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Contemporary Clinical Treatment Options and Outcomes of Aortic Valve Disease

Edited by
Mladen J. Kocica and Igor Rudez

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Guest Editors

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Cover image courtesy of Mladen J. Kocica
Pentacuspid Aortic Valve - Aortic Stenosis and Stanford A Dissection

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Editorial

Aortic Valve Repair and Early-Career Surgeons—Nothing Is Impossible

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Aortic valve repair with either the reimplantation of the aortic valve or aortic root remodelling with the external annuloplasty procedure is the most effective means of treating aortic regurgitation and/or aortic root aneurysms. Because a large body of evidence supports both the effectiveness and safety of AV reconstruction, the most recent 2021 European Society of Cardiology/European Association of Cardiothoracic Surgery Guidelines for the management of valvular heart disease endorse its application in suitable patients as a Class IIb recommendation for severe aortic insufficiency and as a Class I recommendation for aortic root aneurysms [1]. Yet, the procedure is presently underused.

How can we explain this widespread failure to treat isolated AV regurgitation and/or aortic root aneurysms? The procedure is undoubtedly complex and requires a thorough theoretical as well as practical knowledge from the whole heart team, especially the primary surgeon. Early-career surgeons, who wish to start their own AV repair program, should be familiar with the anatomy and (patho)physiology of the aortic root with the knowledge gained from both cadaveric specimens [2], echocardiography [3], and novel imaging modalities, such as computer tomography reconstructions [4,5]. Perhaps even more important than with mitral valve repair is a sufficient understanding of the mechanisms leading to aortic root pathology; this is imperative so that one can identify suitable candidates among their patients to achieve durable AV repair.

In regard to surgical experience, an early-career surgeon embarking on this journey should be able to perform a straightforward aortic valve replacement with no difficulties and have performed at least twenty composite valve-graft conduit root replacements. Comprehensive and thorough knowledge of all the surgical steps of either full aortic root replacement or isolated AV repair in both tricuspid and bicuspid valves could and should be obtained from in-depth articles, such as the *How I Teach It* series from *Annals of Thoracic Surgery* [6–9] and further deepened through hands-on courses and interactive surgical atlases.

Nevertheless, the most effective way of preparing oneself for AV repair is more close contact with an experienced colleague in a repair-oriented centre of excellence (for example Paris, Toronto or New York) who can explain concepts and help to minimize the learning curve that is to be expected. This is true especially when it comes down to specific situations or failures. Is the present fenestration too large or too near the commissure to obtain long-term repair durability? Are present (non-obstructing) calcifications (of only one leaflet) precluding safe repair? Are the coronary ostia too high, i.e., too close to the sinotubular junction to prevent reconstructing only the AV in case of isolated regurgitation and thus requiring full aortic root replacement? When exactly is the effective height sufficient when measuring it with a dedicated calliper?

It is the authors' opinion that at the beginning of one's AV repair journey, root remodelling with an external annuloplasty procedure is most suitable for a number of reasons. The first is related to superior haemodynamics with regard to the formation of vortical flow with preserved root expansibility and more physiological valve movements. Second, it is a highly standardised and reproducible technique with no "artistic" decisions

(requiring decades of experience) along the way. Third, the fallback option in full root replacement if there is persistent insufficiency is to re-clamp and perform a straightforward AV replacement, which is difficult in the AV reimplantation technique.

Another very important aspect of failure to perform more AV repairs is the lack of long-term results. However, this is changing as we speak. With their investigation of aortic valve repair in patients with connective tissue disease operated electively for root aneurysm < 60 mm with aortic regurgitation (AR) < 1/4, Van Hoof and colleagues [10] inform us that we should perform AV repair in these patients. In their analysis of 80 patients published in *Heart*, 5-year survival reached 99% with no Stanford type A dissections and 92% freedom from significant postoperative aortic regurgitation. This important article has set the standards for the optimal care of these patients. It is an upgrade on previously published results both in the dystrophic aortic insufficiency population [11] as well as in heritable aortic disorders [12].

Aortic valve repair is dramatically underperformed. In 2023, there are fewer and fewer reasons not to perform an AV repair in suitable patients with either aortic root aneurysm or isolated aortic insufficiency and thus prevent them from structural valve degeneration, significant bleeding, or thromboembolic events, as seen in AV replacement. Learning from one's own failures and ensuring proper follow-up should additionally strengthen every AV repair program, this fact being extremely crucial for an early-career surgeon. With the introduction of multicentre surgical registries [13], this goal is achievable now more than any other time in the past.

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

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Editorial

Contemporary Clinical Treatment Options and Outcomes of Aortic Valve Disease: Integrating Modern Insights into a Cohesive Therapeutic Paradigm

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Historically, the aortic valve (AV) was seen as a passive mechanical structure facilitating unidirectional blood flow by opening and closing in response to pressure changes, with little or no biological activity [1]. Modern insights have redefined the AV as a dynamic, biologically active tissue that plays significant cellular, mechanical, and immunological roles [2–5].

The valve's ability to open and close more than 100,000 times a day is driven by mechanotransduction pathways, influencing cell behavior and matrix remodeling. The interstitial cells of the valve show remarkable plasticity, transitioning between fibroblastic, myofibroblastic, and osteoblastic phenotypes [2,4,6–8], contributing to both adaptive repair and pathological calcification. Moreover, the AV expresses cytokines, chemokines, and adhesion molecules, and can actively recruit immune cells, functioning as an immunologically active interface [2,4,6–11]. Dysfunction of the valve impacts left ventricular geometry, coronary perfusion, and systemic hemodynamics [12–15].

Research has increasingly emphasized that the AV should be understood from two complementary perspectives. The concept of the "aortic valve apparatus" considers the AV as an integrated anatomical and biomechanical unit—including valve leaflets, the annulus, sinuses of Valsalva, sinotubular junction, and left ventricular outflow tract—whose coordinated geometry and motion are critical for optimal valve function and effective ventriculo-arterial coupling (VAC) [16–19]. In parallel, viewing the valve as an "aortic organ" underscores its role as a biologically active tissue capable of mechanotransduction, cytokine expression, extracellular matrix remodeling, and systemic crosstalk [20]. These perspectives emphasize that successful valve interventions must preserve or restore both the mechanical integrity of the AV apparatus and the biological resilience of the aortic organ.

This reconceptualization of the AV has transformed clinical practice. The increasing application of stentless bioprostheses, AV repair, and valve-sparing procedures requires a deeper understanding of AV biomechanics and flow dynamics [13–15]. These advanced interventions seek not only to correct the valve but also to restore the motion of the physiologic leaflet, root elasticity, and annular–ventricular interactions to optimize global cardiovascular performance [21,22].

Importantly, both the structural and biological integrity of the AV profoundly influence VAC, a key determinant of cardiovascular performance. The mechanical dynamics of the AV apparatus modulate the afterload and flow patterns, directly impacting VAC [18,19]. Meanwhile, pathological processes at the level of the aortic organ—such as inflammation, fibrosis, and calcification—can stiffen the valve, disturb VAC, and contribute to maladaptive ventricular remodeling [18]. Modern interventions increasingly aim to restore harmonious

ventriculo-arterial interaction through the preservation or correction of both the apparatus geometry and organ biology [23].

Infective aortic valve disease is also evolving. Changes in microbiology, with a rising incidence of Staphylococcus aureus and healthcare-associated infections, has altered the pathoanatomy of infective endocarditis (IE). Contemporary imaging reveals a more complex spectrum of leaflet destruction, abscess formation, and aortic root involvement, often demanding highly individualized surgical approaches [24,25].

Beyond primary AV disease, it is now well recognized that systemic conditions such as chronic kidney disease, metabolic syndrome, and autoimmune diseases significantly impact AV biology [26,27]. These systemic influences accelerate fibro-calcific remodeling and alter valve biomechanics, contributing to earlier valve dysfunction and influencing treatment outcomes. Thus, the AV serves not only as a target organ in systemic disease but also as a potential biomarker of broader cardiovascular risk [21,26].

Within this context, the management of AV disease is undergoing a remarkable transformation. Aortic valve disease remains a major global contributor to cardiovascular morbidity and mortality, particularly in aging populations [24,26,28,29]. Contemporary interventions now encompass an expanding spectrum: surgical aortic valve replacement (SAVR), transcatheter aortic valve implantation (TAVI), valve repair and sparing procedures, stentless and rapid-deployment bioprostheses, and novel pharmacologic approaches [30,31].

Clinical decision-making is now highly multidisciplinary and patient-centered, guided by heart teams and supported by advanced imaging, computational modeling, and precision medicine [24,28,29]. Future advances will increasingly rely on high-quality longitudinal data, the integration of genomic and AI-driven diagnostics, and a further elucidation of the valve's dynamic interplay within systemic physiology [32,33].

This Special Issue of JCDD, entitled "The Evolving Understanding and Management of Aortic Valve Disease", focuses on the contemporary achievements in clinical medicine and basic sciences that could provide new opportunities for understanding, diagnosing and treating AV disease. The nine papers featured in the First Edition of this Special Issue of JCDD, offer a multidimensional perspective on challenges and innovations in the field, collectively contributing to a more nuanced and integrated approach to care.

A comprehensive review by Notenboom and colleagues (Contribution 1) integrates insights from embryology, mechanobiology, and signalling pathways to contextualize aortic valve degeneration and therapeutic targets. The exploration of Notch, TGF-β, and second messenger systems bridges the translational gap between bench and bedside, paving the way for biologically informed interventions.

Several studies have explored the ongoing evolution of valve replacement and repair strategies. Lebehn and colleagues (Contribution 2) provide a state-of-the-art analysis of aortic regurgitation (AR) management, highlighting the application of advanced imaging techniques and biomechanical assessment to detect early myocardial fibrosis and subclinical dysfunction. This corresponds with the increasing focus on pre-emptive therapy in valve disease. The study supports earlier intervention to prevent irreversible left ventricular dysfunction and describes the evolution of transcatheter approaches, which may eventually compare with surgical techniques in certain AR patients.

Beyond procedural success, long-term ventricular function remains a decisive factor in patient prognosis. Iliuță and associates (Contribution 3) evaluate the long-term persistence of diastolic dysfunction after aortic valve replacement (AVR) in patients with aortic stenosis (AS) versus AR, highlighting differences in ventricular remodeling. AS patients showed earlier postoperative improvements in systolic and diastolic function in the left ventricle, whereas restrictive diastolic filling patterns (LVDFPs) persisted more frequently in AR

patients post-AVR, which significantly impacted prognosis. This underscores the need for earlier intervention and refined patient selection based on diastolic function metrics.

Alhijab and colleagues (Contribution 4) evaluated the age-specific outcomes of mechanical versus bioprosthetic valves, reaffirming the durability of mechanical prostheses in patients under 50, while validating bioprosthetic use in older cohorts without compromising survival.

Fazmin and Ali (Contribution 5) provide a practical review of prosthesis–patient mismatch (PPM), supporting the application of proactive root enlargement when aiming to optimize hemodynamic outcomes, a principle supported by the data from multiple centers.

Toto et al. (Contribution 6) compare the mid-term clinical outcomes and hemodynamic performance of Trifecta and Perimount bioprostheses following AVR. While Trifecta valves showed lower early postoperative gradients, this advantage diminished over time, with both prostheses showing comparable mid-term outcomes in terms of major adverse cardiac and cerebrovascular events (MACCEs) or structural valve degeneration (SVD) rates. The findings underscore the importance of long-term follow-up to assess durability and performance, particularly as bioprosthetic valve use expands to younger populations.

Baric and colleagues (Contribution 7) demonstrate that aortic valve repair with external annuloplasty is feasible and durable in both bicuspid and tricuspid anatomies, finding similar survival rates (96.3% BAV vs. 97.2% TAV), no significant differences in freedom from valve reintervention, or severe AR after four years. Their results challenge the replacement-dominant mindset and emphasize repair as a viable, often underutilized alternative.

This is also the primary message of a comprehensive editorial by Djordjevic and Rudez (Contribution 8), who emphasize the need for early-career surgeons to develop expertise in AV repair through anatomical studies, advanced imaging, and mentorship in specialized centers.

Haidari and colleagues (Contribution 9) critically examine the impact of applying local antibiotics in the abscess cavity following radical debridement and patch reconstruction in patients with AV-IE. Despite theoretical benefits, their data do not support superior outcomes with antibiotic-fibrin glue compared to patch repair alone, suggesting that radical debridement remains paramount. This finding is crucial reducing the complexity of already high-risk procedures.

Collectively, these contributions underscore the transition from a binary view of surgical and transcatheter therapy to a far more layered and mechanistically informed model. Contemporary AVD management is no longer defined solely by valve gradients and procedural survival, but by the integration of structural, functional, developmental, and molecular factors that influence long-term outcomes.

The future of AVD therapy lies in personalization: tailoring interventions based not only on anatomy and the surgical risk, but also on underlying myocardial remodeling, the etiology of disease, and the molecular phenotype. As these papers demonstrate, meaningful progress comes not only from novel devices or procedures, but from the convergence of clinical rigor, surgical innovation, and basic science into a cohesive therapeutic vision.

The AV is no longer seen as a simple mechanical gate but as a complex, biologically responsive organ that is central to cardiovascular health and disease. Ongoing innovation in surgical and transcatheter therapies, coupled with a deeper understanding of valve biology and its systemic interactions, promises truly individualized care and enhanced outcomes for patients with aortic valve disease.

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Review

Aortic Valve Embryology, Mechanobiology, and Second Messenger Pathways: Implications for Clinical Practice

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Abstract: During the Renaissance, Leonardo Da Vinci was the first person to successfully detail the anatomy of the aortic root and its adjacent structures. Ever since, novel insights into morphology, function, and their interplay have accumulated, resulting in advanced knowledge on the complex functional characteristics of the aortic valve (AV) and root. This has shifted our vision from the AV as being a static structure towards that of a dynamic interconnected apparatus within the aortic root as a functional unit, exhibiting a complex interplay with adjacent structures via both humoral and mechanical stimuli. This paradigm shift has stimulated surgical treatment strategies of valvular disease that seek to recapitulate healthy AV function, whereby AV disease can no longer be seen as an isolated morphological pathology which needs to be replaced. As prostheses still cannot reproduce the complexity of human nature, treatment of diseased AVs, whether stenotic or insufficient, has tremendously evolved, with a similar shift towards treatments options that are more hemodynamically centered, such as the Ross procedure and valve-conserving surgery. Native AV and root components allow for an efficient Venturi effect over the valve to allow for optimal opening during the cardiac cycle, while also alleviating the left ventricle. Next to that, several receptors are present on native AV leaflets, enabling messenger pathways based on their interaction with blood and other shear-stress-related stimuli. Many of these physiological and hemodynamical processes are under-acknowledged but may hold important clues for innovative treatment strategies, or as potential novel targets for therapeutic agents that halt or reverse the process of valve degeneration. A structured overview of these pathways and their implications for cardiothoracic surgeons and cardiologists is lacking. As such, we provide an overview on embryology, hemodynamics, and messenger pathways of the healthy and diseased AV and its implications for clinical practice, by relating this knowledge to current treatment alternatives and clinical decision making.

Keywords: aortic valve disease; embryology; hemodynamics; second messenger pathways

1. Introduction

Heart valve disease stands for a major worldwide burden and is associated with substantial mortality and morbidity [1]. Absolute numbers of deaths attributed to aortic valve disease (AVD) have increased over the past 30 years [2], making AVD responsible for the largest proportion of deaths within the spectrum of valvular heart disorders. When left untreated, the natural course of AVD, especially aortic valve stenosis (AS), is progressive [3,4] and associated with high mortality rates across the entire spectrum [5].

