comorbidities (compound), atrial fibrillation and tricuspid valve regurgitation as predictors of death. Of these, only age and extracorporeal circulation time remained significant predictors in the multivariable Cox regression model.
Increased extracorporeal circulation and cross-clamp times can be interpreted as proxy variables for repair complexity or severity of cardiac disease. More extensive cardiac disease, such as regurgitation of multiple heart valves, can require several concomitant surgical procedures, thereby extending the time spent on extracorporeal circulation.
Importantly, grade of pre- or post-operative AR, the number of fenestrations requiring repair, or the number of prolapsed cusps requiring repair did not predict late mortality. Operation in the first or second half of the sample was analysed to investigate whether the learning curve associated with greater experience influenced patient survival. There was no evidence of such a trend in this cohort.
The results are similar to those published by Tamer and colleagues [115], who identified age, arteriopathy and chronic hemodialysis as univariable predictors of death; only age and chronic hemodialysis stayed significant in their multivariable model.

Interestingly, there was a significant difference in late survival between the two groups studied, with patients who had undergone fenestration repair showing significantly better survival (10-year survival fenestration + prolapse: 84.5%; prolapse: 72.4%).
This finding was unexpected. However, it must be considered that cardiac comorbidities requiring concomitant interventions, such as atrial fibrillation, were more common in patients with cusp prolapse secondary to myxomatous degeneration. As discussed above, survival was significantly better among patients without concomitant cardiac comorbidities. Thus, the uneven distribution of comorbidities is one possible explanation for the statistical difference in survival between the two groups. This hypothesis is supported by another subgroup analysis,

which showed that survival did not differ between patients without comorbidities from either group.

The use of different types of fenestration repair and annuloplasty techniques did not influence post-operative survival among patients with cusp fenestration. In addition, there was no difference in survival between patients requiring repair of 1 or multiple fenestrations. Thus, repair of ≥ 2 fenestrations does not automatically result in poorer post-operative survival. Continuous follow-up of this cohort will help establish whether any differences between the subgroups might emerge in the very long term.

5.3.2 Freedom From AV Reoperation

Overall 5- and 10-year freedom from AV reoperation was 93.2% and 86.1%, resulting in a linearized rate of AV reoperation of 1.2% per patient-year. Furthermore, reoperation-free survival was 87.2% and 66.9% after 5 and 10 years, respectively.
These results are slightly better than those reported by Tamer and colleagues [115]. In their cohort, 10-year freedom from AV reoperation was 80%, while 10-year reoperation-free survival was 64%. Furthermore, they reported a linearized rate of AV reoperation of 2.2% per patient-year. Thus, the current results are in line with findings from another high-volume cardiothoracic centre with an established track-record in AVr [115].

More importantly, freedom from AV reoperation in this study was superior to freedom from AV reoperation found in patients of a similar age following biological aortic valve replacement [21, 29]. Chan et al. [29] reported an overall freedom from reoperation of 78.9% and 54.7% after 10 and 15 years, respectively; 10-year freedom from reoperation in patients aged 40 to 60 years at implantation was 63.2%. Similarly, Bourguignon and colleagues [21] reported a 10- and 15-year freedom from reoperation of 84.3% and 65.8% in patients under 60 years, as well as a linearized rate of reoperation of 2.6% per valve-year. Thus, the superiority of AVr in terms of freedom from reoperation in this age group is already detectable after 10 years, but may increase further in the future: structural valve deterioration of biological valves – with subsequent reoperation – is known to increase after 10 years post-implantation [29, 57, 67].

Crucially, with a linearized rate of AV reoperation of 1.2% per patient-year, freedom from AV reoperation was also similar to freedom from reoperation following mechanical valve implantation, which is estimated at around 1% per year [57, 60, 91]. For example, Ikonomidis and colleagues found a linearized rate of reoperation of 0.9% and 0.6% per patient-year after a mean follow-up of 7 and 11 years, respectively [60, 66]. However, the durability of mechanical prostheses must be balanced against the increased risk of thromboembolic complications (1.7% per patient-year in [66]) and the risk of bleeding associated with the need for lifelong anticoagulation (2.4% per patient-year in [66]), which is generally not required following AVr.

Additionally, reoperation-free survival following AVr in this cohort (66.9% after 10 years) appears to be similar to that of mechanical AVR. In two large cohorts of patients who had undergone mechanical AVR, 10-year reoperation-free survival[8] was approximately 60.0% [91] and 50.0% [60]. In a third study, it was approximately 24.0% after 15 years [57].

In summary, these comparisons suggest that the durability of AVr for cusp prolapse is similar to the overall durability of AVR with biological and mechanical prostheses. Thus, the current results reinforce the argument that AVr is an attractive alternative to AVR. Furthermore, with follow-up now approaching 20 years, it is conceivable that AVr may result in a stable valve function over two decades in a significant number of patients. As a result, AVr may help a proportion of these patients avoid undergoing subsequent AVR altogether. Ongoing follow-up investigating the very long-term outcomes of AVr will be necessary to confirm or rebut these suggestions.

A number of variables have been found to predict AV reoperation in the past, including age, LCC repair, severity of preoperative AR, and severity of AR at discharge [109, 115]. In this study, AR grade at discharge was the only univariable predictor of AV reoperation, with greater AR resulting in a higher risk of reoperation. In total, 80.5% of patients were discharged with trivial or less AR (AR grade 0 or 0-1; 43.4%) or mild AR (AR grade 1; 37.1%). Only 3.4% of patients had AR grade 2 at discharge. As discussed above, these numbers compare favourably to the existing literature. Tamer et al. [115] discharged 7.9% of patients with no AR, 79.5% had AR grade 1+, and 11.8% of patients were discharged with AR graded 2+.

The role of AR at discharge as a predictor of AV reoperation may help explain the differences in outcomes regarding AV reoperation between these two TAV repair studies. In our study, the median interval between operations was longer (median 4.8 vs 3.7 years), and AV reoperation was less frequent, although this difference failed to reach statistical significance (8.0% vs. 14.2%; $p = 0.064$). More importantly, in our cohort, 19 patients underwent AV reoperation over a cumulative follow-up of 1 530 patient-years, whereas Tamer and colleagues [115] recorded 18 AV reoperations over a period of 809 patient-years. Thus, the linearized event rate for AV reoperation in our study was lower (1.2% vs. 2.2% per patient-

[8] Reoperation-free survival was not explicitly analysed in these studies. It has therefore been approximated by subtracting the proportion of patients who underwent reoperation from those who were still alive after 10 or 15 years.

year). In summary, the results provide support for the practice of immediate reintervention to correct any residual AR exceeding grade 1 (“mild AR”) at the end of the initial procedure. This practice may help reduce the need for subsequent AV reinterventions in the long run.

Involvement of the LCC was found to predict reoperation in a previous study [115]. In our study, this association could not be replicated. Neither LCC involvement, nor the technique of fenestration repair, or the type of annuloplasty were found to predict AV reoperation. Furthermore, a geometric height of less than 20mm, the number of fenestrations or prolapsed cusps, and the presence of comorbidities did not predict reoperation, either. Finally, the systematic measurement of effective height, introduced in 2004, did not predict need for AV reoperation. However, this result has to be considered carefully, as the number of patients who underwent AVr before 2004 was very limited (n = 14). Thus, the role of effective height in predicting AV repair failure needs to be evaluated in a more appropriate sample in the future.

The specific repair results of cusp prolapse secondary to myxomatous degeneration and fenestration have not been systematically analysed and compared before. However, previous studies have postulated that tissue defects such as fenestrations, which often require patch repair, represent a risk factor for repair failure [98, 106, 115].
On the other hand, a 2010 study by the Homburg group, which analysed early outcomes of tricuspid AVr in 39 patients with fenestrations, found no evidence of reduced repair stability [102]. These findings are in line with a recent study investigating outcomes of patch repair for different valve pathologies [69]. Karliova and colleagues [69] presented two conclusions of relevance to the current study: First, freedom from reoperation following pericardial patch repair was significantly better in TAVs than in BAVs. Second, repair stability differed depending on the underlying cusp pathology. For example, the durability of patch repair for cusp fenestration was superior to patch repair of retracted or calcified cusps.
The current results support and extend the early findings published in 2010. Specifically, they suggest that TAV repair of prolapsed fenestrated cusps is as durable as that of prolapsed non-fenestrated cusps. There was no difference in freedom from AV reoperation between the two groups, and reoperation-free survival at 5 and 10 years was also similar: it was 89.4% and 69.6% in patients requiring fenestration repair, and 85.6% and 64.7% in patients with cusp prolapse secondary to myxomatous degeneration.
In summary, this study supports the notion that fenestrated TAVs causing AR can be repaired with acceptable long-term stability. Thus, our current evidence suggests that fenestrations per se do not represent a risk factor for repair failure in TAVs.

Within group I (fenestration + prolapse) neither the type of fenestration repair, nor the type of annuloplasty, nor the number of fenestrations requiring repair were found to influence freedom from AV reoperation.
No previous study has systematically investigated the outcomes of different techniques of fenestration repair, therefore a comparison with previous studies is not possible. Different techniques may be chosen depending on a fenestration's size, the quality of the remaining cusp tissue, and depending on whether the marginal strand covering the fenestration has ruptured. Small fenestrations can often be closed directly, while larger defects and ruptured fenestrations usually require patch repair. Any remaining tissue redundancy can be corrected using central plication or – in the case of excessive tissue redundancy – triangular resection [102]. Some surgeons prefer to reinforce the free margin with a PTFE suture [37], however data on its differential impact on outcomes in fenestration repair have not been published yet.
In our study, 5- and 10-year freedom from AV reoperation was 94.2% and 85.1% for autologous pericardium, and 94.7% following direct closure of a fenestration (Appendix 6). For heterologous pericardium 5- and 7-year freedom from AV reoperation was 83.3%. Thus, fenestration repair using a direct suture, an autologous pericardial patch or a heterologous pericardial patch did not result in differences in freedom from AV reoperation.
However, it must be noted that heterologous pericardium has been used regularly for fenestration repair at this institution since 2012. As a result, the average follow-up of these patients is still limited, and only 3 patients remained at risk after 72 months of follow-up (14.3% of the original cohort size). Continuous follow-up of this cohort will be necessary to investigate whether differences between the three approaches may emerge in the future.