Taking a deeper look into the process of valve degeneration, this appears to be a multifactorial process which includes embryological, genetic, hemodynamic, structural, and cellular factors [6]. Importantly, healthy aortic valve (AV) leaflets consist of multiple layers which communicate with surrounding tissues through humoral [7,8] and mechanical stimuli [9]. Neurofilaments, (myo)fibroblasts, endothelial cells, extracellular matrix (ECM)

components, and even smooth muscle cells (SMCs) play crucial roles in these regulatory processes [7], which are adaptive to shear stress (mechanotransduction) and blood compositions (humoral). Chronic or acute disturbance of an AV's homeostatic state may induce AS and/or aortic valve regurgitation (AR) through various mechanisms [10]. More than just the visible, clinically documentable structural defects to the AV, which are measured using current routine clinical imaging techniques, are associated with AV dysfunction; it is acknowledged that pathophysiology induces morphologic changes. Messenger pathways that are disturbed by altered flow dynamics or humoral stimuli may in itself induce an effect on a functional level [7,11]. Importantly, the AV is known to generate contractile, secretory, and proliferative responses to these stimuli [7–9,12] and the interplay between physics and biology as well as the interplay between form and function play essential roles.

Treatment of AVD is commonly limited to prosthetic AV replacement (AVR). However, insights into the benefits of preserving one's native valve and functional abilities have led to an expansion of the surgical armamentarium by development of innovative techniques, including the Ross procedure [13] and AV repair techniques [14]. A perfect solution does not exist, and the preferred treatment for an individual with AVD should be patient-tailored. But understanding the healthy and diseased AV on a cellular and biomechanical level is essential in appreciating the benefits of particular treatment options. The aim of this review is to provide an overview of the embryology, genetics, structure, pathophysiology, messenger pathways, and hemodynamics of the AV, while linking these to their implications for treatment.

2. Embryology of the Aortic Valve

Normal Outflow Tract and Valve Formation

Twenty–thirty percent of congenital cardiovascular malformations contain some form of defective heart valves. Its incidence has been estimated to be as high as 5% of live births [15]. Several seminal papers have been published on the different steps of cardiac development [16–18]; within the scope of this paper, we will solely focus on the embryogenesis of the heart valves.

The formation of endocardial cushions in the atrioventricular canal (AVC) and outflow tract (OFT) marks the start of valvulogenesis in the primitive looped heart at approximately 31–35 days after conception [19,20]. Contrary to the endocardial cushion and valvular leaflet relationship in the AVC, less is known about how the semilunar valves arise from the complex arrangement of the endocardial cushions in the OFT [15]. Opposing dextro-superior and sinistro-inferior endocardial cushions grow at the cephalad portion of the truncus arteriosus [21]. Simultaneously to the creation of these conotruncal cushions, two intercalated cushions form in between the aforementioned cushions. Upon fusion of the conotruncal cushions, the truncal septum is formed. At the early developmental stages, those conotruncal cushions appear bulky and cellularized, because the endothelial cells overlying the primitive endocardial cushions invade the conotruncal cushion matrix [22,23]. This highly proliferative state of endocardial cushions is lost in later remodeling and mature valves [15,22]. The growth of these valvular primordia continues, leading to the formation of thin fibrous cusps for the semilunar valves until they have become highly organized structures containing a rich collagen, proteoglycan, and elastin ECM by the end of gestation [22]. Valve maturation and microarchitectural remodeling will continue into juvenile stages in all mammalian species [15,22,24] with similar stratification patterns between species [22]. The evolutionary basis for this similar semilunar valvulogenesis throughout mammalian species resides on highly preserved molecular pathways and physiological processes that were present in species with tubular hearts driving unidirectional flow and have been maintained throughout the formation of a four-chambered heart [17].

During truncal septal differentiation with conotruncal rotation and caudal shift, mesenchymal derivation from the endocardium takes place [25], where dedifferentiation from a myosin-heavy chain to an alpha-smooth muscle actin phenotype takes place. This allows for the formation of (mature) semilunar valves from the conotruncal and intercalated cush-

ions of the OFT (Figure 1) [23,25]. The conotruncal cushions give rise to the semilunar right and left leaflets; that is, the right and left coronary cusp leaflets for the aorta. The opposing right and left intercalated cushions develop into the posterior aortic (non-coronary cusp) and anterior pulmonic leaflet, respectively [23]. During endocardial cushion fusion, cavities are formed through apoptosis leading to the formation of a central lumen of each of the cushions separating the three valves and creating the wall of the supporting sinuses through peripheral arterialization [23,26]. During this process of cavitation the muscular portion of the proximal OFT contributes to the formation of valves and sinuses in a paracrine, rather than a direct cellular fashion [23]. Eventually, rudimentary valves will elongate and the endocardial cushions thin out, thus remodeling the valves with a compartmentalized microarchitecture consisting of five layers: endothelium, fibrosa (comprising mainly valvular interstitial cells (VICs) and collagen fibers), spongiosa (comprising mainly proteoglycans), ventricularis (comprising mainly elastin sheets), and endothelium [22] (Figure 2). The microarchitectural composition of the valve leaflets together with the biomechanical properties and vasoactivity are critical for normal valve function allowing for optimal interplay between form and function. A striking example of this interplay is the occurrence of hypoplastic left heart syndrome during heart development, where the obstruction or atresia of left-sided valves produces a lack of blood flow, in turn affecting the functional stimuli–i.e., flow–to form a compact left ventricle (LV) [27,28]. Such findings emphasize the role of blood flow perturbations as a causal factor in, not only early organogenesis, but also pathogenesis of valvular (structural) disease.

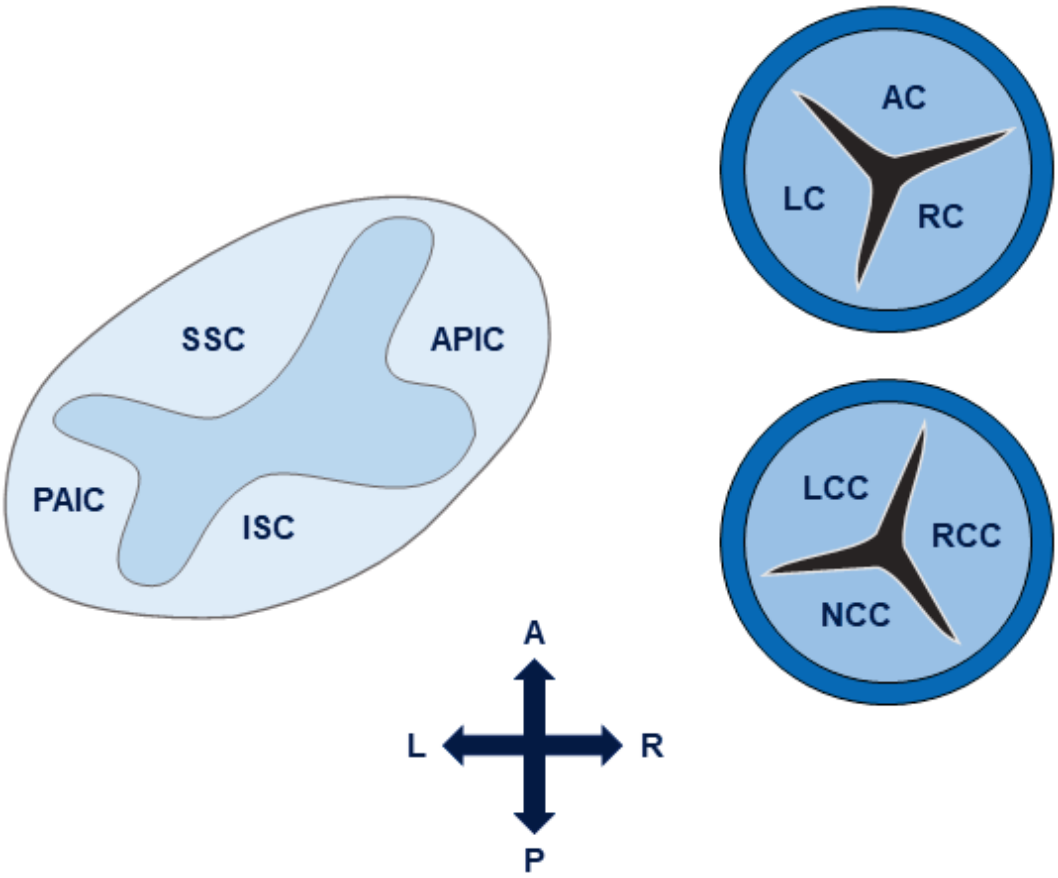

Figure 1. Leaflet development of the semilunar valves (aortic and pulmonary). The left and right valve leaflets of both the pulmonary and aortic valve arise from the conotruncal cushions, whereas the non-coronary aortic leaflet and anterior pulmonic leaflet arise from the intercalated cushions. Adapted from Martin et al., 2015 [23], distributed under the terms and conditions of the Creative Commons Attribution license (CC BY 4.0 DEED, Attribution 4.0 International), 2015, the authors.

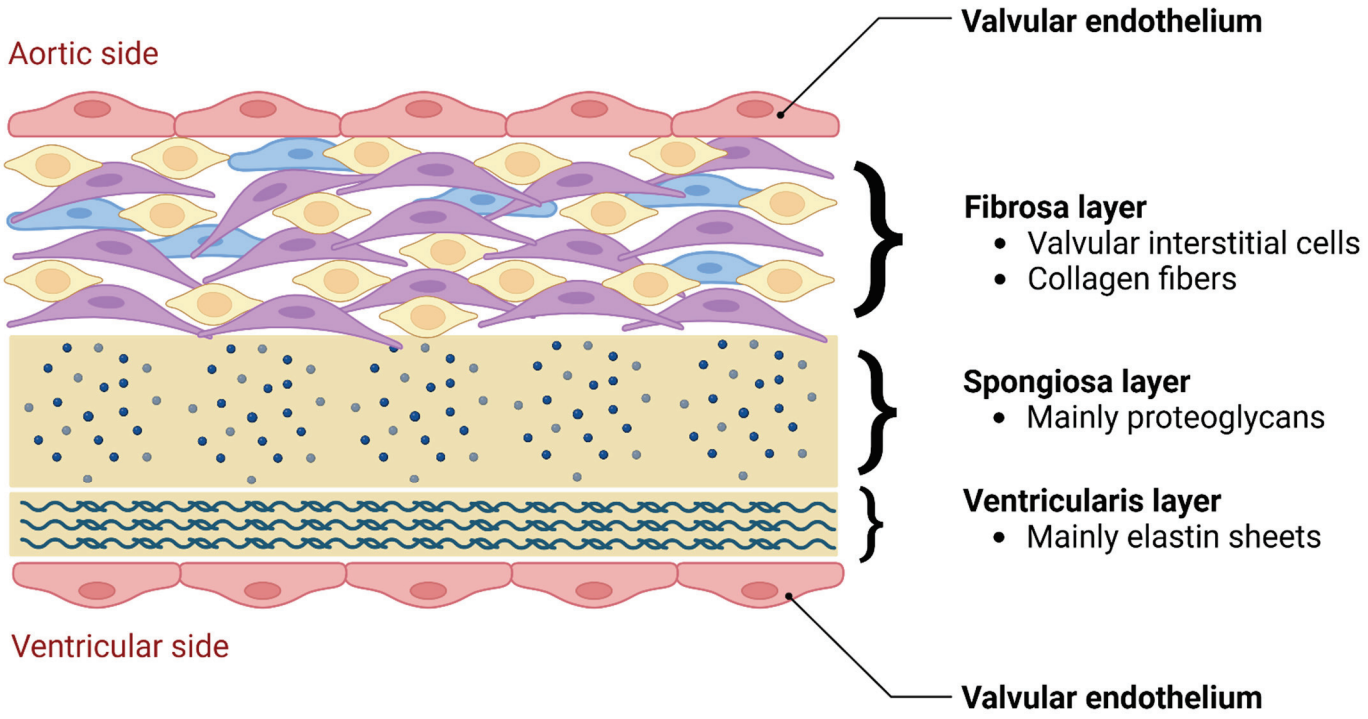

Figure 2. Microarchitectural composition of aortic valve leaflets, consisting of a bilayer of endothelial cells (aortic and ventricular side), fibrosa layer, spongiosa layer, and ventricularis layer.

3. Transcriptional Regulation of Valvulogenesis

Normal development and function require tightly regulated interactions between molecules and gene transcription, and any genetic defect or signaling alteration may disturb this process, leading to structural malformations. There is a complex genetic regulatory network that generates valve progenitor cells through endothelial-to-mesenchymal transformation (EMT), effectuates ECM remodeling, and is involved in leaflet stratification (Figure 3). Importantly, calcific aortic valve disease (CAVD), a progressive condition often stimulated by inflammatory processes—in which a tricuspid AV or a congenital bicuspid AV (BAV) becomes thickened, fibrosed, and, consequently, calcified [29]—is characterized by the expression of transcription factors also involved in valve development and comparable to osteogenesis [21]. Moreover, mechanosensitive systems, e.g., RhoA/ROCK and YAP/TAZ, detect substrate changes and initiate mineralization pathways leading to CAVD [30]. Figure 4 plays a central role in this synopsis, as it possesses important clues on several aspects of CAVD pathophysiology and progression. During EMT, cells on the endocardial side of the primitive heart tube undergo a phenotypic switch from a endothelial-like phenotype to a mesenchymal-like phenotype [31]. These cells migrate into the cardiac jelly portion of the tube, where they form the cardiac cushions which are essential for, among other things, OFT formation [32]. Many transcription factors and signaling pathways have been linked to EMT, as well as neural crest (NC) cell migration to the distal cushions [32]. In absence of NC cells, OFT septation will not occur [33,34]. After fulfilling their role in septation, most NC cells go into apoptosis [35]. Their further role beyond this developmental stage remains largely unknown. Some signaling pathways that play a crucial role during heart valve development include Notch, transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), and Wnt/beta–catenin pathways [15]. Besides signaling pathways, transcription factors expressed in the endocardial cushions represent progenitors of AV leaflets, such a Tbx20, Msx1, Msx2, and Twist1, as well as ECM protein regulators, such as Sox9 and NFATc1 [36]. There has recently been interest in EMT, as it has been shown that adult cardiovascular patients also experience similar transitions when presenting with degenerative diseases of their cardiovascular system [31,37].

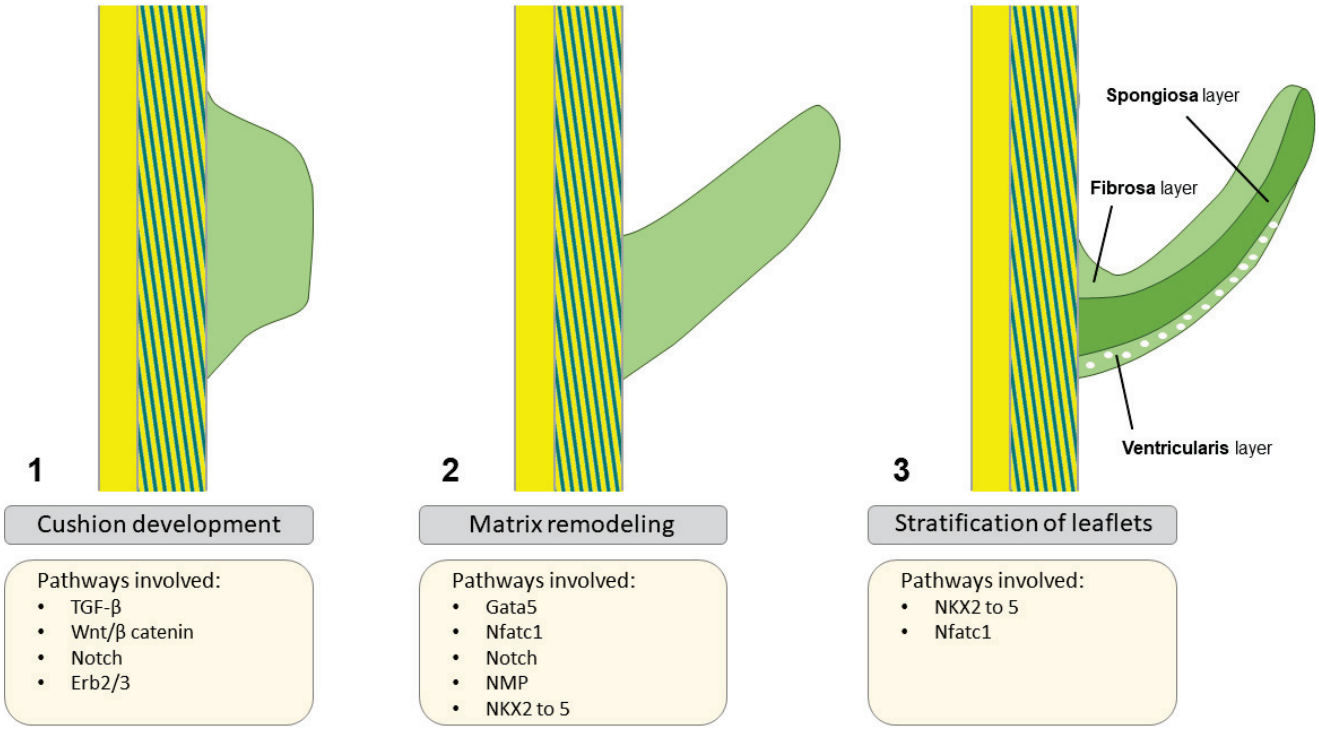

Figure 3. Aortic valve formation: starting with cushion formation (1), proceeding with matrix remodeling (2), and ending with leaflet stratification (3). Adapted from Martin et al., 2015 [23], distributed under the terms and conditions of the Creative Commons Attribution license (CC BY 4.0 DEED, Attribution 4.0 International), 2015, the authors.

Timing/Expression of Transcription Factors and Deficient Aortic Valve Formation

Valvulogenisis regulatory systems are similar in AVC and OFT development and AVC endocardial cushion formation precedes OFT endocardial cushion formation by one day [15,38]. Given the presumed similarities, the larger AVC endocardial cushions in mouse or chick embryos, and the fact that examination of the OFT cushions is complicated due to the presence of NC derived progenitors (responsible for the formation of the aorto-pulmonary septum), many research extrapolates results from the AVC to the OFT regulatory system [39]. This assumption holds true and has been discussed elsewhere [38,40,41]; here, we highlight some of the pathways that have a more OFT specificity.

Cardiac progenitor cells of the second heart field give rise to several cell lines that play a role during formation of the aortic outflow tract, mediated by Nkx2.5, vascular smooth muscle cells (SMC), endocardial cushion cells, and OFT myocardium [42,43]. Secondary heart field deficiencies preferentially compromise semilunar valve (but not atrioventricular valve) defects that are related to defects in the formation of the OFT [15,41]. Next to that, vascular SMCs of the aortic root originate from these progenitor cells deriving from the second heart field as well as NCC; in contrast, in the ascending aorta and aortic arch, these cells form solely out of neural crest cells [44]. Multiple cell lines and signaling systems are involved in AV and ascending aortic formation; defects in these pathways may induce malformations of the AV, such as BAV. Despite the vast importance of Nkx2.5 in secondary heart field development and the fact that this homeodomain factor is the most commonly mutated single gene in congenital heart disease (CHD), many of its actions remain to be elucidated [45].

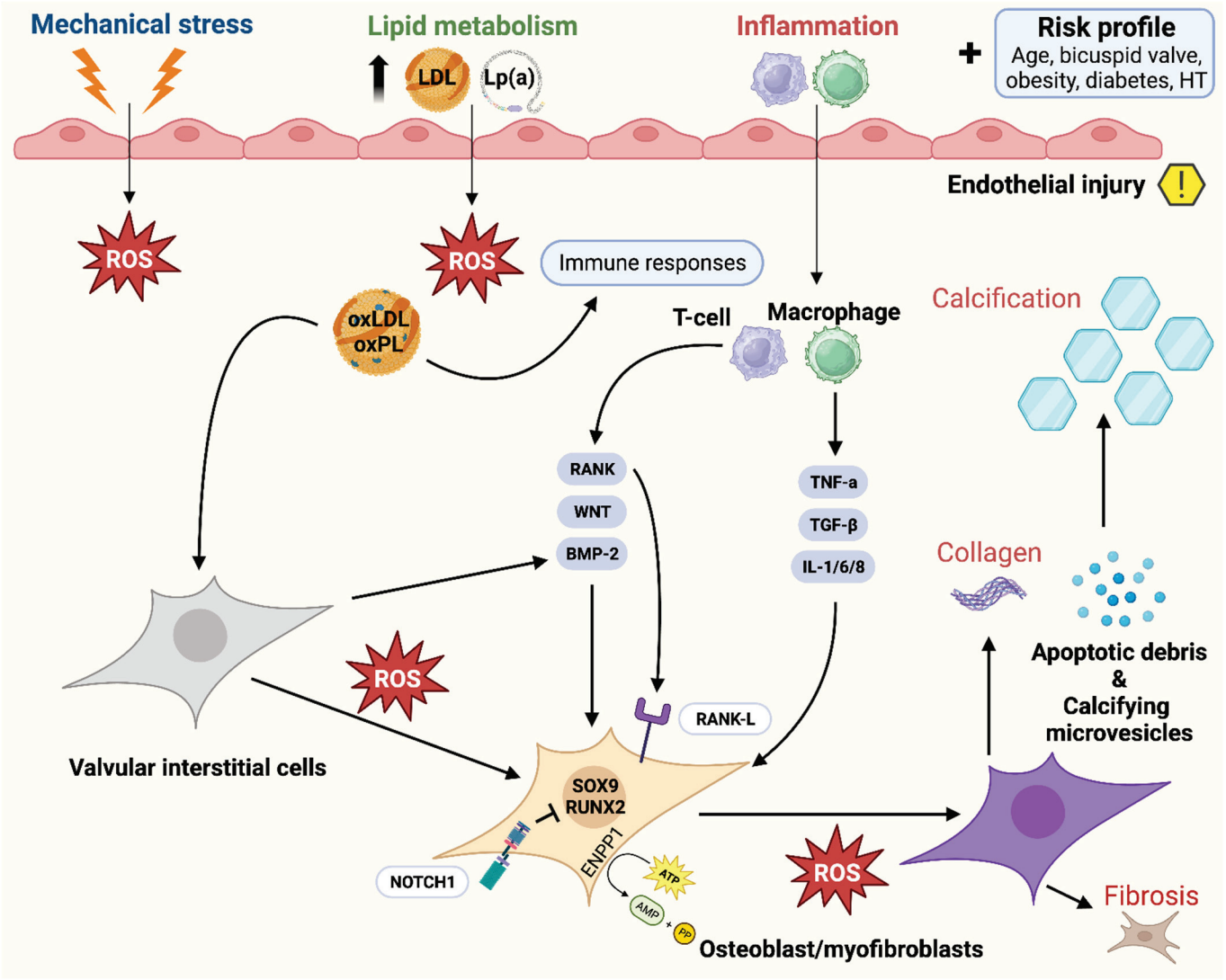

Figure 4. Pathophysiology of calcific aortic valve disease: activation of bone-formation pathways induces aortic valve calcification through various ligands, ranging from inflammation to metabolism. Adapted from Greenberg et al. [29], distributed under the terms of the Creative Commons CC BY license, 2021, the authors. Legend: Calcific aortic valve disease is initiated by endothelial injury (right upper quadrant), and propagated by a complex cascade of signaling involving osteoblasts and myofibroblasts (bone formation pathways). Abbreviations (alphabetical): ATP = adenosine triphosphate; AMP = adenosine monophosphate; BAV = bicuspid aortic valve; BMP2 = bone morphogenic protein 2; ENPP1 = ectonucleotide pyro phosphatase/phosphodiesterase family member 1; IL = Interleukin; LDL = low-density lipoprotein; Lp(a) = lipoprotein a; ROS = reactive oxygen species; NOTCH1 = Notch homolog 1; PP = inorganic pyrophosphate; RUNX2 = runt-related transcription factor 2; SOX9 = SRY-box 9; TGF-β = transforming growth factor beta; TNF = tumor necrosis factor alpha.

The TGF-β superfamily consists of BMPs (BMP2-7) and TGF-β in the embryonic heart where BMPs are responsible for the promotion of endocardial cushion growth. Next to that, BMP, Notch, and TGF-β promote EMT, cell invasion into the cardiac cushions, and remodeling of the valves [23,38,46]. Furthermore, TGF-β has been linked to activation of VICs and their transformation into myofibroblasts in the adult valve [47]. Importantly, Notch signaling disruption markedly decreased the Snail transcription factor responsible for the initial steps in EMT and cushion development [48], placing the Snail pathway at the

center of valve development. Notch 1, 2, and 4 receptors and their ligands (Jag 1/2 and Dll4) are specifically expressed in the OFT and its cushions [49–51], where inactivation of this pathway leads to a multitude of CHD including BAV [52–54]. From a hemodynamical point of view, Notch and downstream pathways have also been linked to a process called valve polarity, distinguishing the lamina fibrosa from the flow side of the valve [15,52] and allowing for valve leaflet maturation [55] (Figure 3). However, this is not yet fully established; reports emphasize the role of Notch signaling in altered shear stress possibly promoting valve stratification and even calcification [51,56] (Figures 4 and 5). A recently published study pointed out the role of the MIB1 gene, an essential regulator for Notch ligands signaling, in the pathophysiology of non-syndromic BAV [57]. Future research should further investigate its potential as a treatment target, along with other genes linked to BAV formation, such as Jag1 [57,58].

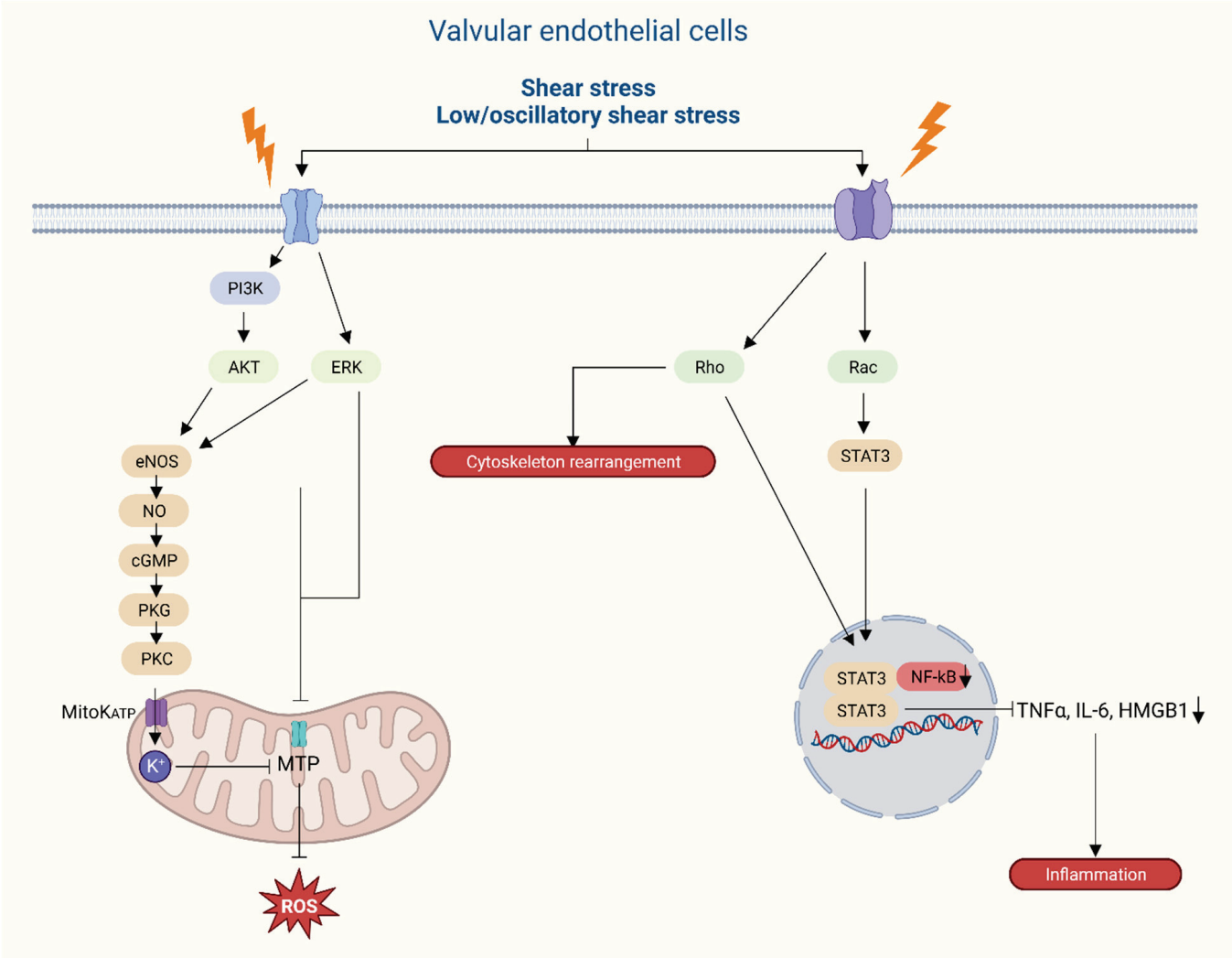

Figure 5. Graphical representation of intracellular responses of aortic valvular endothelial cells following external mechanical stress on the aortic valve leaflets.

In patients with AVD, findings at a transcriptional level may provide clues for innovative treatment strategies. Multi-omics techniques, including proteomics, especially when applied on a population level, aid in understanding the origins and mechanisms of valvar (patho)physiology. For example, studies in the past five years have identified molecular regulatory networks in CAVD that aid in the search for therapeutic targets [59], as well as proteins that were elevated years before CAVD onset, and may be linked to atherosclerotic coronary disease [60]. More recently, using transcriptomic analysis, biological pathways of

cardiac ageing, inflammation, and chondrocyte development—through which lipoproteins may cause CAVD—were identified [61]. The metabolic profile of healthy versus diseased cardiac valves have also been mapped using these techniques [62]. The application of such novel methods on failing valve substitutes meets great interest as it may provide valuable insights in the mechanistic basis of valve deterioration, be it native or replaced [63], and possibly its prediction and prevention.

Genome-wide association studies furthermore suggest a role for transcription factors with important embryological functions in the development of AS [64] and bicuspid AS [65], which may help prioritize gene and pathway targets for medical CAVD therapy.

4. Anatomy and Hemodynamics

Heart valves open and close around 100,000 times a day, adding up to around 3 billion cycles in a 75-year lifespan, and are subject to a variety of stresses. For many years, the AV has been seen as a "static" structure responsible for unidirectional flow of blood coming from the LV and aiding in coronary perfusion. However, evolving insights shifted our perception of the AV and is now seen as functionally complex regulatory system necessary for optimal mechano-biological coupling of the heart.