In BAV repair, addition of an annuloplasty has become standard practice, because studies from experienced centres have shown a beneficial impact on repair outcomes [5, 38, 75, 107]. However, a number of different annuloplasty techniques have been proposed, and comparing these techniques can be difficult. Cabrol's subcommissural plication was introduced in 1966, and became widely adopted [25]. Nevertheless, alternative approaches have been put forward since, including circumferential annuloplasty techniques such as a single or double external ring annuloplasty [75, 76] or a suture annuloplasty [5, 107]. Another technique used for annular stabilisation is the prosthetic-based circumferential annuloplasty that is automatically provided as part of valve-sparing root replacement using the reimplantation technique [38, 40].
Oftentimes, studies evaluating different annuloplasty techniques are not comparable, as repair approaches can differ substantially beyond the respective chosen annuloplasty (e.g., some surgeons do not measure the valve's geometric properties). This results in a multitude of potential confounding factors that cannot easily be accounted for. Furthermore, direct comparisons between different techniques used at one centre are rare. Nevertheless, two

studies suggest that suture annuloplasty and valve-sparing reimplantation are associated with greater freedom from AV reoperation than subcommissural plication in BAVs [38, 106]. In summary, while the value of adding an annuloplasty in BAVs is widely acknowledged, opinions on the implementation diverge.
Tamer et al. [115] were the first to compare repair outcomes among patients with TAVs who had undergone subcommissural plication (n=93), or either valve sparing root replacement with AV reimplantation or external ring annuloplasty (n=33). Contrary to the studies on BAV repair, no difference in freedom from AV reoperation was found. Tamer and colleagues argue that a few factors may contribute to this difference between BAV and TAV repair. First, annular diameters in BAVs tend to be larger than in TAVs [74, 110]. Thus, the absolute benefit of adding an annuloplasty for additional stabilisation might be smaller in TAVs.
Second, they suggest that severity of cusp lesion might be the single most important factor determining repair stability in TAVs with severe isolated AR. Consequently, the scope of annuloplasty techniques to have a beneficial impact on freedom from AV reoperation in TAVs may be limited.
In the current study, there was no difference in freedom from AV reoperation between patients with fenestrated cusps who had received additional annular stabilisation (subcommissural plication, suture annuloplasty) and those who had not. This is in line with results presented by Tamer and colleagues [115].
In summary, the type of annuloplasty does not seem to influence freedom from AV reoperation in TAV repair for fenestration-induced cusp prolapse. However, it must also be noted that the low rate of AV reoperations makes it harder to detect differential effects of any particular annuloplasty technique in a sample of roughly 100 patients. As the size of this cohort grows, future studies will be able to provide more clarity on the role of different annuloplasty techniques in TAV repair for isolated AR secondary to cusp fenestration.

Finally, freedom from AV reoperation in group I did not differ depending on whether patients required closure of 1 or ≥ 2 fenestrations. The results of this study show that TAVs with 2 fenestrations can also be repaired safely, without compromising repair durability. Thus, the presence of more than 1 fenestration requiring intervention should not automatically be considered a contraindication for TAV repair.

5.3.3 Freedom From Post-Operative Complications

For the purpose of this study, 'post-operative complications' were defined as any reoperation, operated-valve endocarditis, thromboembolic event (e.g., stroke, TIA), and any episode of major bleeding. AVr is generally associated with low rates of post-operative complications, and reoperation has repeatedly been identified as the most common complication [2, 95, 115]. Tamer and colleagues [115] reported that reoperation accounted for 58.1% of complications in their cohort. Additionally, they found a composite linearized event rate for post-operative complications of 3.8% per patient-year; individual linearized event rates of AV reoperation, thromboembolic events, endocarditis and major bleeding were 2.2%, 1.2%, 0.3%, and 0.1% per patient-year, respectively.

In this study, 5- and 10-year freedom from post-operative complications was 88.6% and 78.0%, respectively. There was no significant difference between the two groups investigated. The most common post-operative complication was reoperation (57.5%), followed by bleeding (22.5%), and thromboembolic events (17.5%). Endocarditis (2.5%) was extremely rare. The composite linearized event rate for post-operative complications was 2.6% per patient-year. Individual linearized event rates per patient-year were 1.5% for any reoperation, 0.6% for major bleeding, 0.5% for thromboembolic events and 0.1% for endocarditis[9]. Thus, the number of post-operative complications was slightly lower than that reported by Tamer et al. [115], but reoperations accounted for the majority of post-operative complications in both studies.

The results provide further evidence that AVr is associated with low rates of post-operative complications, especially when compared to mechanical AVR. For example, Oxenham et al. [91] reported major bleeding and thromboembolic events in 12.2% and 9.8% of patients after 10 years of follow-up, while Ikonomidis et al. [60] found rates of 18% and 23%, respectively. In the Veterans Affairs Trial, the 15-year incidence of bleeding and systemic embolism after mechanical AVR was 51% and 18%, respectively [57]. Thus, major bleeding and thromboembolic events, which each affected 3% of patients in this cohort, are observed less frequently after AVr than following mechanical AVR. The same is true for endocarditis, which only affected 0.4% of patients in our study, but has been found in approximately 5% of patients following mechanical – and biological – AVR [60, 66, 91].

Finally, this study's relatively low number of post-operative complications is reflected in the linearized event rates, which compare favourably to those found after mechanical AVR: Johnson et al. [66] reported linearized rates of bleeding, thromboembolic events, reoperation, and endocarditis of 2.4%, 1.7%, 0.6%, and 0.5% per patient-year, respectively. This results in

[9] Individual rates do not add up to 2.6% because of rounding.

a composite linearized event rate of 5.2% per patient-year, which is approximately twice as high as the 2.6% per patient-year found after AVr in this study.

In patients with cusp fenestration, neither the different techniques of fenestration repair, nor the different types of annuloplasty, or the number of fenestrations requiring intervention resulted in differences in freedom from post-operative complications.
Thus, closure of fenestrations in TAV repair is associated with low rates of post-operative complications, independently of whether cusps are repaired using autologous pericardium, heterologous pericardium, or a direct suture. Furthermore, the results provide yet further evidence that the presence of more than 1 fenestration requiring intervention should not be considered a contraindication for AVr.

5.3.4 Freedom From AR ≥ 2 or AV Reoperation

In the only comparable study, Tamer and colleagues [115] recently reported a 41% probability of maintaining freedom from AR ≥ 2 after 10 years of follow-up. In our cohort, freedom from recurrent moderate to severe aortic regurgitation (AR ≥ 2) or AV reoperation was 78.3% and 52.7% at 5 and 10 years of follow-up. Thus, the results are in line with the available TAV repair literature.
A conservative cut-off of AR ≥ 2 was chosen because the absolute number of patients with AR grades of 2 – 3 (n=6; 2.5%) and 3 (n=2; 0.8%) was very small. So far, only 15% of patients with recurrent AR ≥ 2 have had to undergo AV reoperation, although approximately one third of patients have experienced a recurrence of AR ≥ 2. Thus, in most patients, recurrent AR ≥ 2 did not automatically result in AV reoperation. Furthermore, 82% of patients who have experienced a recurrence of AR ≥ 2, who are still alive and have not had to undergo reoperation, have a current NYHA functional class of I or II; only 4% are graded as NYHA III.
In summary, recurrent AR ≥ 2 affects a relevant number of patients following TAV repair. However, the results of this study suggest that the majority of patients with recurrent AR ≥ 2 will remain stable for a considerable number of years.

Tamer et al. [115] identified age, left ventricular end-diastolic diameter, ventriculoaortic junction diameter, free-margin resuspension, cardiopulmonary bypass time, and patch repair as univariable predictors of recurrent AR severity. Only age, left ventricular end-diastolic diameter, and patch repair remained significant in the multivariable model. None of these variables were found to be significant predictors of recurrent AR ≥ 2 or AV reoperation in this study.

In our cohort, repair of the LCC was the only univariable predictor of recurrent AR ≥ 2 or AV reoperation, with LCC repair resulting in a higher risk of recurrent AR or reoperation. Interestingly, LCC repair was found to predict AV reoperation by Tamer and colleagues [115]. Thus, both studies concur that involvement of the LCC may be a risk factor for reduced repair durability. It has been suggested that LCC involvement could be an expression of more severe or more diffuse disease [115]. On the other hand, the number of prolapsed cusps or the number of fenestrations requiring intervention were not associated with reduced repair durability in our series. This suggests that severity of disease may not be the sole explanation for the link between LCC involvement and reduced repair durability. Thus, the causal mechanisms that may be driving the association between LCC involvement and limited repair durability are currently unclear, and warrant further investigation.
Pre- and post-operative AR, patients' comorbidity status, the number of prolapsed cusps, or cusps' geometric height were not found to predict recurrent AR or reoperation. In summary, the current results suggest that TAV repair is durable, even in patients with severe AR secondary to cusp prolapse. This also seems to hold true in patients with complex cusp lesions, such as multiple prolapsed cusps, and those who require patch repair for valve fenestration. Nevertheless, LCC repair appears to be a risk factor for reduced repair durability, and the reasons for this association need to be explored in detail in the future.

There was a significant difference in freedom from recurrent AR ≥ 2 or AV reoperation between the two groups studied; patients with prolapsing cusps secondary to cusp fenestration showed significantly better freedom from AR ≥ 2 or AV reoperation after the repair. However, this difference was predominantly seen in patients with cardiac comorbidities and could not be replicated in a subgroup of patients without comorbidities. A separate subgroup analysis showed that patients' comorbidity status did not influence freedom from AV reoperation, and it is currently unclear why cardiac comorbidities may be associated with a higher incidence of AR recurrence in patients with prolapse secondary to myxomatous degeneration. Thus, more research is needed to investigate what may be driving this group difference, and it will be interesting to see if these findings can be replicated in other cohorts in the future.

No within-group differences were found in group I (fenestration + prolapse). Interestingly, there was no significant difference in freedom from AR ≥ 2 or AV reoperation between patients whose fenestration was closed using a direct suture, an autologous pericardial patch, or a heterologous pericardial patch. Thus, the current results suggest that the insertion of patch material per se does not seem to be associated with reduced freedom from AR ≥ 2 or AV reoperation in the mid- to long term. They also provide further evidence that the use of

autologous or heterologous pericardium in fenestration repair leads to comparable repair durability in this time frame.
Continuous follow-up of this cohort will show whether repair durability following direct closure of a fenestration may turn out to be superior to patch repair in the very long term. It will also help determine whether differences in repair durability between the two patch materials will eventually emerge as follow-up time continues to increase.

Tamer et al. [115] reported no difference in freedom from severe recurrent AR among patients who had undergone subcommissural plication or had received a circumferential annuloplasty. The current results are in line with these findings. The use of subcommissural plication, suture annuloplasty, or no additional annuloplasty did not result in statistically significant differences in freedom from AR ≥ 2 or AV reoperation.
However, it is possible that the benefits of a circumferential annuloplasty in fenestrated TAVs are essentially similar to those in BAVs, but less pronounced. In this study, only 14% (n=7) of the original cohort who had undergone suture annuloplasty remained at risk after 8 years of follow-up. Thus, it is conceivable that the current statistical analysis may have failed to identify differences between the groups because of a relatively small sample size, or an insufficiently long follow-up period. Careful analysis of the second decade following AVr will be necessary to evaluate this hypothesis.

Finally, the number of fenestrations requiring surgical intervention did not result in a significant difference in freedom from AR ≥ 2 or AV reoperation. These results provide yet further evidence that the presence of more than 1 fenestration requiring intervention should not be considered a contraindication for valve repair in TAVs.