4.1. The Aortic Valve and Root

Located in the middle of the heart, the AV is commonly referred to as the center of the heart. This is likely no coincidence, as it has several advantages for this particular valve that is subject to the highest levels of pressure and shear stress of all heart valves in a physiological situation [66]. Supported by the fibrous skeleton of the heart and atrioventricular valves, the AV is able to transduce mechanical stress like no other valve, as evidenced by its continuity with the mitral valve (MV) [67]. The pulmonary valve has no fibrous support to it, as it was pushed upwards by the underlying infundibulum, a freestanding rim of muscle seated on the right ventricle and septum directly below the pulmonary leaflets, separating the two right-sided valves during OFT formation [16]. Infundibular muscle, in its turn, is not seen on the left side, where the mitro-aortic fibrous continuity connects the two left-sided valves [68,69]. The AV apparatus was previously described as "a tale of dynamism and crosstalk" by Yacoub [67], which is also underpinned by several treatment modalities respecting the morphology and function of native roots, i.e., the Ross [13], remodeling [70], and reimplantation operations [71].

Throughout evolution, functionality has clearly dictated its morphological counterparts and, as such, the AV can be divided into several functional units (annulus, cusps, sinuses of Valsalva, and sinotubular junction), accumulating into one biomechanical unit. The geometrical, crown-shaped structure of the semilunar valves allows for optimal responsiveness and efficacy during the cardiac cycle as different forces are exerted on the valves [12,72]. Next to that, the precise shape and building plan of the leaflets (including the nodules of Arantius) allow for competent seal and force distribution so that the AV remains competent throughout life. Microarchitectural and geometrical changes may therefore result in biomechanical dysfunction and lead to valvular disease [72], through the pathways illustrated in Figures 4 and 5.

4.2. Valvular Fluid Dynamics

A complex interplay between the cardiac cycle, AV biomechanics, transvalvular hemodynamics, and the compliant properties of the aorta all represent different mechanical stresses that act individually or combined to exert a physiological response through the cellular components of the AV (Figure 6).

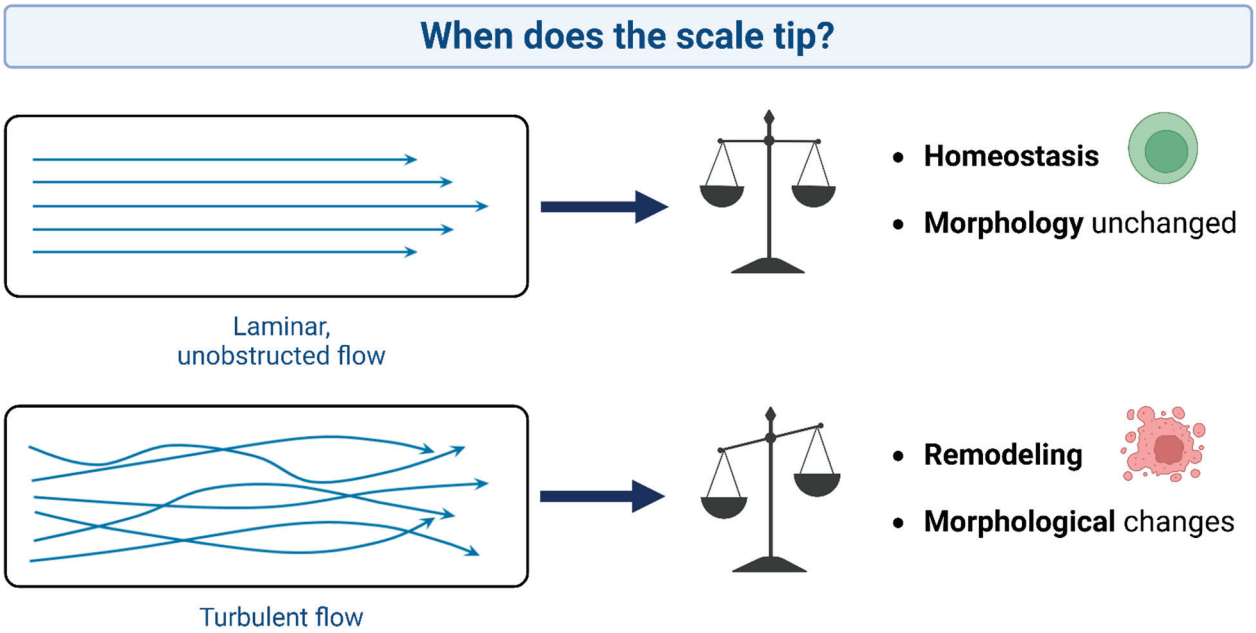

Figure 6. The concept of laminar and turbulent flow and their implications for aortic valve remodeling.

The AV is embedded in a crown-shaped annulus [68,69], providing optimal support to the AV under high pressures and dynamic flow patterns. The opening of the AV is a harmonized process and this is crucial to guarantee unimpeded blood flow [73]. Coordinated and competent opening of the valve is essential in decreasing afterload and, therefore, ventricular systolic workload. Nonetheless, alterations in mechanical stress or blood flow near the AV may activate several pathways that in turn may lead to situations in which function deteriorates, as a result of which the LV is exposed to pressure (e.g., in case of AS) or volume (e.g., in case of AR) overload. The opening of the AV lasts for about 330 ms at a heart rate of 70 bpm, where blood rapidly accelerates through the valve, reaching a peak velocity of 1.2 m/s [74,75]. The ensuing deceleration causes a pressure gradient of only several millimeters of mercury with preferential flow at the center of the aorta and low momentum fluid near the aortic wall, thereby causing flow reversal at the sinus regions [74,76,77]. As such, vortices of blood are created by the end of systole, aiding efficient and swift AV closure with an estimated volume (closing volume) to be less than 1% [74,78].

In order to aid fluid dynamics and dictated by transvalvular pressure, the aortic annulus changes shape during cardiac cycle, albeit in an asymmetric fashion, with the greatest expansion during isovolumetric contraction at the left coronary cusp annular region in respect to the non-coronary cusp annular region. Due to its morphological anchoring and continuity with the MV at the site of the non-coronary cusp [68,69], annular stability is provided and allows for energetic transfer from the MV. Next to that, the physiological consequence of this anatomical feature translates into a circumferential increase in diameter at the commissural level, which is proportional to the end-diastolic volume [79]. This biomechanical behavior—where the annulus reaches its minimum size at the end of systole and maximizes in size at the end of diastole [75,78,79]—is a teleonomic hallmark of evolutionary hemodynamics in all mammals. Systolic workload of the ventricle should be as low as possible and, by anticipating the accommodation of each stroke volume, transvalvular hemodynamics are optimized [79], thereby minimizing the possibility of turbulent damage to the valvular cusps. Furthermore, the compliant properties of the surrounding aorta are of vital importance to facilitate ejection as, from a physiological perspective, energetics from cyclic LV contraction need to be addressed in order to provide a continuous flow and pressure downstream in the arterioles [80]. This allows for optimal ventriculo–arterial coupling, and the vertical motion of the aortic

root during the heart cycle is important for absorbing stress. In such, both the annulus and the ascending aorta expand to dampen the pressure and flow during systole. This so-called Windkessel effect allows for better energetics where a portion of stroke volume is temporarily maintained by the expanding aorta and later propelled into the circulation by the recoil of the elastic aortic wall [81]. Next to that, another compliancy mechanism takes place regarding the topographical anatomy of the aortic root as it sits at an angle of around 16 degrees to posterior and the left (angle between basal and commissural planes) during diastole. During systole, an alignment of the LV outflow tract (LVOT) and the aorta takes place reducing this angle to around 7 degrees, thereby straightening the tube and thus aiding ejection [12,77,80].

It might be clear that the underlying mechanobiology of the AV is very complex and no sole intervention can preserve all its aspects. Prosthetic valves in the aortic position fix the annulus, are intrinsically obstructive and therefore associated with suboptimal fluid dynamics through the OFT [82]. Even a mild gradient over the valve may have major implications in the long run [5,83], although not directly life-threatening. Image a large closed system, e.g., a bowl, filled with water; should you have a large opening at the bottom, blood will flow out seamlessly, but if it has a small opening, pressure must be increased to maintain equal flow over the defect. The same holds true for AS; the smaller the opening, the more difficult it is for blood to flow out under the same workload. To increase flow, one should increase pressure (workload) before the stenosis or increase the diameter of the opening. Consequently, the velocity of the fluid through the opening has to increase to achieve equal flow, which is in accordance with Bernoulli's law [84].

In this context, a lifetime of suboptimal gradients and loss of root dynamics, as seen after mechanical or bioprosthetic valve replacement [82], will undoubtedly translate to a higher ventricular workload [85]. In patients undergoing AVR, small reductions in mean transvalvular gradients are associated with significant reductions in heart failure [85]. In such, the Ross procedure, which replaces the diseased AV with the native, living pulmonary valve, enables natural gradients and hemodynamics, coupled with optimal coronary perfusion and ventricular mass regression [86,87]. Physiologic flow patterns and low wall shear stresses after the Ross procedure (full root technique) and valve-sparing root replacement—whether combined with reconstruction of neosinuses or not—are major benefits of these reconstructive approaches [88]. With the current discussions on the lifetime approach to patients with AVD, this holds significant importance.

5. Biomechanics and Cellular Responses

The opening of the AV should be atraumatic as well as symmetric to ensure retained morphology of the apparatus in the long run. Any failure to comply with these terms, i.e., in situations with non-physiological pressures, resistance, or volumes, leads to the activation of second messenger pathways based on mechanical stimuli such as stretch, shear, and transvalvular pressure (Figure 7). Mechanotransduction is the translation of mechanical processes to biological signals, which also affects the aortic valve and root. In a normally functioning AV, the ultimate goal is to efficiently transfer these mechanical stimuli into a well-orchestrated cascade of complex signals. This is reportedly regulated through the cooperative action of valve endothelial cells and VICs [8]. Intrinsic nerve networks are likely responsible for part of these adaptations by regulating synthesis, contraction, repair, and homeostasis within the valve, although evidence for this is not abundantly available.

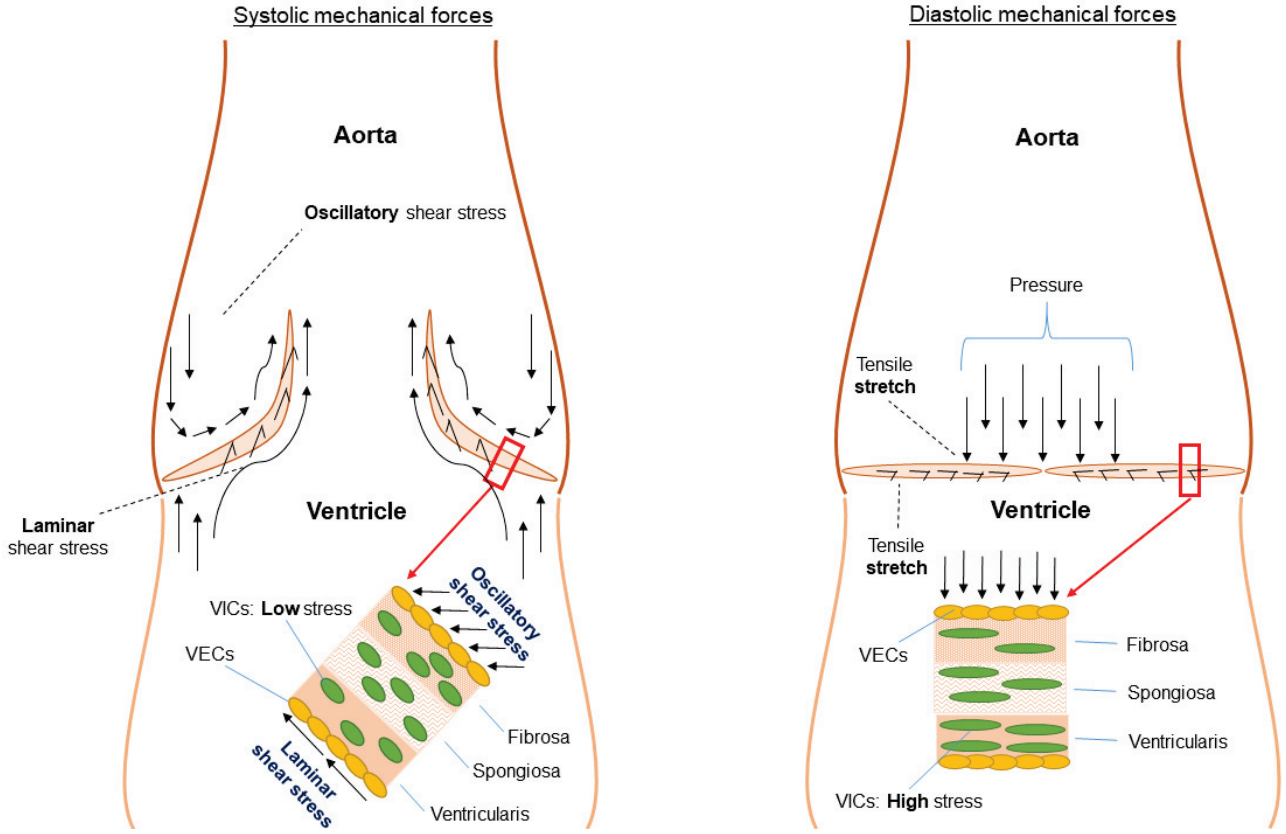

Figure 7. Mechanical stimuli experienced by valvular endothelial cells as well as valvular interstitial cells (fibrosa layer). Adapted/modified from Balachandran et al., 2011 [74], distributed under the CC BY 3.0 DEED Attribution 3.0: Unreported license.

5.1. Functional Morphology and Mechanical Stimuli

Several studies have already highlighted the intricate relationship between hemodynamics and the mechanical microenvironment [77,80,89,90], corroborating the fact that AV degradation is not a passive process. The active interplay between hemodynamics and valvular biomechanical function is attributed to a dense and highly organized ECM network and is defined by the building plan of the leaflets. Different layers are specifically built to cope with different mechanical stresses such as leaflet strain, laminar shear stress, oscillatory shear stress, and pressure as evidenced by the ECM composition of the leaflets that are packed with interstitial cells for structural stability, collagen, elastic fibers, proteoglycans, and glycosaminoglycans, which are lined on both sides with endothelial cells.

Endothelium forms a monolayer of cells, providing a barrier function for the blood and the underlying cells and are the first to be exposed to shear stress (Figures 4 and 7). Based on a bulk of endothelial function research throughout the body, it is rather peculiar that it took quite some time to place endothelial dysfunction at the basis of valvular degeneration [91]. Studies on functional properties of AV endothelium show unique properties compared to other vascular endothelium where the alignment of endothelial cells with regard to the orientation of flow form the most striking difference [92,93]. AV endothelial cells show a perpendicular alignment to flow, a process that is also present in studies using valvular endothelial cells without the presence of an aligned substrate [12,92]. This particular alignment was shown to be dependent on cytoskeletal reorientation; however, it is stimulated by specific endothelial derived mechanotransduction pathways and differential gene expression. Next to that, compared to vascular endothelial cells, the valvular endothelium shows a higher proliferative rate [94] and location of the valvular endothelium (ventricular or aortic side) also seems to play a role in pathway activation. Specific biomechanical profiles and types of shear on the aortic side lead to higher levels of calcification-associated

gene and BMP-4 expression; meanwhile, on the ventricular side, inflammation-associated gene expression together with BMP-4 expression are upregulated [93,95,96]. Importantly, different shear stresses are exerted onto the two sides of the AV leaflets, where the aortic side is exposed to interrupted low shear stress as compared to the high-shear-stress ventricular side, with a peak of 70 dynes/m^2 [66]. Those differences in flow patterns on either sides of the valve leaflets are sensed by the glycocalyx activating signal pathways thereby releasing endothelium-derived vasoactive substances, such as nitric oxide, that play a role in valvular stiffness [9]. Endothelial dysfunction, initiated by lipid deposition, inflammation, mechanical stimuli, and other risk factors—e.g., smoking—produces reactive molecules called reactive oxygen species (ROS) [29], and stimulates a cascade of signaling molecules through valvular interstitial cells (VICs), including TGF-β, interleukin-6, TNF, and BMP-2 [64,97]. The accumulation of these ROS induces several ROS-mediated mechanisms that, in turn, stimulate calcification, mineralization, apoptosis, and osteogenesis, clinically encountered as CAVD (Figure 4). This figure captures key aspects of the risk factors, origins, and actionable targets of AVD.