5.4 Clinical Implications

This study has a number of important clinical implications. First, isolated AV repair of TAVs for AR caused by cusp prolapse can be performed safely, with acceptable long-term stability and low rates of post-operative complications. In this cohort, AVr was comparable to biological AVR in terms of similarly low rates of reoperation. Additionally, post-operative complications, such as major bleeding or thromboembolic events, were observed less frequently than following mechanical AVR. Consequently, AVr is an attractive alternative to valve replacement, especially in young patients below the age of 60.
In accordance with the current European [121] and American [90] guidelines, the majority of patients with significant AR under 60 would be advised to undergo mechanical AVR in most

centres. Nevertheless, some surgeons – and patients – advocate the use of biological prostheses in this age group to avoid the risks associated with lifelong anticoagulation [24, 29, 47]. These patients subsequently face the prospect of multiple reinterventions to re-replace their biological valves because of structural valve degeneration [12, 29, 48, 67]. The results of this study suggest that valve repair could help delay AVR by many years, possibly decades, in a relevant number of these patients. This delay would have significant implications, because each additional year of age at implantation of a biological prosthesis has been shown to reduce the risk of subsequent reoperation by up to 6% [29]. Thus, delaying the implantation of a prosthesis by over a decade would substantially reduce the likelihood of subsequent interventions, making AVr an attractive alternative to 'early' biological AVR in young patients. In summary, AVr should be discussed as an alternative to valve replacement in patients with TAV morphology and isolated AR secondary to cusp prolapse.

Second, a durable repair result can be expected in the majority of patients with TAV morphology and moderate to severe AR secondary to cusp prolapse. Severe preoperative AR [109], multiple prolapsing cusps, or cusp fenestration were not found to be risk factors for poor repair durability in this study. Based on these results, a repair approach appears justified even in cases of more complex valve lesions.

However, more severe AR at discharge was identified as a predictor of AV reoperation, while involvement of the LCC was predictive of recurrent AR $\geq$ 2 or AV reoperation. Thus, adopting a low threshold for reintervention following detection of more than mild residual AR (AR > 1) at the end of the initial procedure appears reasonable and may help improve repair durability further. Furthermore, surgeons should be aware that involvement of the LCC may be a risk factor for repair failure.

Third, the results of this study suggest that outcomes of patch repair, if used for fenestration repair, are surprisingly good. Despite the increased repair complexity, evidenced by a longer clamping time, the results were almost identical to those of cusp prolapse secondary to myxomatous degeneration. Repair outcomes appear to differ depending on the underlying cusp pathology and valve morphology [9, 69], and in TAVs with isolated AR secondary to cusp prolapse because of cusp fenestration, patch repair appears to offer satisfactory long-term durability. Thus, patch repair should be considered an acceptable repair technique in fenestrated TAVs.

Fourth, the results suggest that there is no difference in the performance of autologous or heterologous pericardium as substrates for patch repair in fenestrated TAVs. Therefore, both materials should remain an acceptable choice for closing fenestrations in TAVs.

Finally, the presence of more than 1 fenestration requiring surgical intervention should not preclude aortic valve repair in TAVs. It seems that these valves can also be repaired safely. Moreover, the current results suggest that there are no significant differences in repair outcomes following closure of 1 or 2 fenestrations in TAVs.

5.5 Study Limitations

This study is a retrospective analysis of data from a single-centre cohort of patients, and operations were performed by a highly experienced surgical team. This may affect the generalisability of the results. Data collection largely relied on documentation from patients' treating physicians, as well as patient histories. As a result, there were differences in the amount of data recorded for each patient visit, especially in terms of echocardiographic measurements. However, follow-up was complete for the outcome variables analysed in this study. To minimise recall bias and to improve accuracy of patient histories, regular updates of patient histories were sought throughout the follow-up period. This was achieved through regular contact with the patients themselves, or by closely following updates of the history taken by their treating physician at follow-up appointments.

Furthermore, the two groups investigated in this study were not completely homogenous. They differed in terms of group size, age, cross-clamp time, distribution of cusp pathology, as well as the frequency of different annuloplasty techniques and cardiac comorbidities. However, subgroup analyses were run to explore the role of potential confounding factors.

Finally, the overall size of this sample is limited, resulting in reduced statistical power [33]. Nevertheless, to the best of the author's knowledge, this study provides an analysis of the largest currently available sample of patients who underwent TAV repair for moderate to severe isolated AR secondary to cusp prolapse. Moreover, it also provides a detailed analysis of what seems to be the largest currently available sample of patients who underwent isolated TAV repair for moderate to severe AR secondary to cusp fenestration.

5.6 Conclusion

Moderate to severe isolated TAV regurgitation is a relatively rare aortic valve pathology [43, 115]. At Saarland University Hospital, 441 patients underwent AVr for isolated AR of a TAV between 2000 and 2020. In just over 50% of these patients, moderate to severe AR was caused by cusp prolapse, which was the result of myxomatous degeneration in 60% of cases, and cusp fenestration in 40% of cases. Thus, although relatively rare, isolated AR will frequently require correction of cusp prolapse, and two common aetiologies are cusp fenestration and myxomatous degeneration.

The results of this study demonstrate that AVr of cusp prolapse in patients with isolated AR and TAV morphology is a safe and durable alternative to valve replacement. Survival is excellent in patients without cardiac comorbidity, and post-operative complications are rare. Moreover, fenestration repair in TAVs is equally safe and durable as simple prolapse correction. The results of this study show that fenestrations can be closed using a pericardial patch or a direct suture, and both approaches will produce comparable mid- to long-term outcomes. Furthermore, both autologous and heterologous pericardium appear to be acceptable substrates for patch repair.

In this cohort, AR at discharge was identified as the only significant predictor of AV reoperation. Consequently, adopting a low threshold for immediate reintervention in cases of more than mild residual regurgitation (AR > 1) at the end of the initial procedure may help improve repair durability. At this time, there is no evidence to support the superiority of circumferential annuloplasty techniques over subcommissural plication in improving durability of TAV repair.

Finally, the results of this study emphasize the importance of carefully selected inclusion criteria that allow for nuanced analyses of different underlying pathologies. It is the only reliable way to determine which repair techniques are appropriate for specific underlying cusp pathologies and valve morphologies.

6 Appendices

6.1 Appendix 1. Results of Univariable Cox Regression Models for Identification of Predictors of Death, by Group

Table 12 summarises the results of univariable Cox regression models testing different variables as univariable predictors of death within groups I and II.

Predictor Variable	Group			
	Fenestration + Prolapse		Prolapse	
	p-value	Hazard Ratio [95% CIs]	*p*-value	Hazard Ratio [95% CIs]
Comorbidities (compound)	$\mathbf{p = 0.045}$	3.153 [1.025 – 9.706]	$p = 0.100$	-
CAD	$\mathbf{p = 0.005}$	5.640 [1.694 – 18.782]	$p = 0.808$	-
Atrial fibrillation	$p = 0.468$	-	$\mathbf{p = 0.016}$	2.552 [1.193 – 5.461]
MVR	$p = 0.491$	-	$p = 0.064$	-
TVR	$p = 0.226$	-	$\mathbf{p = 0.027}$	2.633 [1.113 – 6.226]
Male sex	$p = 0.364$	-	$p = 0.516$	-
Age at operation	$\mathbf{p = 0.005}$	1.083 [1.024 – 1.145]	$\mathbf{p < 0.001}$	1.104 [1.045 – 1.167]
1st vs. 2nd half of sample	$p = 0.984$	-	$p = 0.503$	-
Type of annuloplasty	$p = 0.455$	-	$p = 0.620$	-
AR pre-op	$p = 0.937$	-	$p = 0.834$	-
AR discharge	$p = 0.552$	-	$p = 0.636$	-
Time on ECC	$p = 0.184$	-	$\mathbf{p = 0.002}$	1.018 [1.007 – 1.030]
Cross-clamp time	$p = 0.590$	-	$\mathbf{p = 0.002}$	1.030 [1.011 – 1.050]
Geometric height	$p = 0.624$	-	$p = 0.597$	-
Operation before vs. after 2004	$p = 0.197$	-	$p = 0.454$	-
Type of repair (fenestration)	$p = 0.389$	-	-	-
No. of fenestrations	$p = 0.192$	-	-	-
No. of prolapsed cusps	$p = 0.106$[1]	-	$p = 0.798$	-
LCC repair	$p = 0.706$	-	$p = 0.543$	-
RCC repair	$p = 0.450$	-	$p = 0.951$	-
NCC repair	$p = 0.620$	-	$p = 0.710$	-

Table 12. *Univariable Predictors of Late Death, by Group.*
AR, aortic regurgitation; *CAD*, coronary artery disease; *CIs*, confidence intervals; *ECC*, extracorporeal circulation; *LCC*, left coronary cusp; *MVR*, mitral valve regurgitation; *NCC*, non-coronary cusp; *No.*, number; *pre-op*, preoperatively; *RCC*, right coronary cusp; *TVR*, tricuspid valve regurgitation.
[1] *p*-value after exclusion of the only patient with 3 prolapsing cusps in group I (n=93).

The assumption of proportional hazards was assessed visually using Kaplan Meier curves for all statistically significant categorical predictor variables [126].
In group I, the assumption of proportional hazards was met for comorbidities (compound) and CAD. In group II, the assumption of proportional hazards was met for tricuspid valve regurgitation. It was not met for atrial fibrillation.

Furthermore, only a single patient in group I was found to have 3 prolapsing cusps. Very small sample sizes are vulnerable to the effect of outliers and may disproportionately distort the results of statistical analyses [112]. Thus, this patient was excluded from the analysis. The current study can only evaluate differences between 1 or 2 prolapsing cusps in patients with cusp prolapse secondary to fenestration. In the future, more representative samples are needed to evaluate whether the presence of 3 prolapsing cusps is a predictor of death.

Individual multivariable Cox regression models were not run because of the insufficient number of events in each group. When multiple variables are analysed simultaneously, a minimum of 10 events per variable is generally recommended to ensure that results are reliable [92]. This requirement was not fulfilled in group I (n=13), nor in group II (n=26).

6.2 Appendix 2. Results of Univariable Cox Regression Models for Identification of Predictors of Reoperation, by Group

Table 13 summarises the results of univariable Cox regression models testing different variables as univariable predictors of AV reoperation within groups I and II.

Predictor Variable	Group			
	Fenestration + Prolapse		Prolapse	
	p-value	Hazard Ratio [95% CIs]	*p*-value	Hazard Ratio [95% CIs]
Comorbidities	p = 0.149	-	p = 0.425	-
Male sex	p = 0.330	-	p = 0.148	-
Age at operation	**p = 0.016**	0.956 [0.921 – 0.992]	p = 0.148	-
1st vs. 2nd half of sample	p = 0.526	-	p = 0.624	-
Type of annuloplasty	p = 0.481	-	p = 0.707	-
AR pre-op	p = 0.703	-	p = 0.349	-
AR discharge	p = 0.293	-	p = 0.076	-
Time on ECC	p = 0.861	-	p = 0.246	-
Cross-clamp time	p = 0.846	-	p = 0.532	-
gH	p = 0.908	-	p = 0.335	-
Operation before vs. after 2004	p = 0.718	-	p = 0.500	-
Type of repair (fenestration)	p = 0.451	-	-	-
No. of fenestrations	p = 0.866	-	-	-
No. of prolapsed cusps	p = 0.733[1]	-	p = 0.274	-
LCC repair	p = 0.236	-	p = 0.459	-
RCC repair	p = 0.425	-	p = 0.425	-
NCC repair	p = 0.683	-	p = 0.623	-

Table 13. *Univariable Predictors of AV Reoperation, by Group.*

AR, aortic regurgitation; *CIs*, confidence intervals; *ECC*, extracorporeal circulation; *gH*, geometric height; *LCC*, left coronary cusp; *NCC*, non-coronary cusp; *No.*, number; *pre-op*, preoperatively; *RCC*, right coronary cusp.