VICs are highly plastic cells that can alter phenotype, form the dominant AV cell type, and play a crucial role in architectural maintenance and biomechanical functionality of the valve [98]. Optimal biomechanics can be attributed to the ECM as it functions as an integrator between form and function and provides several signaling molecules.

In healthy adults, extracellular homeostasis is regulated by these interstitial cells and mediate valvular remodeling through a balanced secretion of matrix degradation enzymes, including matrix metalloproteinases (MMPs) and their inhibitors (TIMPs), and deposition of structural ECM components within the layers [91], which also play a role in thoracic aortic aneurysm formation [99]. VICs and inflammatory cells stimulate expression of MMP1,2,9 and cathepsins, resulting in abnormal ECM remodeling, which lies at the basis of valvular deterioration [93,98,100]. Deterioration of the valve is based on activated MMP's and cathepsins degrading collagen and elastin with ensuing pro-inflammatory response, leading to calcification [101]. Furthermore, VICs secrete ECM components such as hyaluronan and collagen, which will deposit in a disorganized fashion, thereby altering valvular stiffness and biomechanical profile; this is aggravated by a VIC transition to osteoblast-like cells [102]. It may be clear that both altered shear stresses and the whole complex interaction between endothelial (dys)function and the ECM will have their effect on the valvular phenotype, resulting in inflammation, degeneration, and calcification.

5.2. Calcific Aortic Valve Disease

The macroscopic pathologic anatomy of aortic sclerosis is characterized by nodular calcification and leaflet thickening, which impair the motion—and thereby the function—of the valve. In severe cases, this may contribute to a reduced orifice area, clinically known as AS [103]. Microarchitectural hallmarks of such aortic valve sclerosis include the invasion of inflammatory cells, the induction of fibrosis, and the formation of osteogenic cells, contributing to inflammation and ossification [103,104], indicating that this is an active process. These valvar cells undergo a phenotypic switch or enter apoptotic pathways, driven by increased shear stress, producing ROS, ECM stiffness, and the presence of signaling molecules such as TFG-β1 [102,105].

Portrayed in Figure 4, CAVD is governed by important and unalterable risk factors, such as BAV morphology and patient age. An additional risk is posed by elevated blood pressure, elevated plasma lipoprotein(a) levels, and the presence of diabetes mellitus or obesity—i.e., truly modifiable factors.

Several examples of potential therapeutic targets contributing to CAVD initiation include 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, low-density lipoprotein, lipoprotein(a), angiotensin II, angiotensin-converting enzyme, and matrix metalloproteinases [6,106–108]. Key studies support a principal, and perhaps causal, role for lipoprotein(a) in CAVD [107,109] and its progression [110]. The effects of statins and angiotensin-converting enzyme inhibition on CAVD progression have been vigorously

studied, but the clinical results of such therapies have been variable [108,111]. Administration of statins in asymptomatic AVD patients without risk factors, at this time, should be avoided, as they may induce new risk factors such as diabetes [112,113]. Toll-like receptors (TLRs) function at the interface between tissue repair and innate immunity pathways [114] and it was very recently shown that the TLR3 pathway is an evolutionarily conserved pathway that governs CAVD later in life [114]. Several clinical trials targeting calcium metabolic pathways are ongoing [115].

There have been seminal genetic and molecular studies that have claimed the WNT–β-catenin, Notch, and MYOCD pathways to be involved in the control and commitment of heart valve cells to a fibrocalcific lineage [116]. The activation of these pathways, also involved in the varying embryological steps of AV formation, may contribute to CAVD. The endothelial activation of second messenger pathways related to inflammation, metabolism, and bone formation, instigating this fibrocalcific lineage of the valvular cells, have been shown to lie at the basis of CAVD (Figure 4). Furthermore, circulating osteoprogenitors, likely arising from the bone marrow, that are recruited and are capable of creating a bone-like microenvironment, contribute to valve ossification [117–119]. Indeed, the effects of such pathways of valvar degeneration were described more than a decade ago. The next step is the identification of actionable targets based on these hypotheses, which is the subject of extensive ongoing studies [116].

With our increasing understanding of regulatory cellular and genetic pathways, therapeutic targets may be identified and further investigated in a (pre)clinical setting. The yet-unmet potential of these targets is to be elucidated by research focusing on cellular mechanisms of these drugs.

5.3. Adaptive Remodeling

To couple the aforementioned concepts to clinical practice, the adaptive capabilities of the pulmonary autograft (Ross procedure) are used to demonstrate this. Prosthetic valve replacement may not sufficiently reproduce biology by restoring native valve function; meanwhile, the Ross procedure allows for a living, dynamic substitute, even showing growth abilities in children [120,121]. It has been correctly postulated that the pulmonary autograft possesses the ability to adapt to the systemic environment by a phenotypic switch to an aortic phenotype after the Ross procedure, as the pulmonary and aortic roots share a common embryological genesis—the conotruncus [122]. However, neural crest cells, compromised in congenital AS, are less commonly seen in pulmonary than in aortic roots in murine embryological studies [123]. Such findings may explain why anatomic pulmonary valve anomalies, impeding use of a pulmonary autograft, are rare (incidence: 0.1%) and usually associated with other heart defects [124]. Explanted autografts are populated by viable valvular interstitial and endothelial cells after several years [125]. This process is called adaptive remodeling and is facilitated by gradually exposing the autograft to the systemic environment—for example, through systolic blood pressure management below 110 mmHg during the first 6–12 months postoperatively [126]. These adaptive capabilities all result from the concepts of mechanotransduction and activation of adaptive messenger pathways, as described here. This is also suggested by expression of the gene EphrinB2 in autograft endothelium after the Ross procedure, which is a biomarker of left-sided, but not right-sided, heart valve endothelium. This induced expression of EphrinB2 stimulates ECM remodeling, leading to increased production of smooth muscle actin [125,127]. In CAVD, as well as adaptive autograft remodeling, there exists a desire to understand whether there is a point of no return—i.e., a tipping point—in native tissue's ability for adaptation, after which a state of maladaptation and disease is produced. Further insights into biomarkers, leaflet stress and innovative imaging techniques may aid in objectifying a patient's physiological reserve, identifying such thresholds [128], and moving towards personalized medicine.

Surgical modifications—i.e., autograft reinforcement [126,129,130]—and adjuncts to conventional postoperative management strategies—i.e., beta-blocker-driven blood pressure regulation—have been proposed, some to promote adaptive remodeling and all to

prevent autograft dilatation. Given the concepts put forward in this review, it appears salient to realize that no technique is perfect, all choices will affect outcomes, and there should be a balance between the support provided and dynamism preserved.

From a biomechanical standpoint, the suboptimal alignment of the components of the AV will increase shear (oscillatory) stress on the AV leaflets and proximal aorta in addition to the systolic loss of energy in the LV [131]. As an example, chronic oscillatory stress of the different component parts is thought to cause premature deterioration after the subcoronary Ross operation [131]. Adjuncts performed to the total root technique of the Ross procedure should thoughtfully balance support with maintenance of valve dynamism.

6. (Surgical) Treatment

The embryology, transcription, fluid dynamics, mechanobiology, and cellular pathways involved in AVD have been the subject of extensive study. Integration of these concepts into the clinical decision-making process is complex given the widely differing levels of information provided through the learnings in these varying fields of interest.

6.1. Evidence-Based Medicine

Evidence-based medicine has previously been elegantly illustrated as a three-legged stool, which exemplifies that the best available evidence is just one leg of this stool [132]. The other two legs, physician's skills and expertise and patient values and expectations, cannot be left out of the equation during clinical decisions. In other words, evidence-based medicine is not "cookbook" medicine [132,133]. Prosthetic valve selection still carries several challenges pertaining to a lack of robust evidence and widely varying patient values and expectations between individuals. Current options for AVR include bioprosthetic AVR (surgically or transcatheter), mechanical AVR, the Ross procedure, and homograft AVR [134,135]. Bioprostheses are commercially available and do not require lifelong anticoagulation, but they exhibit limited durability [134]. Mechanical prostheses are designed to last a lifetime, but they produce a ticking sound and have a thrombogenic surface, therefore requiring lifelong anticoagulation, translating to increased bleeding and thromboembolism hazards [136]. Homografts come from human donor tissue and do not require anticoagulation, but they show premature calcifications and early failure [137,138]. The Ross procedure is the only living aortic valve substitute available [13], translating to optimal hemodynamics, requiring no anticoagulation, and having excellent long-term outcomes in experienced hands [137,139]. However, it transforms single-valve disease to double-valve disease and is technically demanding [140]. The unique benefits and drawbacks of all substitutes become immediately clear, but it remains a challenge to implement this into the decision-making process. Prostheses still cannot reproduce the complexity of human nature, and Donald Ross in 1967 correctly postulated that a living valve substitute was necessary to ensure longevity of a valve substitute [13]. The Ross procedure has known times of little acceptance and adoption in clinical practice, with a trough around the year 2010 [141]. Previous data on the long-term outcomes of this operation have been discouraging in some instances, but novel, contemporary data show excellent long-term results with survival that is comparable to the matched general population [137,139,142]. Besides anticoagulation avoidance, low rates of endocarditis have been reported after the Ross procedure [139,142], which should be considered when contemplating the optimal lifetime management of AVD patients. Insights into the technical success factors and improvements in patient selection have led to a standardized operation that is reproducible. The growing data favoring the Ross procedure support a reevaluation of the guidelines for the treatment of AVD, but the increased enthusiasm for the Ross procedure should be carefully balanced with its increased technical complexity by concentrating them in Ross centers of excellence [139,143,144].

6.2. Clinical Decision Making

Decision making in AVD is complex and entails much more than the available evidence and the clinical state of the patient. There is an ongoing shift toward tailoring treatment to the individual patient's needs and circumstances, taking patient values and goals into account, as well as the short- and long-term advantages and disadvantages of different treatment options (survival and complications, quality of life). The lifetime aspect of AVD adds another dimension to the decision-making process, as decisions made now will undoubtedly influence later decisions and outcome. This makes one appreciate the potential harm of avoiding risk in the short term, since this may produce higher risks in the long term [145]. So, individuals do not only benefit from tailored treatment options in the present day, but also in the future, all while taking into account patient values. Hence, one should aim for strategic planning of interventions over a lifetime, bearing in mind the options for a second and perhaps third intervention during index procedure planning, in an informed, shared decision-making process together with the patient.

We can acknowledge that no valve substitute or treatment solution is perfect. Circling back to the basis of this review, on the other hand, we can now appreciate that the Ross procedure comes closest to an ideal solution in terms of its biomechanics, embryological origin, anatomy/geometry, gene transcription and cellular responses, although the longitudinal functional decline hazards of the autograft can be improved. Novel treatment options are direly needed to meet the needs of patients with AVD. For the future, tissue engineering of heart valves (TEHV), to be regarded a byproduct of the Ross procedure, meets great interest. TEHV can produce a living valve able to emulate the sophisticated functions of a native valve [146,147]. The concept of in situ regeneration, which uses the microenvironment as a natural bioreactor, has produced encouraging results in recent years [148–150]. Cellular repopulation of an acellular scaffold has recently been successfully shown in a sheep model [150], with endothelial cells and nerves connecting with contractile cells and blood vessels, just like in a native valve [150].

A method able to simulate individual patient lives and generate disease-, age-, and sex-specific estimates of patient outcome, microsimulation models may fulfill a role in objectifying these different lifetime treatment pathways and their outcomes [120,134,136,151,152]. For the future, these models should become more patient-tailored and its potential for modeling the effect of certain treatment decisions and sequential treatments over a lifetime should be explored.

7. Conclusions and Directions

The mechanistic basis of AVD, and in particular aortic sclerosis, is that it is an active process, modulated by endothelial and interstitial valvar cells, that is also governed by the biomechanical environment of the valve. Techniques such as proteomics represent a promising avenue to enhance our understanding of the mechanistic basis of CAVD, and its prevention. In practice, treatment decision making for AVD is complex and is based on much more than scientific evidence, be it cellular or clinical. The interplay seen in a healthy, native aortic valve is a perfectly synchronized, almost magical, dynamic process and the undeniable clinical benefits of a living valve have been repetitively addressed.

The Ross procedure provides AVD patients with a viable therapeutic option integrated into the functional aortic root unit, also demonstrating an optimal postoperative quality of life and a favorable life expectancy. This review furthermore identified gaps that invite research on AVD (mechano)biology, proteomics, and (epi)genetics to identify cellular therapeutic targets and biomarkers of maladaptation.

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Review

Contemporary Evaluation and Clinical Treatment Options for Aortic Regurgitation

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Abstract: Aortic regurgitation (AR) is the third most frequent form of valvular disease and has increasing prevalence with age. This will be of increasing clinical importance with the advancing age of populations around the globe. An understanding of the various etiologies and mechanisms leading to AR requires a detailed understanding of the structure of the aortic valve and aortic root. While acute and chronic AR may share a similar etiology, their hemodynamic impact on the left ventricle (LV) and management are very different. Recent studies suggest current guideline recommendations for chronic disease may result in late intervention and suboptimal outcomes. Accurate quantitation of ventricular size and function, as well as grading of the severity of regurgitation, requires a multiparametric and multimodality imaging approach with an understanding of the strengths and weaknesses of each metric. Echocardiography remains the primary imaging modality for diagnosis with supplemental information provided by computed tomography (CT) and cardiac magnetic resonance imaging (CMR). Emerging transcatheter therapies may allow the treatment of patients at high risk for surgery, although novel methods to assess AR severity and its impact on LV size and function may improve the timing and outcomes of surgical intervention.

Keywords: aortic regurgitation; echocardiography; transcatheter aortic valve replacement

1. Introduction

Valvular heart disease has been shown to increase in prevalence with advancing age [1,2]. The World Health Organization reports that by 2030, one in six people will be 60 years of age or older (1.4 billion people) [3] and the OxVALVE population Cohort Study of patients $\geq$ 65 years old found a prevalence of mild aortic regurgitation (AR) of 15% and moderate or severe AR of 1.6% [4]. These findings are in line with the Framingham Offspring Study which found that in patients 60–69 years old, the prevalence of $\geq$moderate AR was 0.6% in men and 0.8% in women, and between 70 and 83 years the prevalence increased to 2.2% in men and 2.3% in women. A recent community-based study reported a 4.5% prevalence of moderate or severe AR in patients >65 years old [5]. An understanding of the diagnosis and management of AR will thus have increasing clinical importance in the setting of an aging population.

2. Aortic Valve Anatomy

An understanding of the etiologies of AR begins with an understanding of the structure of the aortic valve and aortic root. The aortic valve is composed of three cusps attached to the root in a semilunar fashion with their nadir of coaptation at the level of the annulus and highest point of attachment of the leaflet commissures at the sinotubular junction (STJ) (Figure 1) [6]. The leaflet coaptation surface is only a few millimeters in length. Variation can be seen between leaflets in height, width, surface area, and volume of each of the supporting sinuses of Valsalva [7]. The aortic root is defined as the portion of the aorta between the basal attachment point of the leaflets within the left ventricle (LV) and the STJ.