[1] *p*-value after exclusion of the only patient with 3 prolapsing cusps in group I (n=93).

In group I, age at operation was the only univariable predictor of AV reoperation. In this group, only a single patient was found to have 3 prolapsing cusps. Very small sample sizes are vulnerable to the effect of outliers and may disproportionately distort the results of statistical analyses [112]. Thus, this patient was excluded from the analysis. The current study can only evaluate differences between 1 or 2 prolapsing cusps in patients with cusp prolapse secondary to fenestration. In the future, more representative samples are needed to evaluate whether the presence of 3 prolapsing cusps is a predictor of AV reoperation.

6.3 Appendix 3. Linearized Event Rates of Individual Post-Operative Complications

Type of Complication	Linearized Event Rate (in % per Patient-Year)		
	Fenestration + Prolapse	Prolapse	All
Endocarditis	0.00	0.12	0.07
Stroke/TIA	0.43	0.48	0.46
Bleeding events	0.43	0.71	0.59
Reoperation (total)	1.45	1.55	1.50
AV Reoperation	1.30	1.19	1.24
Reoperation for post-operative complications	0.14	0.36	0.26

Table 14. *Linearized Event Rates of Post-Operative Complications, by Group.*
AV, aortic valve; *TIA*, transient ischaemic attack.

6.4 Appendix 4. Results of Univariable Cox Regression Models for Identification of Predictors of Aortic Regurgitation ≥ 2 or Aortic Valve Reoperation

Table 15 summarises the results of univariable Cox regression models testing different variables as potential univariable predictors of AR ≥ 2 or AV reoperation within groups I and II.

Predictor Variable	Group			
	Fenestration + Prolapse		Prolapse	
	p-value	Hazard Ratio [95% CIs]	*p*-value	Hazard Ratio [95% CIs]
Comorbidities	$p = 0.086$	-	$p = 0.638$	-
Male sex	$p = 0.378$	-	$p = 0.472$	-
Age at operation	$p = 0.385$	-	$p = 0.755$	-
1st vs. 2nd half of sample	$p = 0.360$	-	$p = 0.080$	-
Type of annuloplasty	$p = 0.265$	-	$p = 0.398$	-
AR pre-op	$p = 0.195$	-	$p = 0.252$	-
AR discharge	$p = 0.574$	-	$p = 0.079$	-
Time on ECC (min)	$p = 0.099$	-	$p = 0.480$	-
Cross-clamp time (min)	$p = 0.061$	-	$p = 0.539$	-
gH	$p = 0.540$	-	$p = 0.131$	-
Operation before vs. after 2004	$p = 0.450$	-	$p = 0.839$	-
Type of repair (fenestration)	$p = 0.352$	-	-	-
No. of fenestrations	$p = 0.070$	-	-	-
No. of prolapsed cusps	$p = 0.486$[1]	-	$p = 0.921$	-
LCC repair	$p = 0.158$	-	$p = 0.110$	-
RCC repair	$p = 0.745$	-	$p = 0.450$	-
NCC repair	$p = 0.311$	-	$p = 0.320$	-

Table 15. *Univariable Predictors of AR ≥ 2 or AV Reoperation, by Group.*
AR, aortic regurgitation; *CIs*, confidence intervals; *ECC*, extracorporeal circulation; *gH*, geometric height; *LCC*, left coronary cusp; *NCC*, non-coronary cusp; *No.*, number; *pre-op*, preoperatively; *RCC*, right coronary cusp.
[1] p-value after exclusion of the only patient with 3 prolapsing cusps in group I (n=93).

No significant predictors of AR ≥ 2 or AV reoperation were identified in either group. In group I, only a single patient was found to have 3 prolapsing cusps. Very small sample sizes are vulnerable to the effect of outliers and may disproportionately distort the results of statistical analyses [112]. Thus, this patient was excluded from the analysis. The current study can only evaluate differences between 1 or 2 prolapsing cusps in patients with cusp prolapse secondary to fenestration. In the future, more representative samples are needed to evaluate whether the presence of 3 prolapsing cusps is a predictor of AR ≥ 2 or AV reoperation.

6.5 Appendix 5. Within Group Analyses: Group II (Prolapse)

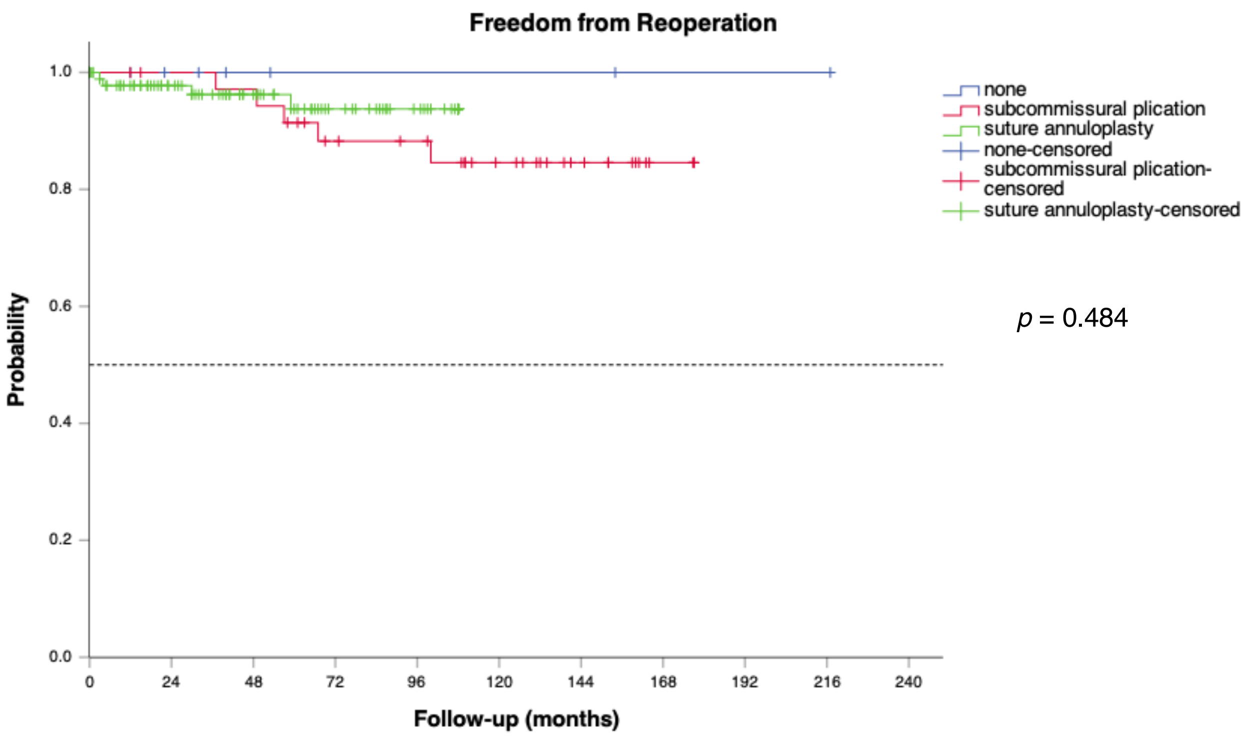
6.5.1 AV Repair Using Plication vs. Triangular Resection of Valve Tissue

There was no significant difference in survival (p = 0.568), freedom from AV reoperation (p = 0.989), freedom from post-operative complications (p = 0.378), or freedom from AR ≥ 2 or AV reoperation (p = 0.629) between group II patients who had undergone cusp plication (n=132) or triangular resection of cusp tissue (n=11).

Furthermore, a subgroup analysis comparing only group II patients who had undergone AVr using plication (n=132) and patients in group I (n=94) found a significant difference in survival (p = 0.027) and freedom from AR ≥ 2 or AV reoperation (p = 0.034). There was no significant difference in freedom from AV reoperation (p = 0.728) or freedom from post-operative complications (p = 0.635). These results closely reflect the results found for the entire group II sample.

6.5.2 Type of Annuloplasty

There was no significant difference in survival (p = 0.615), freedom from AV reoperation (p = 0.484; Figure 28), freedom from post-operative complications (p = 0.340), or freedom from AR ≥ 2 or AV reoperation (p = 0.391) between patients who had undergone annular stabilisation using subcommissural plication (n=37) or suture annuloplasty (n=98), or patients who had not undergone additional stabilisation of the aortic annulus (n=8).



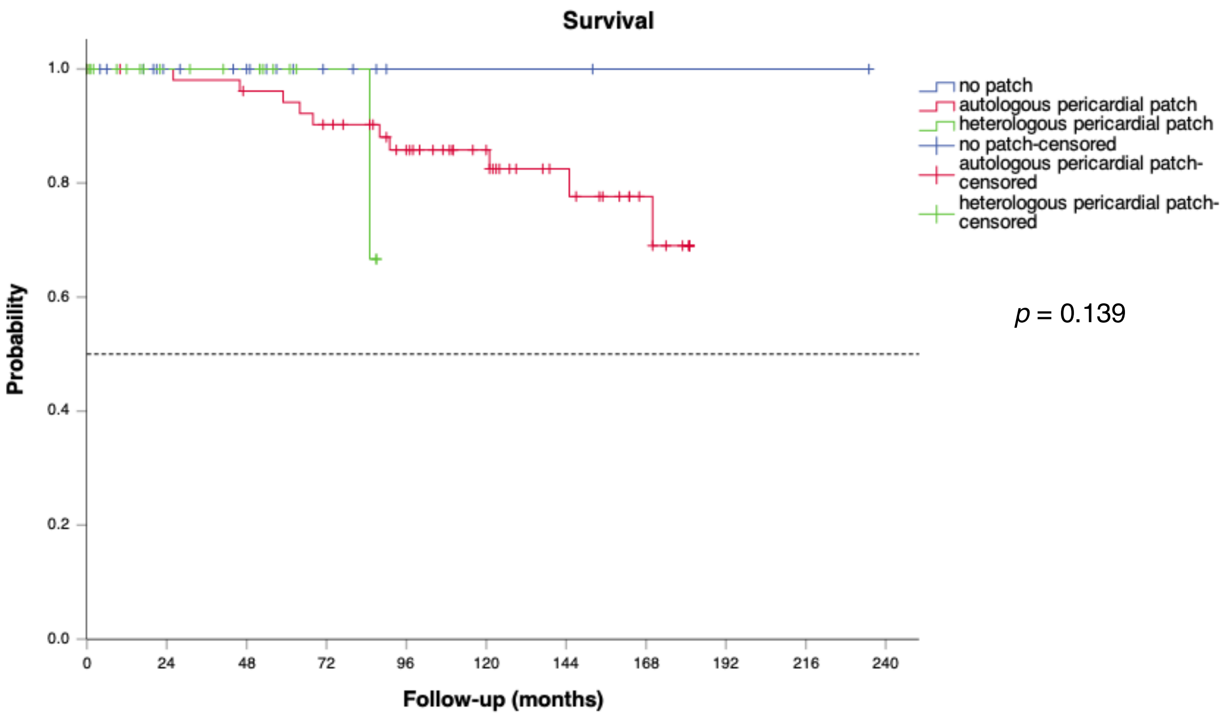
No. at Risk											
None	8	5	3	2	2	2	2	1	1	1	-
Subcommissural plication	37	35	34	27	25	18	11	3	-	-	-
Suture annuloplasty	98	67	45	27	16	-	-	-	-	-	-

Figure 28. *Group II Freedom From AV Reoperation Following AV Repair, by Type of Annuloplasty. AV*, aortic valve.

6.6 Appendix 6. Influence of Technique of Repair on Outcomes in Group I

6.6.1 Survival

There was no difference in survival between the three groups (p = 0.139; Figure 29). Five-, 7- and 10-year survival rates for each group are summarised in Table 16.



No. at Risk											
No patch	19	13	10	5	2	2	2	1	1	1	-
Autologous patch	54	52	49	45	36	26	17	9	-	-	-
Heterologous patch	21	11	9	3	-	-	-	-	-	-	-

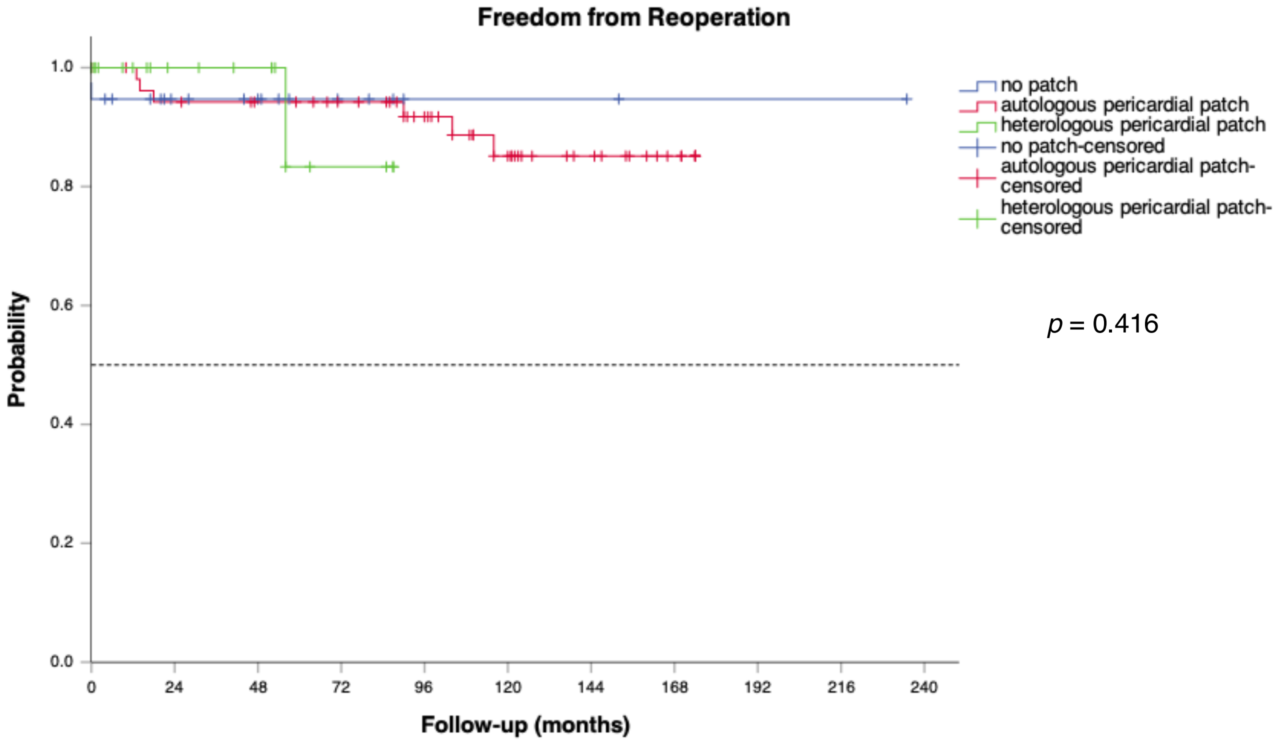
Figure 29. *Group I Survival Following AV Repair, by Technique of Repair. AV*, aortic valve.

Survival	No Patch	Autologous Patch	Heterologous Patch
5 years	100%	94.2%	100%
7 years	100%	90.3%	100%
10 years	100%	85.8%	-

Table 16. *Group I Survival, by Technique of Repair.*

6.6.2 Freedom From AV Reoperation

There was no difference in freedom from AV reoperation between the three groups (*p* = 0.416, Figure 30). Five-, 7- and 10-year freedom from reoperation rates for each group are summarised in Table 17.



No. at Risk											
No patch	19	12	9	5	2	2	2	1	1	1	-
Autologous patch	54	49	46	42	33	22	14	7	-	-	-
Heterologous patch	21	11	9	3	-	-	-	-	-	-	-

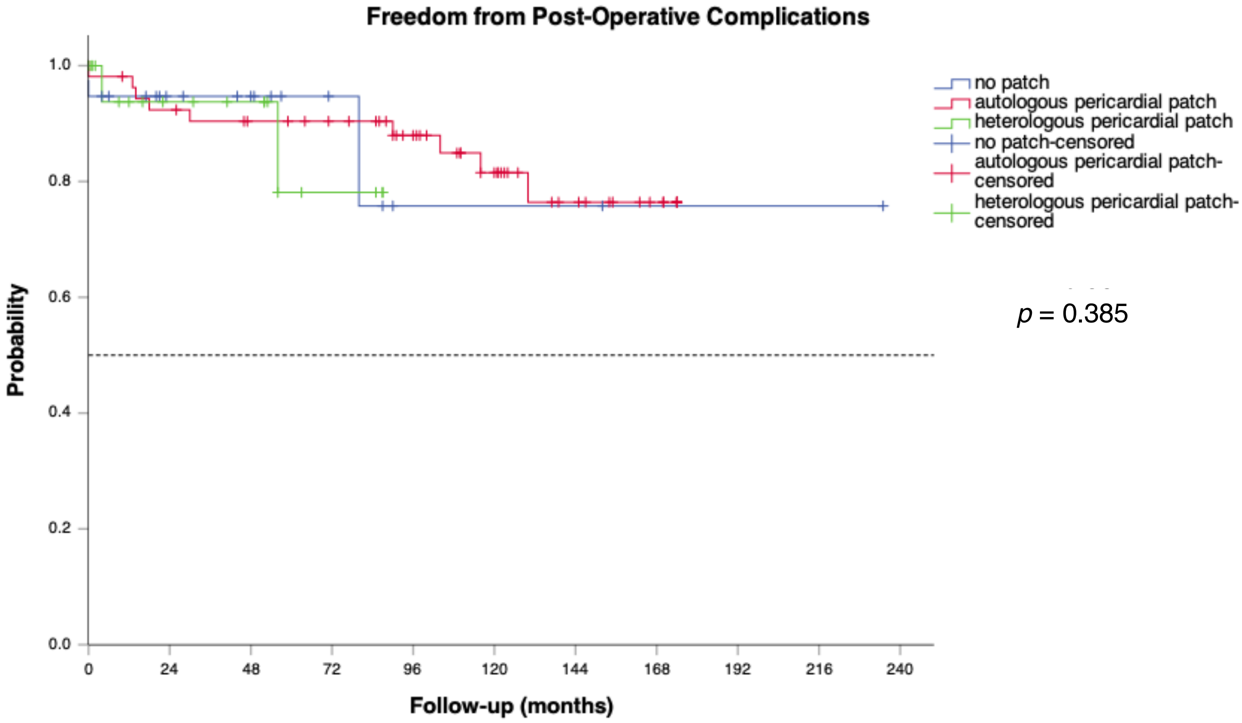
Figure 30. *Group I Freedom From AV Reoperation Following AV Repair, by Technique of Repair. AV*, aortic valve.

Freedom from AV Reoperation	No Patch	Autologous Patch	Heterologous Patch
5 years	94.7%	94.2%	83.3%
7 years	94.7%	94.2%	83.3%
10 years	94.7%	85.1%	-

Table 17. *Group I Freedom From AV Reoperation, by Technique of Repair. AV,* aortic valve.

6.6.3 Freedom From Post-Operative Complications

There was no difference in freedom from post-operative complications between the three groups (p = 0.385; Figure 31). Five-, 7- and 10-year rates of freedom from post-operative complications are summarised in Table 18.



No at risk											
No patch	19	12	9	5	2	2	2	1	1	1	-
Autologous patch	54	48	44	41	32	22	13	7	-	-	-
Heterologous patch	21	11	9	3	-	-	-	-	-	-	-

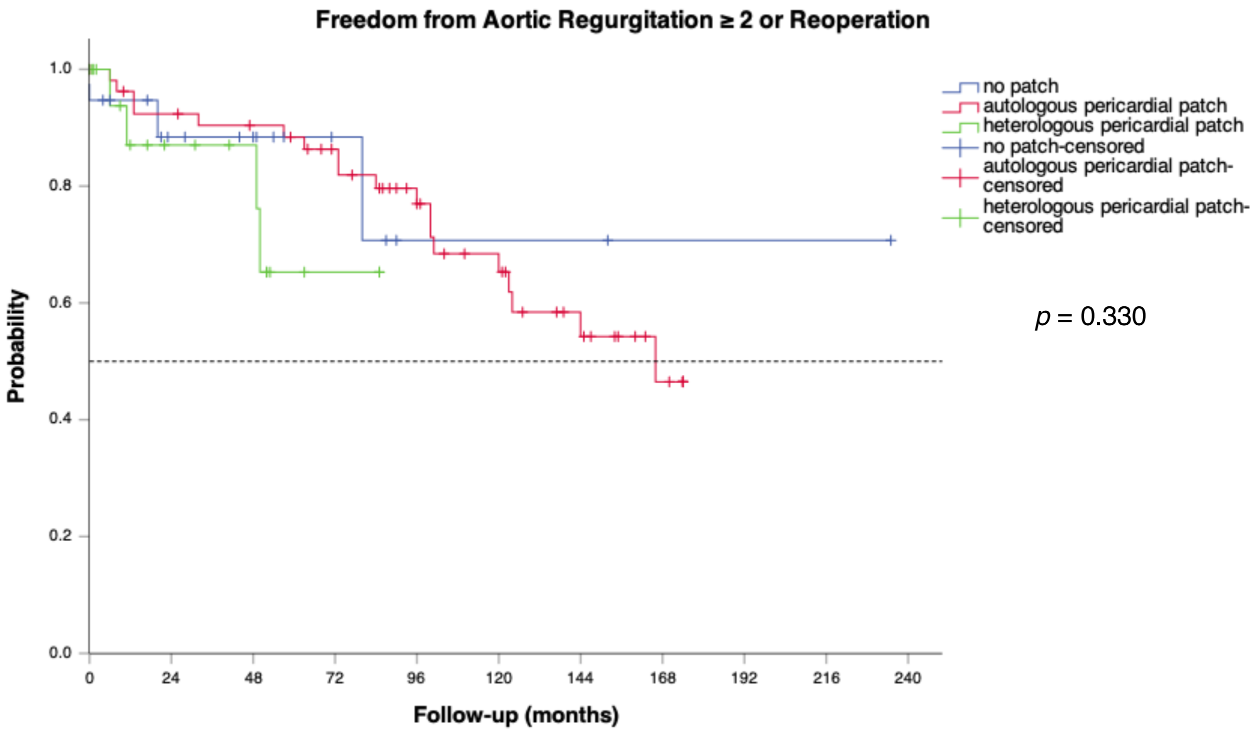
Figure 31. *Group I Freedom From Post-Operative Complications Following AV Repair, by Technique of Repair. AV*, aortic valve.