Its components include the leaflets, commissures, interleaflet triangles, STJ, and sinuses of Valsalva. The root is described as containing three circular rings (virtual ring at the basal attachments of the leaflets, ring at the level of ventriculo-arterial junction and ring at the level of the STJ) and a crown-like ring (formed by the suspended leaflets) (Figure 2) [8]. The posterior aspect of the aortic root is supported by fibrous tissue for approximately 55% of its circumference (membranous part of the septum to the left fibrous trigone) while the remainder is supported by ventricular muscle [9].

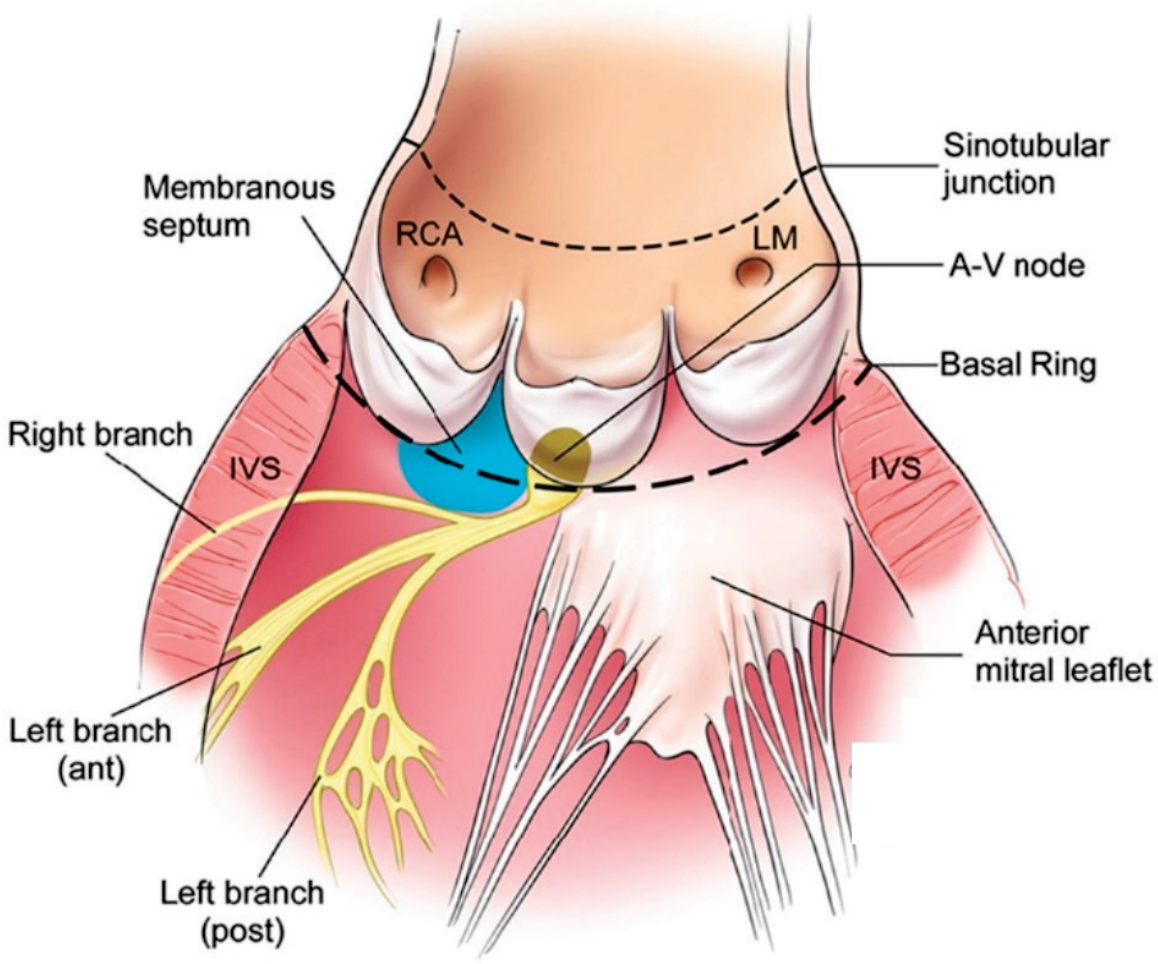

Figure 1. Anatomy of the Aortic Valve. In this figure, the anatomy of the aortic valve complex is shown. The aortic valve is composed of three cusps attached to the root in a semilunar fashion with their nadir of coaptation at the basal ring, representing the level of the annulus, and highest point of attachment of the leaflet commissures at the sinotubular junction. The atrioventricular (AV) node is typically located on the floor of the right atrium just posterior (post) and inferior to the membranous septum (*blue shaded region*). The atrioventricular (AV) node and bundle then courses on the top of the muscular septum under the membranous septum (blue area), where it divides into the left and right bundles. Abbreviations: *ant*, Anterior; *IVS*, interventricular septum; *LM*, left main coronary artery; RCA, right coronary artery. (Reproduced with permission from Hahn RT, Nicoara A, Kapadia S, Svensson L, Martin R. Echocardiographic Imaging for Transcatheter Aortic Valve Replacement. *J. Am. Soc. Echocardiogr.* [6].

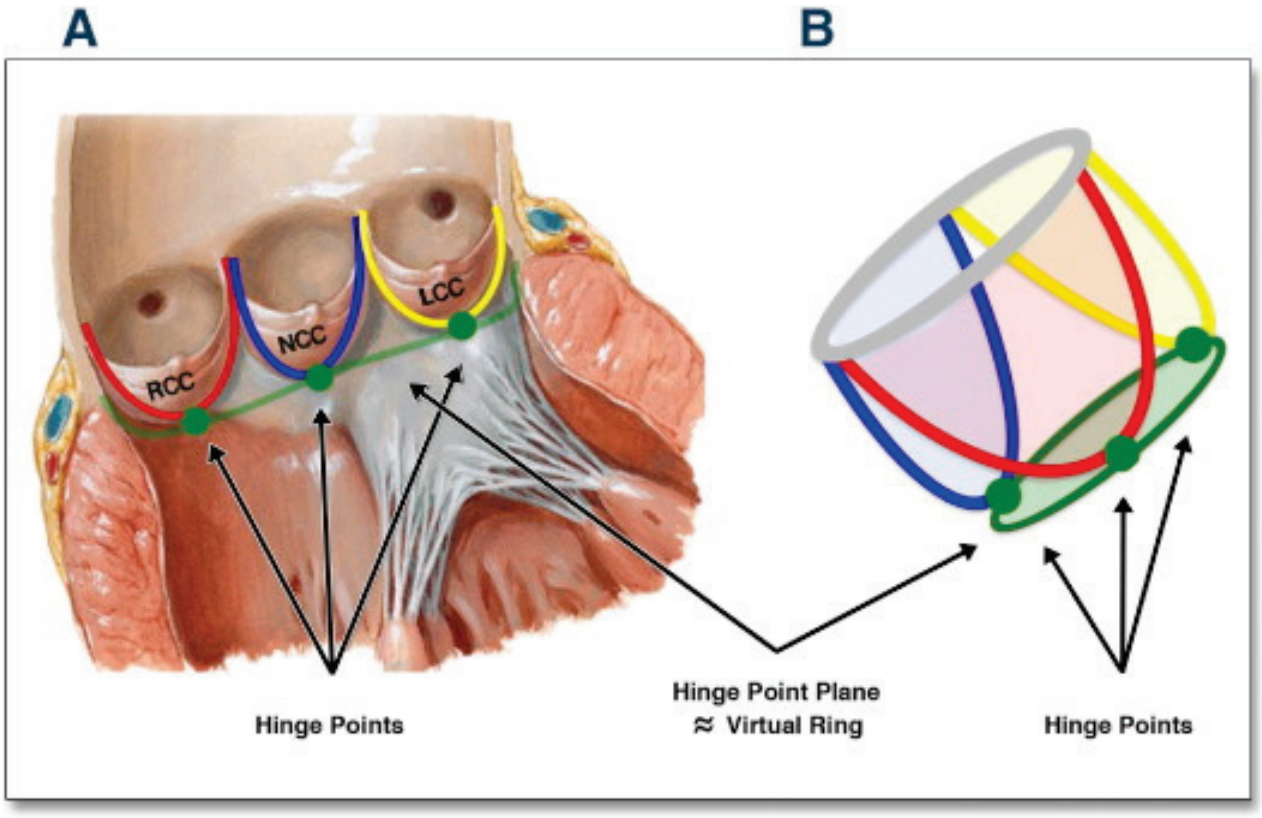

Figure 2. Anatomy of the aortic root. The aortic root is defined as the portion of the aorta between the basal ring within the left ventricle (green line, panel (**A**)) and the sinotubular junction (gray circle, panel (**B**)). The root is described as containing three circular rings: virtual ring at the basal attachments of the leaflets (green line/area), the crown-like ring composed of the semilunar attachments of the leaflets (red-blue-yellow lines) and ring at the level of the STJ. (Reproduced from Kasel AM, Cassese S, Bleiziffer S, Amaki M, Hahn RT, Kastrati A, Sengupta PP. Standardized imaging for aortic annular sizing: implications for transcatheter valve selection. *JACC Cardiovasc. Imaging* [8].

3. Etiologic Classification of Aortic Regurgitation

In the setting of a trileaflet valve, AR may be caused by primary leaflet disease or abnormalities of the aortic root and ascending aorta. Primary etiologies can be categorized as degenerative, inflammatory, infectious, due to trauma, tissue disruption, iatrogenic, or congenital [10] (Table 1, Supplementary Videos S1–S6). Functionally there can be leaflet prolapse, restriction of leaflet motion, leaflet retraction, fenestration, or perforation [11]. In the surgical literature, a classification scheme constructed after the Carpentier classification for mitral valve disease is used (Figure 3) [10,12]. Leaflet motion can be normal with reduced coaptation due to aorta dilation with central regurgitation (Type I), excessive leaflet motion (Type II), or restricted leaflet motion (Type III) [13]. Rheumatic heart disease remains the leading cause of AR in many low- to middle-income countries [14]. In high-income countries, it is bicuspid aortic valves or secondary to primary disease of the ascending aorta or the sinuses of Valsalva [14].

Table 1. Primary etiologies of aortic regurgitation: Primary causes of aortic regurgitation (AR) can be categorized as degenerative, inflammatory, infectious, due to trauma, tissue disruption, iatrogenic, or congenital. Functionally there can be leaflet prolapse, restriction of leaflet motion, leaflet retraction, fenestration, or perforation (after Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* [10]).

Mechanism	Etiologies
Leaflet Abnormalities-Congenital	Bicuspid, unicuspid, or quadricuspid aortic valve Ventricular septal defect
- Acquired	Senile calcification Infective endocarditis Rheumatic disease Radiation-induced valvulopathy Toxin-induced valvulopathy; anorectic drugs, 5-hydroxtryptamine (carcinoid)
Aortic root abnormalities-Congenital/Genetic	Annuloaortic ectasia Connective tissue disease: Loeys–Deitz, Ehlers–Danlos, Marfan syndrome, osteogenesis imperfecta Idiopathic aortic root dilation
- Acquired	Systemic hypertension Autoimmune disease: systemic lupus erythematosus, ankylosing spondylitis, Reiter's syndrome Aortitis: syphilitic, Tayayasu's arteritis Aortic dissection Trauma

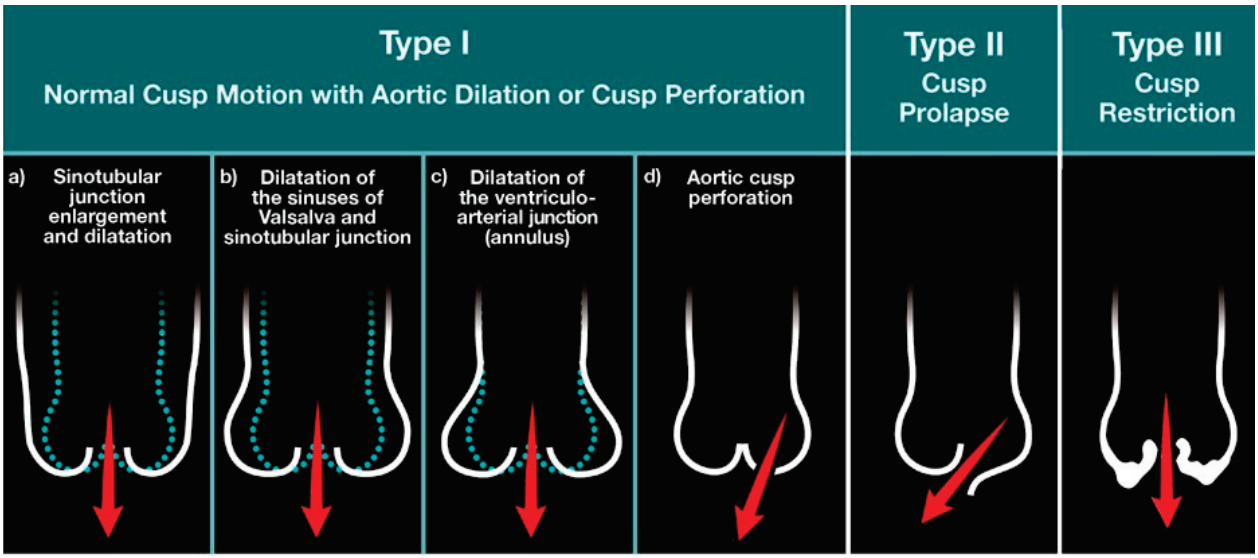

Figure 3. Carpentier Classification of Etiologies of Aortic Regurgitation. Aortic regurgitation can be classified by the etiology of aortic regurgitation as: leaflet malcoaptation/perforation (Type I), excessive leaflet motion (Type II), or restricted leaflet motion (Type III). Type I disease can be further subclassified into the location of the aortic root dilatation: sinotubular junction, sinuses of Valsalva, or ventriculoarterial junction. (After Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* [10]).

Diseases of the aortic root and ascending aorta include idiopathic aortic root dilatation, systemic hypertension, annuloaortic ectasia, autoimmune disease (systemic lupus erythematosus, ankylosing spondylitis, Reiter's syndrome), connective tissue disease (Loeys–

Deitz, Marfan syndrome, Ehlers–Danlos, osteogenesis imperfecta), aortitis (syphilitic, Takayasu's arteritis), aortic dissection, trauma (Table 1) [10,15]. The 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease provides recommendations on the timing of imaging, timing of intervention depending upon aortic size in specific disease states, and recommendations on indexing to the patients' BSA or height [16]. With an aortic dissection, AR and poor leaflet coaptation can result from: dilation of the root and annulus, propagation of a false lumen leading to leaflet prolapse/flail, or a dissection flap prolapsing across the valve [10].

Mixed etiologies of regurgitation and mixed aortic valve disease (MVAD) should be considered when interrogating the aortic valve. In a large retrospective series of patients referred for surgical aortic valve replacement or repair, Yang et al. found the most common form of mixed etiologies was prolapse with aortic root dilation in both patients with bicuspid and tricuspid aortic valves [11]. A nationwide epidemiology study in Sweden by Andell et al. found 17.9% of patients with AR had concomitant aortic stenosis (AS) and MVAD was the most frequent form of mixed valve disease [17,18]. Co-existing AS is important to note as studies have shown the prognosis of combined moderate AS and moderate AR is similar or worse than with either isolated AS or AR [17,19,20].