Freedom from Post-Operative Complications	No Patch	Autologous Patch	Heterologous Patch
5 years	94.7%	90.4%	78.1%
7 years	75.8%	90.4%	78.1%
10 years	75.8%	81.5%	-

Table 18. *Group I Freedom From Post-Operative Complications, by Technique of Repair.*

6.6.4 Freedom From Aortic Regurgitation ≥ 2 or AV Reoperation

There was no difference in freedom from AR ≥ 2 or AV reoperation between the three groups (p = 0.330; Figure 32). Five-, 7- and 10-year freedom from AR ≥ 2 or AV reoperation rates are summarised in Table 19.



No. at Risk

No patch	19	12	9	5	2	2	2	1	1	1	-
Autologous patch	54	48	45	39	28	21	13	6	-	-	-
Heterologous patch	21	10	8	2	-	-	-	-	-	-	-

Figure 32. *Group I Freedom From AR ≥ 2 or AV Reoperation Following AV Repair, by Technique of Repair. AR*, aortic regurgitation; *AV*, aortic valve.

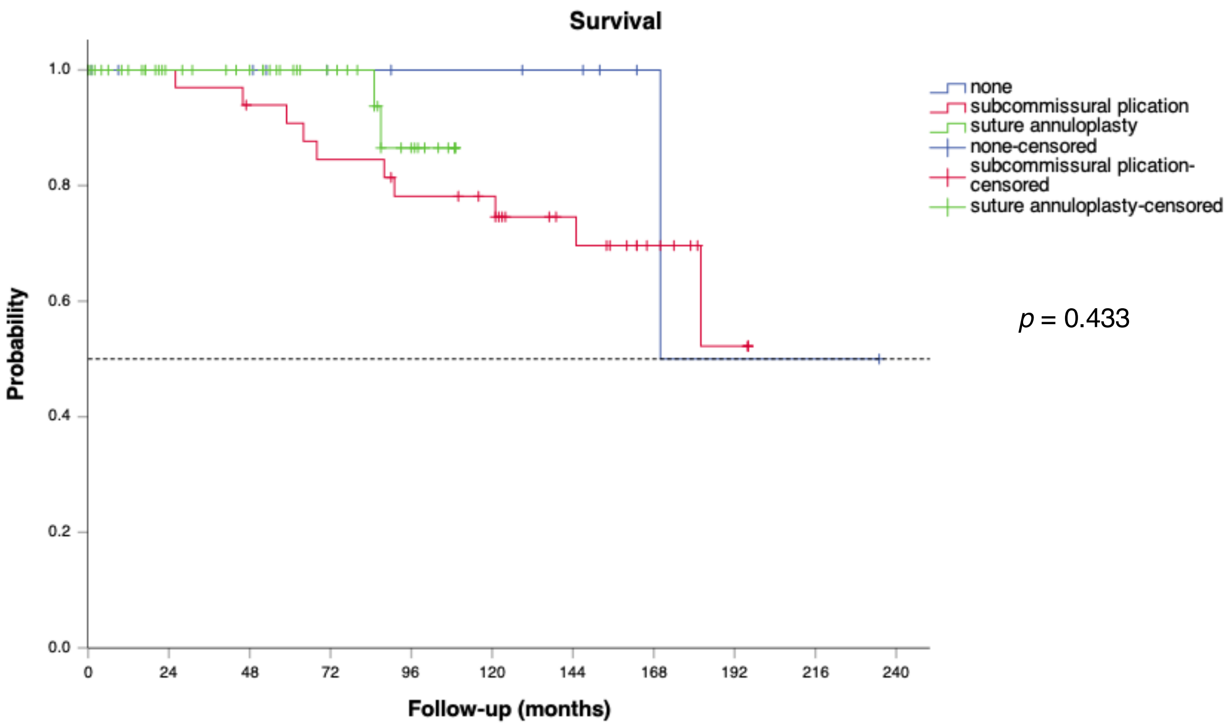
Freedom from AR ≥ 2 or Reoperation	No Patch	Autologous Patch	Heterologous Patch
5 years	88.4%	88.4%	65.3%
7 years	70.7%	79.6%	65.3%
10 years	70.7%	65.3%	-

Table 19. *Group I Freedom From AR ≥ 2 or AV Reoperation, by Technique of Repair. AR*, aortic regurgitation; *AV*, aortic valve.

6.7 Appendix 7. Influence of Type of Annuloplasty on Outcomes in Group I

6.7.1 Survival

There was no difference in survival between the three groups (p = 0.433; Figure 33). Five-, 9- and 10-year survival rates are summarised in Table 20.



No. at Risk											
None	12	10	10	7	6	6	5	2	1	1	-
Subcommissural plication	33	33	30	27	24	22	15	8	3	-	-
Suture annuloplasty	49	33	28	19	9	-	-	-	-	-	-

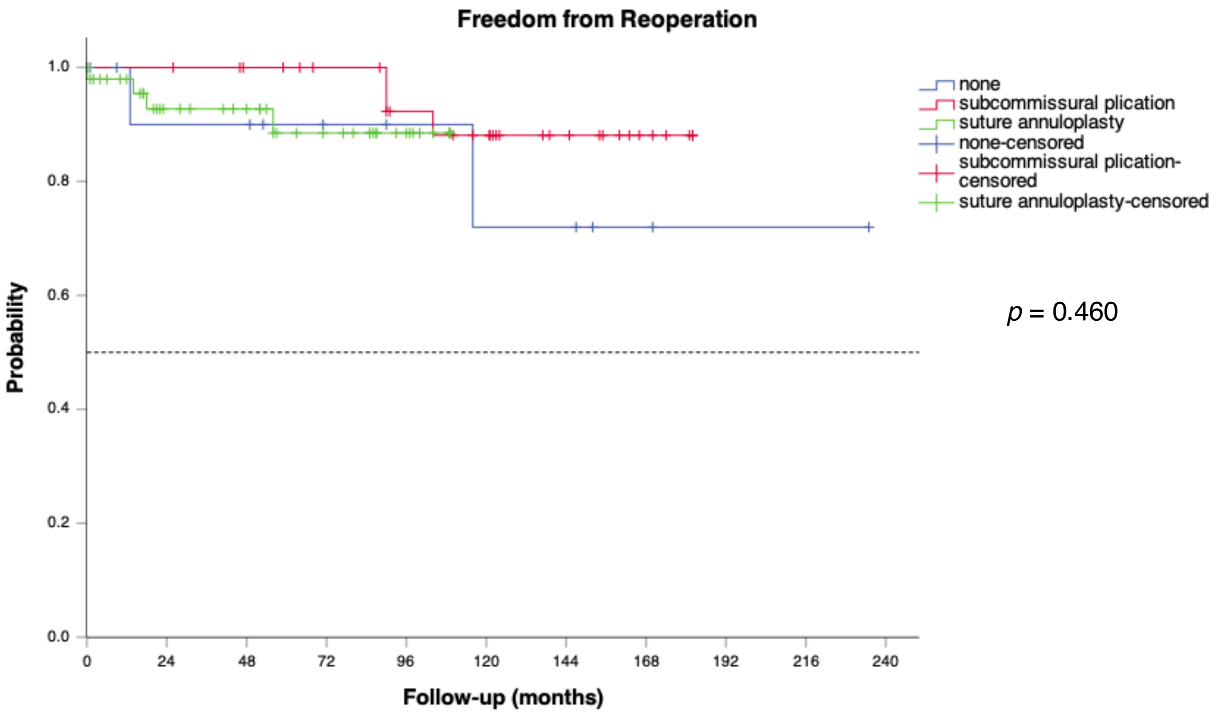
Figure 33. *Group I Survival Following AV Repair, by Type of Annuloplasty. AV*, aortic valve.

Survival	None	Subcommissural Plication	Suture Annuloplasty
5 years	100%	90.8%	100%
9 years	100%	78.2%	86.5%
10 years	100%	78.2%	-

Table 20. *Group I Survival, by Type of Annuloplasty.*

6.7.2 Freedom From AV Reoperation

There was no difference in freedom from AV reoperation between the three groups (p = 0.460; Figure 34). Five-, 9- and 10-year freedom from reoperation rates are summarised in Table 21.



No. at Risk											
None	12	9	9	6	5	4	4	2	1	1	-
Subcommissural plication	33	33	30	27	22	19	12	6	-	-	-
Suture annuloplasty	49	30	25	17	8	-	-	-	-	-	-

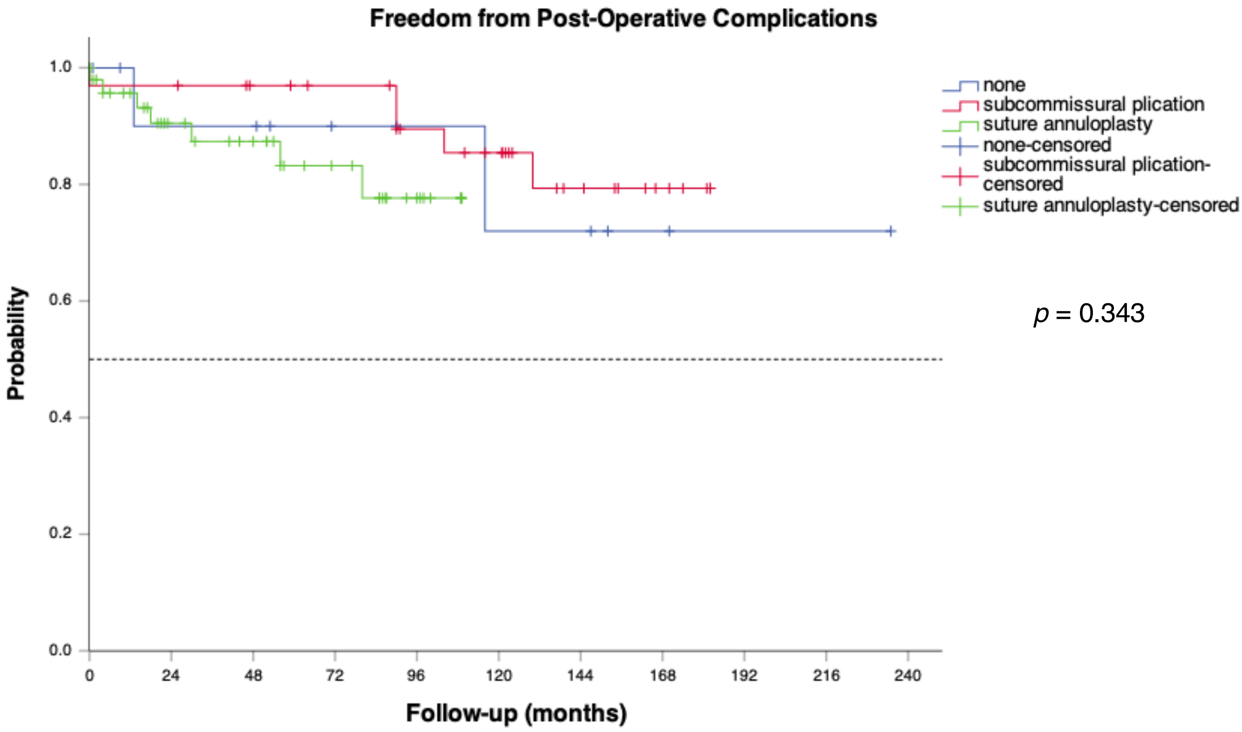
Figure 34. *Group I Freedom From AV Reoperation Following AV Repair, by Type of Annuloplasty. AV*, aortic valve.

Freedom from AV Reoperation	None	Subcommissural Plication	Suture Annuloplasty
5 years	90.0%	100.0%	88.5%
9 years	90.0%	88.1%	88.5%
10 years	72.0%	88.1%	-

Table 21. *Group I Freedom From AV Reoperation, by Type of Annuloplasty. AV*, aortic valve.

6.7.3 Freedom From Post-Operative Complications

There was no difference in freedom from post-operative complications between the three groups (*p* = 0.343; Figure 35). Five-, 9- and 10-year rates of freedom from post-operative complications are summarised in Table 22.



No. at Risk

None	12	9	9	6	5	4	4	2	1	1	-
Subcommissural plication	33	32	29	27	22	19	11	6	-	-	-
Suture annuloplasty	49	30	24	16	7	-	-	-	-	-	-

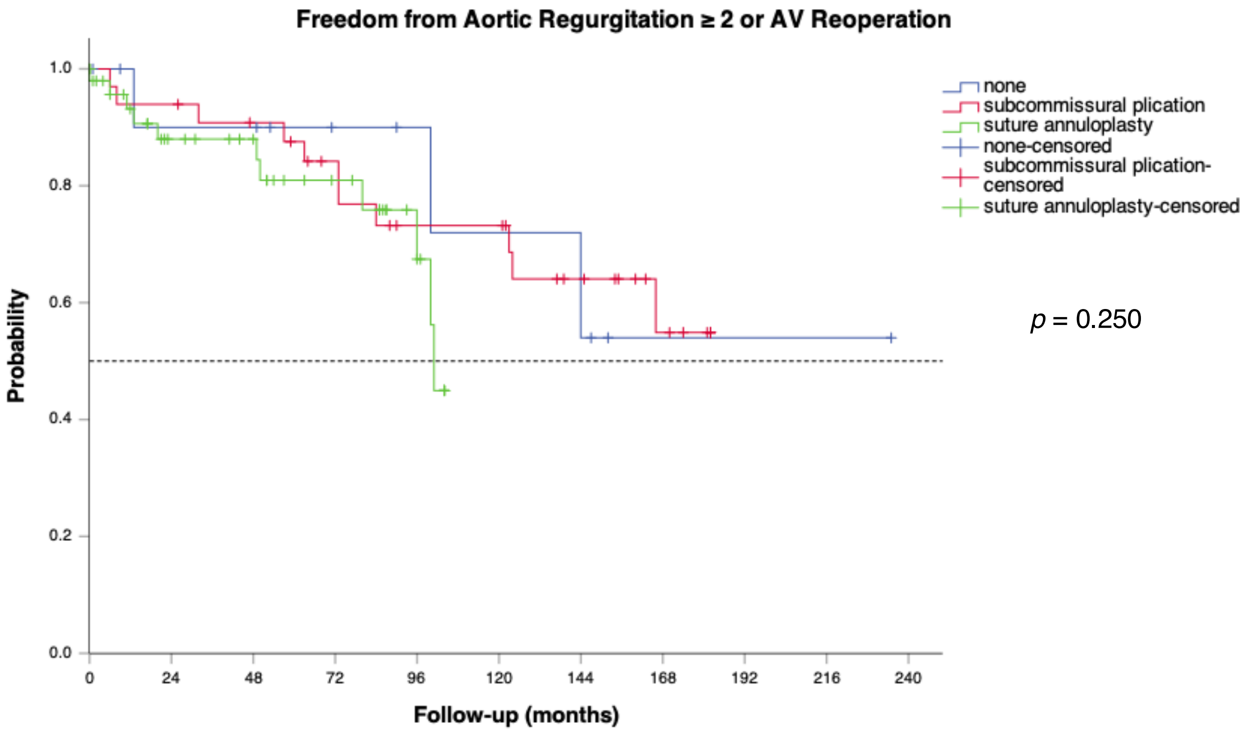
Figure 35. *Group I Freedom From Post-Operative Complications Following AV Repair, by Type of Annuloplasty. AV*, aortic valve.

Freedom from Post-Operative Complications	None	Subcommissural Plication	Suture Annuloplasty
5 years	90.0%	97.0%	83.2%
9 years	90.0%	85.4%	77.7%
10 years	72.0%	85.4%	-

Table 22. *Group I Freedom From Post-Operative Complications, by Type of Annuloplasty.*

6.7.4 Freedom From Aortic Regurgitation ≥ 2 or AV Reoperation

There was no difference in freedom from AR ≥ 2 or AV reoperation between the three groups (p = 0.250; Figure 36). Five-, 8- and 10-year freedom from AR ≥ 2 or AV reoperation rates are summarised in Table 23.



No. at Risk											
None	12	9	9	6	5	4	3	1	1	1	0
Subcommissural plication	33	31	28	23	18	18	12	6	-	-	-
Suture annuloplasty	49	30	25	17	7	-	-	-	-	-	-

Figure 36. *Group I Freedom From AR ≥ 2 or AV Reoperation Following AV Repair, by Type of Annuloplasty. AR*, aortic regurgitation; *AV*, aortic valve.

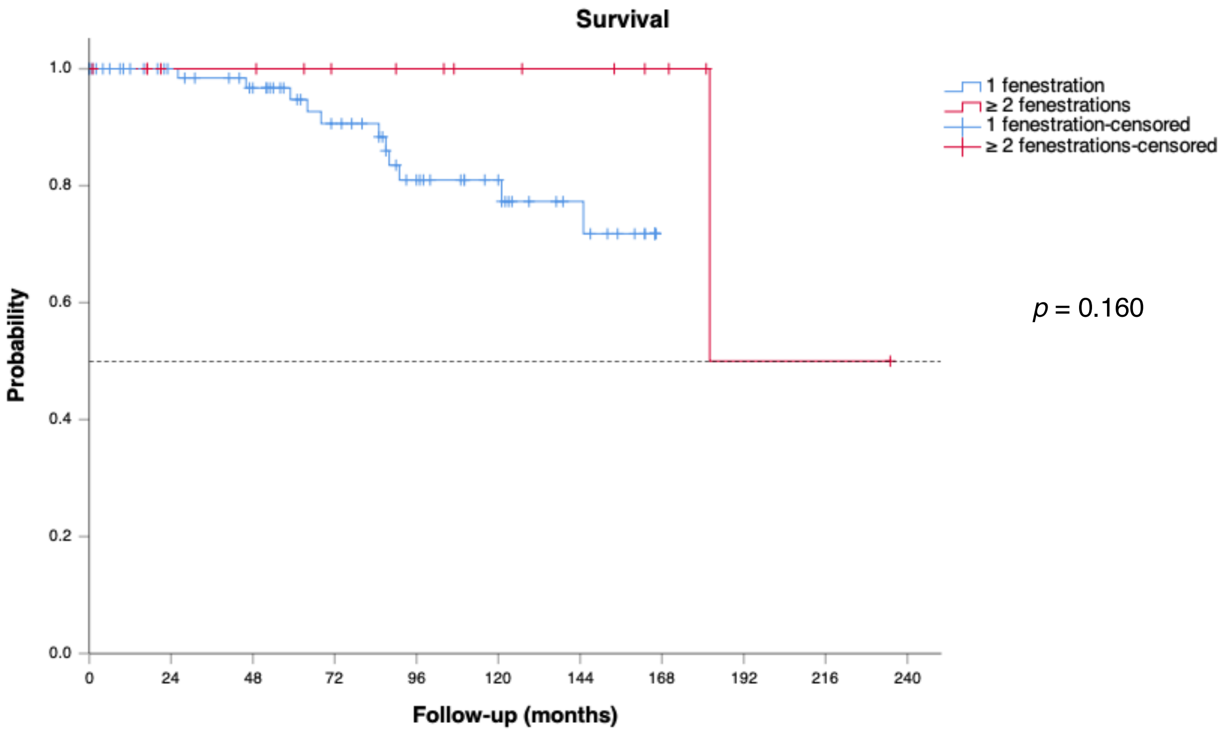
Freedom from AR ≥ 2 or Reoperation	None	Subcommissural Plication	Suture Annuloplasty
5 years	90.0%	87.6%	81.0%
8 years	90.0%	73.2%	67.5%
10 years	72.0%	73.2%	-

Table 23. *Group I Freedom From AR ≥ 2 or AV Reoperation, by Type of Annuloplasty. AR*, aortic regurgitation; *AV*, aortic valve.

6.8 Appendix 8. Influence of Number of Fenestrations Requiring Intervention on Outcomes in Group I

6.8.1 Survival

There was no difference in survival between the two groups (*p* = 0.160; Figure 37). Five- and 10-year survival rates are summarised in Table 24.