4. Natural History of Aortic Regurgitation

Differences are found in the natural history and presentation of patients with bicuspid versus tricuspid valves with AR. Patients with bicuspid valves have been found to present earlier and more frequently have mixed mechanisms of AR [11,21–23]. In a large contemporary cohort of 798 patients comparing bicuspid and tricuspid aortic valve patients with AR, Yang et al. found bicuspid patients presented two decades younger, underwent aortic valve surgery more frequently with fewer complications, and had a robust association between baseline symptoms and chamber remodeling [21]. In bicuspid patients, mortality risk increases in patients over 50–55 years of age. After adjusting for age, survival was found to be similar between bicuspid and tricuspid valve patients [21].

4.1. Acute Aortic Regurgitation

Acute AR can lead to a negative spiral of effects due to acute volume overload to a left ventricle (LV) unable to compensate acutely with chamber dilation. This contrasts with chronic AR where compensatory remodeling allows the patient to remain compensated for years or decades despite the progressing severity of regurgitation. Acute volume overload from AR leads to a rapid rise in left ventricular end-diastolic pressure (LVEDP) and if untreated can lead to hemodynamic compromise. The acute rise in LVEDP leads to a rapid decrease in the gradient across the mitral valve into the LV. Reverberation, reverse doming of the anterior mitral valve leaflet, and premature mitral valve closure can be seen. If LVEDP exceeds left atrial pressure, mitral regurgitation can occur in systole or diastole. Grading of the timing of the mitral valve closure can give an indication of the severity of acute AR and elevation of LVEDP [24]. Further upstream sequelae include congestion with elevation of left atrial pressure and pulmonary edema. Negative effects on the LV from AR are twofold. As LVEDP approaches aortic diastolic pressure, subendocardial hypoperfusion can occur due to a drop in LV myocardial perfusion pressure. In addition to the volume overload, there is an increase in afterload which leads to increased systolic wall stress. Distention of the LV and dilation of the mitral valve annulus can lead to secondary mitral regurgitation. As the LV is unable to acutely increase cardiac output, there is a compensatory increase in heart rate to maintain cardiac output. Acute regurgitation signs and symptoms can include shortness of breath, tachycardia, chest discomfort, peripheral signs of hypoperfusion, and pulmonary congestion. Physical signs in acute AR are less pronounced compared with chronic severe AR.

4.2. Chronic Aortic Regurgitation

With chronic AR, compensatory LV remodeling occurs in response to chronic pressure and volume overload. To maintain forward stroke volume there is an adaptive increase in LV end-diastolic volume and increase in LV compliance to maintain a normal LVEDP. The degree of LV dilation in chronic isolated AR reflects the duration and severity of disease. LV wall stress rises due to increased afterload from increased systolic blood pressure and increasing LV chamber volume [25]. A combination of concentric and eccentric hypertrophy ensues. A reduction in ejection fraction occurs when preload reserve is exceeded, and hypertrophic changes are unable to meet afterload excess [26–28]. In chronic severe AR, end-systolic wall stress can be as high as in aortic stenosis [29,30]. In patients with MVAD, LV remodeling due to AS includes concentric remodeling/hypertrophy with or without replacement fibrosis. These changes reduce LV compliance and the ability of the LV to tolerate increasing LV end-diastolic volume from AR.

Chronic AR is defined by Stages A-D, from at risk of developing AR (Stage A) to severe symptomatic AR (Stage D) [14]. The likelihood of progression to symptoms or LV dysfunction with chronic AR averages 4–5% per year and the average mortality rate is less than 0.2% per year [25,26].

5. Quantification of Disease Severity

In both acute and chronic AR, transthoracic echocardiography (TTE) is the primary imaging modality for diagnosis. The morphology of the leaflets and aortic root, mechanism and severity of regurgitation, and LV size, geometry and function should be delineated. Quantitative, semi-quantitative and qualitative techniques should be integrated when grading the severity (Table 2) [10]. Standardized protocols with use of 2D, 3D, pulsed, color and continuous wave Doppler should be used and supporting guidelines are available [10,14,31, 32]. Supportive findings of severe chronic AR include flail leaflet or wide coaptation gap, dilated left ventricle, pressure half-time < 200 msec, prominent holodiastolic flow reversal in the abdominal aorta, dense continuous wave signal, and large color flow convergence [10]. A multiparametric approach is best as there are inherent limitations in each technique and the diagnosis should not be made by a single parameter. Pitfalls in the assumption of LV adaptive changes can occur with chamber dilation due to another cause, an unknown starting cavity size to compare changes to, and failure to normalize to body size. In asymptomatic patients' accurate assessment of LV, chamber size and LV systolic function become critical as they serve as indicators for the timing of intervention. Stress echocardiography can be used to assess functional capacity, presence of coronary artery disease, and response of LV size and function to exercise [10].

Transesophageal echocardiography (TEE) allows for better visualization of valve morphology and can further define quantitative and qualitative parameters needed to confirm AR severity [33]. TEE is recommended in the evaluation for endocarditis with prosthetic valves, in the evaluation for a root abscess, or in the evaluation for aortic injury or dissection.

Specific guidelines are available for pre-procedural screening and post-intervention assessment in both surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) [33–35]. Similar echocardiographic parameters are used to grade prosthetic aortic regurgitation after TAVR with the use of additional tools including aortography, structural parameters of the valve, and invasive hemodynamic parameters [34]. Systematic use of intraoperative TEE is recommended at key points post procedure to guide decision making post aortic valve repair, aortic valve replacement, and aortic surgery [35].

Table 2. Grading Severity of Aortic Regurgitation: Quantitative, semi-quantitative and qualitative techniques should be integrated when grading the severity (after Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J. Am. Soc. Echocardiogr.* [10]).

AR SEVERITY CLASSES	MILD Grade (1 or 1+)	MILD-TO-MODERATE (Grade 2 or 2+)	MODERATE-TO-SEVERE (Grade 3 or 3+)	SEVERE (Grade 4 or 4+)
QUALITATIVE PARAMETERS				
Aortic valve morphology	Normal/Abnormal	Normal/Abnormal	Abnormal/Prolapse/Moderate coaptation defect	Abnormal/Flail/Large coaptation defect
Color flow AR jet width [$]	Small in central jets	Intermediate	Intermediate	Large in central jet, variable in eccentric jets
Color flow proximal convergence	None or very small	Dense	Intermediate	Large
CW signal of AR jet	Incomplete/Faint	Intermediate	Dense	Dense
Diastolic flow reversal in descending aorta [#]	Brief, early diastolic reversal	Intermediate	Holodiastolic flow reversal (end-diastolic velocity 10 to <20 cm/s)	Holodiastolic flow reversal (end-diastolic velocity ≥ 20 cm/s)
Diastolic flow reversal in abdominal aorta [#]	Absent	Absent	Present	Present
SEMI-QUANTITATIVE PARAMETERS				
VC width (mm)	< 3	3–6	3–6	>6
Jet width/LVOT diameter (%)	<25	25–45	46–64	≥65
Jet CSA/LVOT CSA (%)	<5	5–20	21–59	≥60
Pressure half-time (ms) [#, £]	>500	Intermediate, 500 to 200	Intermediate, 500 to 200	<200
QUANTITATIVE PARAMETERS				
EROA (mm^2)	<10	10–19	20–29	≥30
R Vol (ml)	<30	30–44	45–59	≥60
RF (%)	<30	30–39	40–49	≥50

AR: aortic regurgitation; CSA: cross-sectional area; CMR: Cardiac magnetic resonance; CW: continuous-wave; LA: left atrium; EROA: effective regurgitant orifice area; LV: left ventricle; RF: regurgitant fraction; R Vol: regurgitant volume; VC: vena contracta. [$] At a Nyquist limit of 50–60 cm/s. [£] Pressure half-time is shortened with increasing LV diastolic pressure, vasodilator therapy, and in patients with a dilated compliant aorta or lengthened in chronic AR. [#] These parameters are influenced by LV and aortic compliance. Hence, low transvalvular end-diastolic aorta to LV pressure gradient due to concomitant moderate/severe LV diastolic dysfunction may lead to false positive results. The high dependency of aortic flow reversal on aortic compliance considerably limits the utility of this parameter in the elderly population. These parameters are also influenced by chronotropy. Unless for other reasons, the LV size is usually normal in patients with mild AR. In acute severe AR, the LV size is often normal. Accepted cut-off values for non-significant LV enlargement: LV end-diastolic diameter < 56 mm, LV end-diastolic volume < 82 mL/m^2, LV end-systolic diameter < 40 mm, LV end-systolic volume < 30 mL/m^2.

5.1. Multimodality Imaging

Computed tomography (CT), cardiac MRI (CMR), and cardiac catheterization can provide supplemental information in cases where TTE or TEE images are suboptimal or there is a discrepancy between clinical and echocardiographic findings [14,36]. CMR is the reference standard for evaluating cardiac volumes, mass, and systolic function. CMR should be considered in patients with poor visualization of endocardial borders on echocardiography. CMR can provide supplemental information regarding the morphology of the aortic valve, aortic root and thoracic aorta, quantification of AR severity, and tissue characterization in the evaluation for underlying cardiomyopathy. CMR may be useful in special populations (e.g., competitive athletes) to discern pathological cardiac remodeling in the setting of AR from an athletic heart phenotype [37]. Cardiac CT similarly can provide supplemental information on aortic valve morphology and confirm thoracic aorta dimensions and the evaluation for aortic dissection. CT imaging is the primary imaging choice in the evaluation for aortic dissection.

5.2. Novel Imaging Parameters

Non-invasive methods for imaging the myocardium may detect early mechanical dysfunction and fibrosis, which may inform the timing of intervention [38]. Speckle-tracking echocardiography for the assessment of ventricular longitudinal strain may be more sensi-

tive in detecting structural changes in the myocardium compared to other conventional parameters such as LVEF and has been useful in the risk stratification of patients with AR [39,40]. LV global longitudinal strain and LV myocardial work indices can provide additional insight into LV function in patients with preserved LV ejection fraction [41–45]. In patients with moderate or severe AR, the presence of scars detected by late gadolinium enhancement on CMR is associated with a 2.5-fold increase in death, and aortic valve replacement was independently associated with a lower risk of mortality [46]. Ventricular arrhythmia in aortic valve disease is commonly found when ambulatory monitoring is performed and can be a marker of the impact of aortic regurgitation on the left ventricular myocardium [47,48].

6. Medical and Surgical Management

6.1. Medical Management

Acute AR requires rapid diagnosis and treatment as medical management is limited. Medical therapy includes medications to reduce LV afterload. In patients with acute AR due to endocarditis or aortic dissection who are surgical candidates, surgery should not be delayed if there is evidence of hypotension, pulmonary edema, or low cardiac output [14,49–52]. Prior series have shown that patients undergoing emergent aortic valve surgery for acute AR had low operative mortality and good long-term results [53–56].

In chronic AR, medical management includes treatment of systolic blood pressures >140 mmHg [14]. In severe AR with LV dysfunction with or without symptoms, treatment with Ace inhibitors, ARBs and/or sacubitril/valsartan is recommended in prohibitive surgical risk patients [14]. The interval timing of repeat echocardiograms to monitor for progression is every 3–5 years with mild AR, every 1–2 years with moderate AR, and every 6–12 months with severe AR. In chronic severe AR, surgery is indicated in symptomatic patients regardless of LV systolic function. In asymptomatic severe regurgitation, surgery is indicated with LV systolic dysfunction (LVEF $\leq$ 55%) without another identifiable cause. SAVR is recommended in moderate or severe AR in patients undergoing cardiac surgery for another indication. SAVR is also recommended for asymptomatic severe patients with normal LV systolic function (LVEF > 55%) with severe LV enlargement (LVESD > 50 mm, LVESD > 25 mm/m^2), or in low surgical risk patients with progressive decline in LVEF (to <55–60%) or progressive increase in LV dilation into the severe range (LV end-diastolic dimension > 65 mm) in three studies [14].

6.2. Surgical Management

Historically the definitive therapy has been surgery with aortic valve replacement or repair. Preoperative TEE with morphologic and functional classification of leaflet motion (Class I-III) with surgical anatomic inspection has been shown to be a predictor of success of "valve-conserving" surgical procedures [13]. The goal of surgical repair is to restore adequate leaflet coaptation surface and described repair techniques include cusp plication, triangular resection, Trusler stitch, free edge resuspension, patch repair, and subcommissural annuloplasty (Figure 4) [11]. Surgical replacement is principally performed with bioprosthetic and mechanical valves. Use of pulmonary autografts is considered in young patients with anatomy that is suboptimal for repair. Root repair techniques include STJ remodeling, root remodeling, and valve implantation within a vascular graft [57]. Patients with an aneurysmal aortic root or ascending aorta in combination with aortic regurgitation undergo the Bentall or modified Bentall procedure with a composite graft.

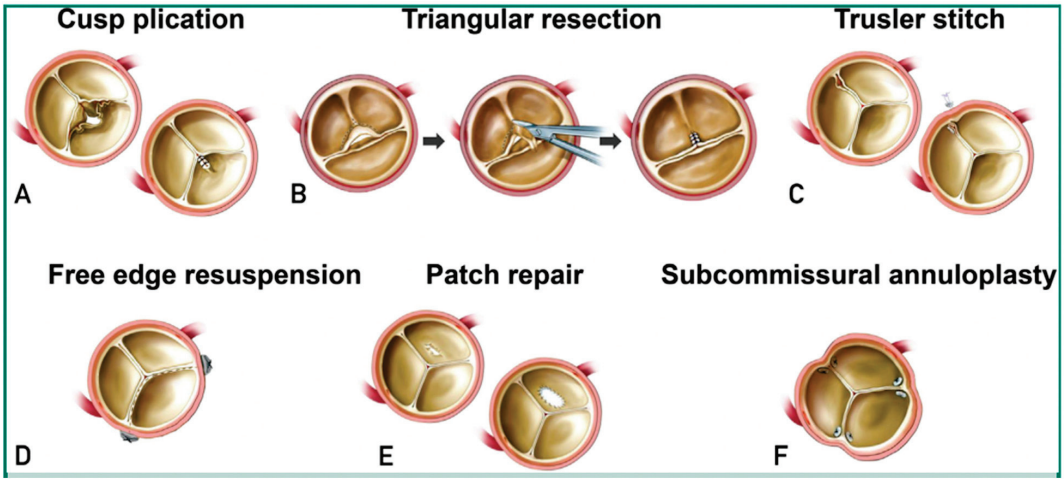

Figure 4. Aortic valve repair techniques. A prolapsed cusp is repaired with central plication (**A**), triangular resection (**B**), Trusler stitch (**C**), or free-edge resuspension (**D**). A perforated cusp is repaired with patch closure using pericardium (**E**). Annular dilation of aortic valve causing central regurgitation is repaired with plication stitches placed in the aortic wall at each commissure (**F**). (Reproduced with permission from Yang LT, Michelena HI, Maleszewski JJ, et al. Contemporary Etiologies, Mechanisms, and Surgical Approaches in Pure Native Aortic Regurgitation. *Mayo Clin. Proc.* [11].

Intervening on valvular heart disease before symptom development may prevent irreversible LV remodeling and improve clinical outcomes [43,58]. Asymptomatic AR is associated with increased mortality and morbidity [59] and current guidelines give a Class I level of recommendation for intervention in asymptomatic patients if the LV is markedly dilated (LV end-systolic [ES] dimension >50 mm or >25 mm/m^2). However, growing evidence shows that poor outcomes are associated with a smaller LVES (and not end-diastolic) dimension of >20 mm/m^2 [60–62]. Lower-indexed LVES dimensions could reduce the overall survival penalty seen for women related to late referral for intervention [63] particularly since women appear to exhibit a blunted LV dilatation response to increasing severity of AR [64].