No. at Risk											
1 fenestration	77	63	55	43	30	22	14	-	-	-	-
≥ 2 fenestrations	17	13	13	10	9	7	6	4	1	1	-

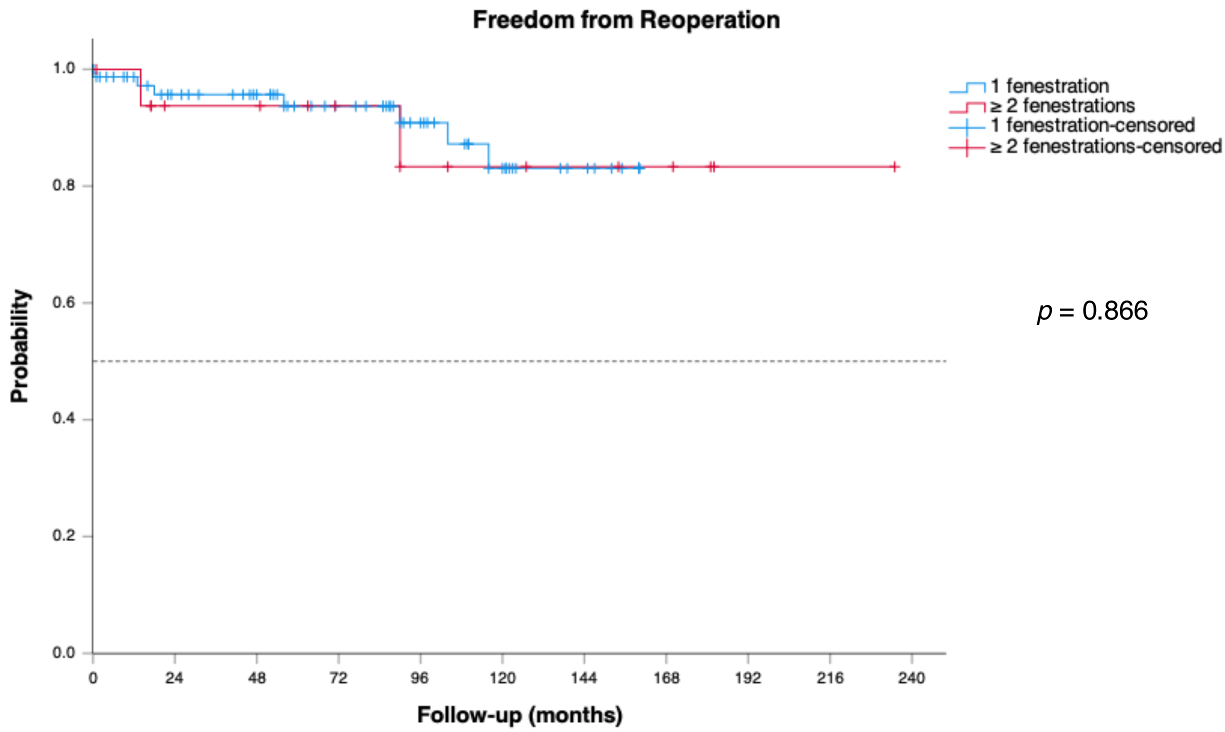
Figure 37. *Group I Survival Following AV Repair, by Number of Fenestrations Requiring Intervention. AV*, aortic valve.

Survival	1 Fenestration	≥ 2 Fenestrations
5 years	94.7%	100%
10 years	81.0%	100%

Table 24. *Group I Survival, by Number of Fenestrations Requiring Intervention.*

6.8.2 Freedom From AV Reoperation

There was no difference in freedom from AV reoperation between the two groups (p = 0.866; Figure 38). Five- and 10-year freedom from AV reoperation rates are summarised in Table 25.



No. at Risk											
1 fenestration	77	60	52	41	28	18	11	-	-	-	-
≥ 2 fenestrations	17	12	12	9	7	6	5	4	1	1	-

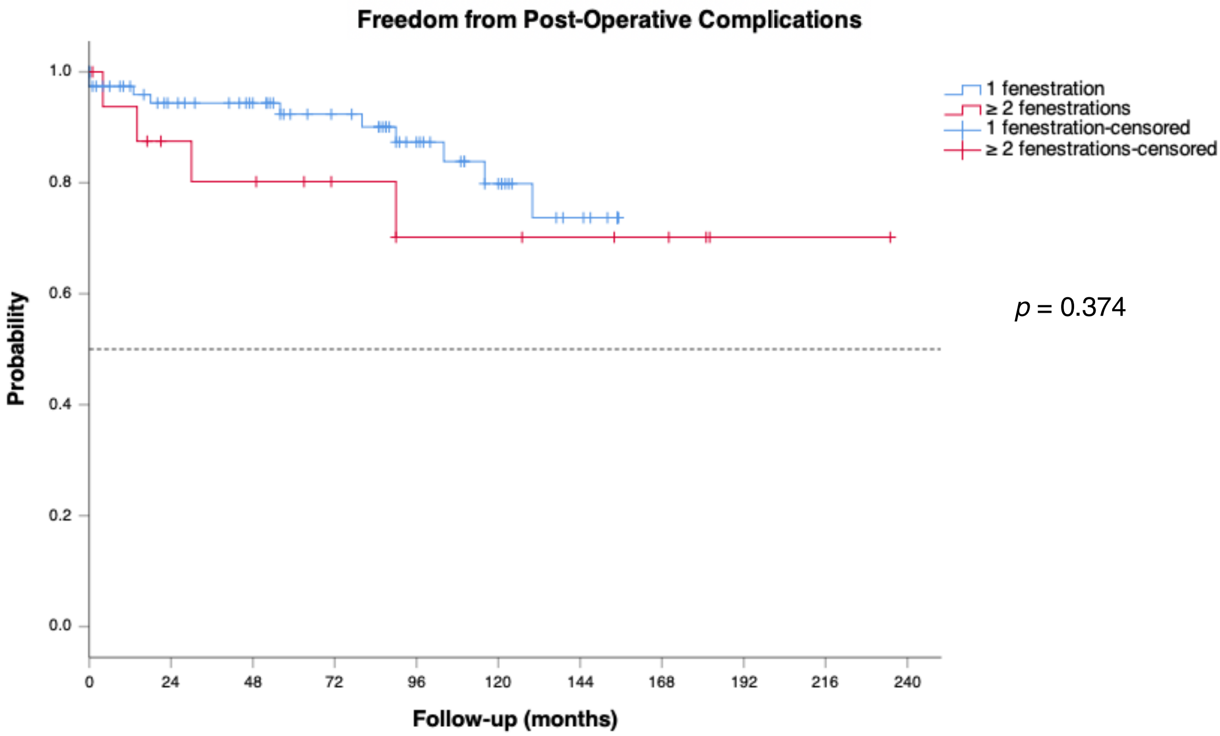
Figure 38. *Group I Freedom From AV Reoperation Following AV Repair, by Number of Fenestrations Requiring Intervention. AV*, aortic valve.

Freedom from AV Reoperation	1 Fenestration	≥ 2 Fenestrations
5 years	93.7%	93.8%
10 years	83.1%	83.3%

Table 25. *Group I Freedom From AV Reoperation, by Number of Fenestrations Requiring Intervention. AV*, aortic valve.

6.8.3 Freedom From Post-Operative Complications

There was no difference in freedom from post-operative complications between the two groups (p = 0.374; Figure 39). Five- and 10-year rates of freedom from post-operative complications are summarised in Table 26.



No. at Risk											
1 fenestration	77	59	51	41	28	18	10	-	-	-	-
≥ 2 fenestrations	17	12	11	8	6	6	5	4	1	1	-

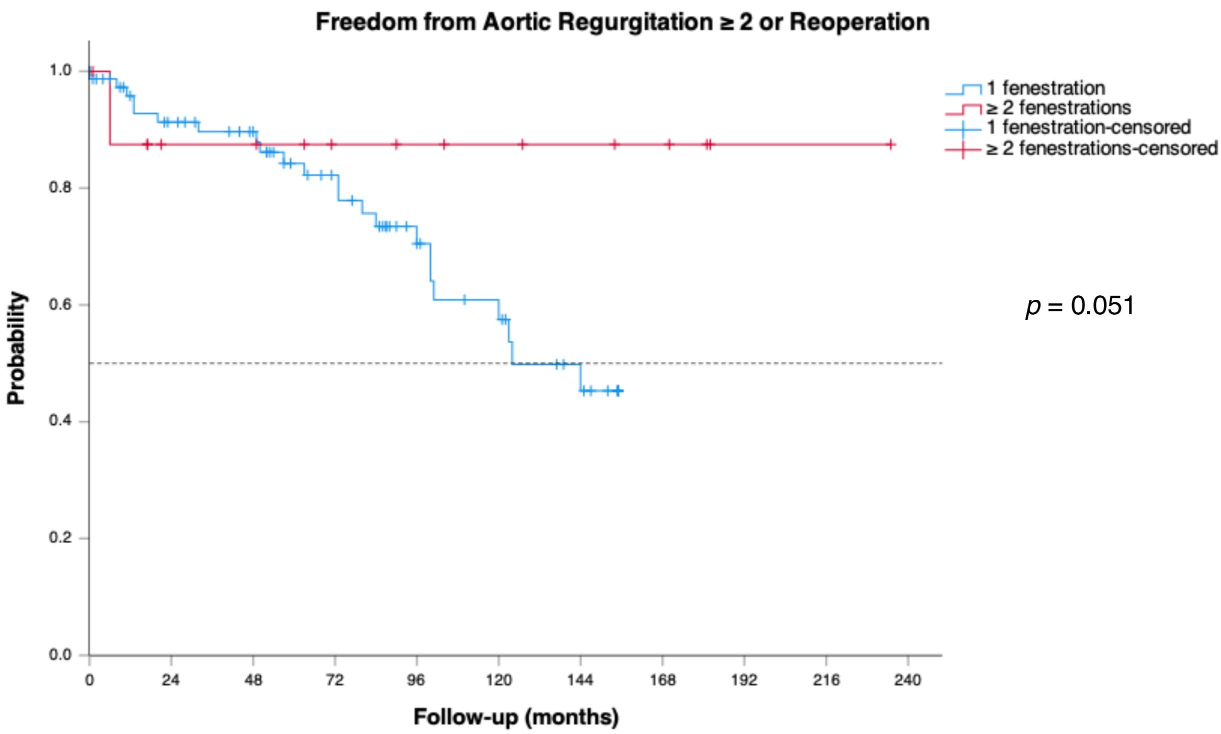
Figure 39. *Group I Freedom From Post-Operative Complications Following AV Repair, by Number of Fenestrations Requiring Intervention. AV*, aortic valve.

Freedom from Post-Operative Complications	1 Fenestration	≥ 2 Fenestrations
5 years	92.4%	80.2%
10 years	79.8%	70.2%

Table 26. *Group I Freedom From Post-Operative Complications, by Number of Fenestrations Requiring Intervention.*

6.8.4 Freedom From Aortic Regurgitation ≥ 2 or AV Reoperation

There was no difference in freedom from AR ≥ 2 or AV reoperation between the two groups (*p* = 0.051; Figure 40). Five- and 10-year freedom from AR ≥ 2 or AV reoperation rates are summarised in Table 27.



No. at Risk

1 fenestration	77	59	51	38	23	17	10	-	-	-	-
≥ 2 fenestrations	17	11	11	8	7	6	5	4	1	1	-

Figure 40. *Group I Freedom From AR ≥ 2 or AV Reoperation Following AV Repair, by Number of Fenestrations Requiring Intervention. AR*, aortic regurgitation; *AV*, aortic valve.

Freedom from AR ≥ 2 or Reoperation	1 Fenestration	≥ 2 Fenestrations
5 years	84.2%	87.5%
10 years	57.5%	87.5%

Table 27. *Group I Freedom From AR ≥ 2 or AV Reoperation, by Number of Fenestrations Requiring Intervention. AR*, aortic regurgitation; *AV*, aortic valve.

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8 Publication

Results of this thesis have been published in the following paper:

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10 Curriculum Vitae

Aus datenschutzrechtlichen Gründen wird der Lebenslauf in der elektronischen Fassung der Dissertation nicht veröffentlicht.