7. Transcatheter Aortic Valve Replacement in Aortic Regurgitation

Historically there has been undertreatment with surgery of patients with significant AR. The Euro Heart Survey on Valvular Heart Disease showed a precipitous drop in the percentage of patients treated with a reduced LVEF and significant AR (2.7% of patients with LVEF <30%, 21.8% of patients with LVEF 30–50%) [65]. By current guidelines, TAVR can be considered only in selected patients at high or prohibitive surgical risk. If a patient is a surgical candidate with isolated severe AR, TAVR is a Class III recommendation [14]. Off-label TAVR with transcatheter heart valves designed for AS is frequently complicated by valve migration and significant paravalvular regurgitation due to the absence of valvular calcification needed for anchoring and aortic annular dilation [66]. To meet the clinical need, there are ongoing efforts to develop dedicated transcatheter heart valves that address the specific requirements for the treatment of pure AR. The JenaValve Trilogy Heart Valve System (JenaValve Technology, Inc., Irvine, CA, USA) is the first transfemoral device that has received CE mark approval for AR and AS treatment in Europe. Initial CE approval was based on the use of a transapical JenaValve device which showed a high procedural success rate of 89.6%, perioperative stroke rate of 3%, need for permanent pacemaker of 9.1%, and up to trace paravalvular leak in 86.4% of patients [67,68]. The JenaValve Trilogy design includes a self-expanding nitinol frame, porcine pericardial leaflets, and locators which attach to the native leaflets to aid with anchoring and sealing. The prosthesis clips onto the native leaflets which provides physiologic orientation, and anchoring is independent of native valve calcification. In the U.S., enrollment of 180 patients in the ALIGN-AR trial (NCT04415047) was completed in August 2022 using the TF JenaValve system and the

one-year outcomes of this study are currently awaited. The J-Valve (Suzhou JieCheng Medical Technology Co., Ltd., Suzhou, China) is a self-expanding porcine tissue valve on a nitinol frame with three U-shaped anatomically oriented claspers developed to treat either AS or pure AR. The J-Valve was initially delivered transapically and the J-Valve TF Delivery System (JC Medical, Inc., Eatontown, NJ, USA) was developed to allow for transfemoral deployment. Two-year outcomes of the transapical Transcatheter Aortic Valve Implantation with J-Valve [57,69] showed a high success rate, and a high rate of improvement in heart failure symptoms. In patients treated with pure AR, at two years all-cause mortality was 11.6% and not significantly different from patients treated for AS. Additional trials with use of the J-valve are underway (NCT03876964, NCT05580952).

8. Future Directions

The AHA/ACC and the ESC/EACTS valvular guidelines use parameters for intervention (symptoms, LVEF, LV dimensions) which are supported by outcomes data [14,70,71]. For the foreseeable future TTE will likely remain the primary tool for following and determining the timing of intervention. Further work is needed to determine which additional tools may provide prognostic value and may be integrated into the decision-making process in the future. In a recent multicenter prospective study evaluating CMR quantitative thresholds and outcomes in asymptomatic patients with moderate or severe AR with preserved LVEF, Malahfij et al. found that indexed LVES volume and indexed LV end-diastolic volume outperformed indexed LV end-systolic diameter [72]. Advanced imaging techniques like strain and myocardial work indices may become more commonly used in clinical practice. In addition to standard stress testing, cardiopulmonary exercise testing and cardiac markers may help in the management of asymptomatic patients.

9. Conclusions

As outlined, the diagnosis, grading of severity, and management of AR requires a multimodality and multispecialty approach. This may be best guided by a Multidisciplinary Heart Valve Team [14,71] and consideration should be given to referral to a Primary (Level II) Valve Center or Comprehensive (Level 1) Valve Center [14]. A full armamentarium including an array of surgical and transcatheter treatment options will be needed to address the increasing clinical needs of an aging global population with AR. The future is bright in this respect with active research in novel transcatheter options to treat patients with an elevated surgical risk.

Supplementary Materials: The following supporting information can be downloaded at: https://drive.google.com/file/d/1fPm1uBO0LTRbhBWk9r12yJQHTboQj33N/view?usp=drive_web (accessed on 20 August 2023), Video S1: Transesophageal echocardiogram short axis view with biplane imaging through the left coronary cusp which is flail (A). Long axis imaging of the aortic valve with color showing eccentric, anteriorly directed regurgitation (B); Video S2: Transesophageal echocardiogram short axis view of a bicuspid aortic valve (Sievers type 0) 2D imaging (A) and with color (B), and biplane imaging with color showing eccentric aortic regurgitation (C); Video S3: Transesophageal echocardiogram short axis view of a quadricuspid valve without (A) and with color (B); Video S4: Transesophageal echocardiogram long axis view of tricuspid aortic valve with aortic dissection (Stanford Type A) (A). Loss of aortic root integrity with leaflet prolapse with aortic regurgitation seen on biplane imaging with color (B); Video S5: Transesophageal echocardiogram biplane imaging of an aortic valve with rheumatic involvement (leaflet doming, commissural fusion and nodular thickening) (A). Short axis aortic valve imaging with biplane showing moderate eccentric regurgitation; Video S6: Transesophageal echocardiogram imaging of an aortic valve with tubular dilation of the ascending aorta and effacement of the sinotubular junction. Biplane imaging of the aortic valve (A) and with color (B). 3D imaging showing a central coaptation gap (C).

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Abbreviations

AR	Aortic regurgitation
AS	Aortic stenosis
CMR	Cardiac MRI
CT	Computed tomography
ES	End-systolic
LV	Left ventricle/ventricular
LVEDP	Left ventricular end-diastolic pressure
MVAD	Mixed aortic valve disease
SAVR	Surgical aortic valve replacement
STJ	Sinotubular junction
TAVR	Transcatheter aortic valve replacement
TTE	Transthoracic echocardiogram
TEE	Transesophageal echocardiogram

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Incidence and Risk Factors for Long-Term Persistence of Diastolic Dysfunction after Aortic Valve Replacement for Aortic Stenosis Compared with Aortic Regurgitation

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Abstract: (1) Background: Severe left ventricular (LV) diastolic dysfunction with a restrictive diastolic pattern (LVDFP) is generally associated with a worse prognosis. Its evolution and reversibility in the short- and medium-term after aortic valve replacement (AVR) has been little-studied. We aimed to evaluate the evolution of LV remodeling and LV systolic and diastolic function after AVR in aortic stenosis (AS) patients compared to aortic regurgitation (AR). Moreover, we tried to identify the main predictive parameters for postoperative evolution (cardiovascular hospitalization or death and quality of life) and the independent predictors for the persistence of restrictive LVDFP after AVR. (2) Methods: A five-year prospective study on 397 patients undergoing AVR for AS (226 pts) or AR (171 pts), evaluated clinically and by echocardiography preoperatively and until 5 years postoperatively. (3) Results: 1. In patients with AS, early post AVR, LV dimensions decreased and diastolic filling and LV ejection fraction (LVEF) improved more rapidly compared to patients with AR. At 1 year postoperatively, persistent restrictive LVDFP was found especially in the AR group compared to the AS group (36.84% vs. 14.16%). 2. Cardiovascular event-free survival at the 5-year follow-up was lower in the AR group (64.91% vs. 87.17% in the AS group). The main independent predictors of short- and medium-term prognosis after AVR were: restrictive LVDFP, severe LV systolic dysfunction, severe pulmonary hypertension (PHT), advanced age, severe AR, and comorbidities. 3. The persistence of restrictive LVDFP after AVR was independently predicted by: preoperative AR, the E/Ea ratio > 12, the LA dimension index > 30 mm/m^2, an LV endsystolic diameter (LVESD) > 55 mm, severe PHT, and associated second-degree MR ($p < 0.05$). (4) Conclusions: AS patients had an immediate postoperative evolution in terms of LV remodeling, and LV systolic and diastolic function were more favorable compared to those with AR. The restrictive LVDFP was reversible, especially after the AVR for AS. The main prognostic predictors were the presence of restrictive LVDFP, advanced age, preoperative AR, severe LV systolic dysfunction, and severe PHT.

Keywords: restrictive diastolic filling pattern; aortic valve replacement; aortic stenosis; aortic regurgitation; systolic dysfunction; postoperative diastolic dysfunction

1. Introduction

The presence of a severely impaired diastolic function with a restrictive left ventricular (LV) diastolic filling pattern (LVDFP) determines a more unfavorable prognosis in any cardiac disease [1–3]. Although there are many studies on diastolic dysfunction, there is little information on diastolic dysfunction in the postoperative cardiac surgical patient undergoing valve replacement [4–6]. There are only a few studies that have evaluated the influence of the restrictive LVDFP on the postoperative course, but these are mostly heterogeneous, with relatively small populations and variable patient selection, being difficult to compare between them to draw a unified conclusion [1–3,7–9].

Diastolic dysfunction has been demonstrated to precede the alteration in systolic function in patients with LV hypertrophy due to aortic valve disease.

After successful aortic valve replacement (AVR) in aortic stenosis (AS), the early postoperative evolution is marked by an immediate hemodynamic improvement by reducing the pressure overload, with a significant regression of LV hypertrophy and the LV mass index/LV end-diastolic volume ratio [10]. This evolution is mainly due to the regression of the muscle tissue, while the total amount of the nonmuscular tissue (fibrous tissue) of the LV remains unchanged and is associated with the deterioration of LV diastolic function. Thus, depending on the amount of fibrous tissue, recovery of LV systolic and diastolic function in patients with AS is progressive and may continue for decades after AVR. That is why the degree of extension of irreversible interstitial fibrosis and the LV architecture are very important in postoperative remodeling, but it is very difficult quantify before surgery [11]. Therefore, it is very important to find clinical and echocardiographic parameters that can be taken into account for preoperative risk assessment and in order to avoid a too-late indication for AVR, with a negative effect on the prognosis.

On the other hand, considering patients with severe chronic aortic insufficiency (AR) undergoing AVR, the postoperative evolution is different. In the first few months after surgery there is a marked decrease in the LV dimensions, accompanied by a significant increase in the LV systolic performance [3–5]. Nevertheless, in some patients with preoperative LV dysfunction, despite the correction of valvular insufficiency, valve replacement leads to a smaller reduction in LV diastolic volume and a minor improvement in LV systolic function. Preoperative identification of these patients using imaging tools remains a challenge.

The patients with severely altered diastolic performance before AVR (either for AS or AR) have a more tedious recovery. The preoperative identification of patients with evidence for irreversible myocardial dysfunction with conventional echocardiographic examination remains difficult. Routine preoperative measurements of ejection fraction (EF) and LV dimensions as an index of the LV function cannot accurately predict how postoperative LV performance will evolve. Thus, they are not sufficient enough in making clinical decisions and for recommending surgery in patients with aortic valve disease [12–15].

On the other hand, serial long-term studies on the effect of AVR on diastolic function and the relation between the reversal of LV dilatation and the increase in LV systolic and diastolic performance has not been reported. Moreover, there are no studies which compared patients with AS to patients with AR undergoing AVR regarding the influence and evolution of the diastolic filling pattern. To address these issues, we studied a series of patients undergoing AVR for chronic AR and AS with preoperative and serial long-term postoperative echocardiographic and clinical evaluations.

Objectives

The first objective of this study was to evaluate the evolution of left ventricular (LV) remodeling and LV systolic and diastolic function after AVR, comparing patients with preoperative AS to patients with preoperative AR. In addition, we tried to define the parameters which can be taken into consideration as independent predictors for immediate- and medium-term evolution (in terms of cardiovascular hospitalization or death and quality of life) in AS compared to AR patients, and their adjusted value for identifying a high-risk

group. Finally, we tried to establish the independent predictors for the persistence of the restrictive LVDFP after isolated AVR in patients with AS or AR.

2. Materials and Methods

2.1. Study Population

A total of 410 patients met the criteria for inclusion (surgical aortic valve disease) in the study, but 13 were excluded due to exclusion criteria (9 patients with associated significant coronary lesion, 1 patient with postoperative prosthesis mismatch, and 3 patients who required a postoperative pacemaker implantation). The study was prospective and finally included 397 patients undergoing AVR for AS or AR who were followed-up clinically and by echocardiography with a median duration of 6.1 years (between 1st of January 2015 and 1st of January 2022). Only 5 patients were lost at the mid-term follow-up visits.

All patients signed the written informed consent and were required to attend the follow-ups. The protocol of the study was approved by the designated ethics committee.

Patients were assessed by clinical examination and by echocardiography before surgery and after surgery at 10 days, 1, 3, and 6 months, and yearly thereafter until 5 years.

Exclusion Criteria

- Previous or associated mitral or tricuspid valve replacement or repair;
- Aortic dissection;
- Acute endocarditis;
- Congenital disease unrelated to AR or AS;
- Coronary significant lesions (more than 50% stenosis);
- Chronic atrial fibrillation;
- Left or right bundle-branch block;
- Postoperative prosthesis mismatch;
- Pacemaker implantation.

We did not exclude patients undergoing concomitant procedures associated with AVR, such as ascending aortic surgery.

According to the hospital's preoperative evaluation protocol for AVR, coronarography was performed in all patients over 35 years of age, as well as in patients under 35 years with angina pectoris. We excluded patients with associated coronary artery disease (>50% reduction in luminal diameter of any coronary artery).

2.2. Ultrasound Methods

For echocardiographic examinations, we used a Philips Affinity 30 or a portable General Electric VIVID machine with a 3.5 MHz probe. For measurements, we followed the recommendations of the European and American Society of Echocardiography [16,17].

The main echographic parameters assessed before surgery were: LV end-diastolic and end-systolic volume and diameter, left atrium (LA) diameter and indexed volume, LV systolic and diastolic function (including tissue doppler imaging—TDI—evaluation), and hemodynamic parameters for AS and AR severity evaluation. Dimensions of the heart diameters and wall thickness were measured by 2-dimensional echocardiography with M-mode guiding.

For the diagnosis of surgical AS, we used the hemodynamic parameters primarily recommended for evaluation: AS jet velocity, mean transaortic gradient, and the valve area by continuity equation. The degree of AR (grade 3 or 4) was determined by composite analysis of either continuous Doppler or color flow Doppler.

At postoperative visits, we measured also the dimensions of the heart chambers, LV systolic and diastolic performance, and the hemodynamic parameters of the aortic prosthesis [18]. Echocardiographic measurements and clinical evaluations were collected and electronically transferred in a dedicated application.

LV systolic performance was appreciated by the calculation of the LVEF using the volumetric Simpson's method. LV diastolic filling was evaluated using a comprehensive echocardiographic study for the assessment of diastolic function integrating all available parameters from two-dimensional, Doppler, and Tissue Doppler examination [18,19]. We used the traditionally echocardiographic evaluation of diastolic function by measuring the transmitral-flow parameters and assessing the early (E) and late (A) diastolic filling velocities, the E/A ratio, and the E-wave deceleration time (EDT).

For TDI, using the sample volume placed at the lateral border of the mitral annulus in the apical four-chamber view, we measured: the peak annular systolic velocity (Sa), early diastolic velocity (Ea), and late-diastolic (Aa) velocity.

The restrictive LVDFP was considered to be present if either of the following echographic findings were found: E/A ratio > 2 or EDT < 150 msec or IVRT < 60 msec and Ea/Aa < 1 with elevated filling pressures (E/Ea ratio > 12) [20].

2.3. Follow-Up Visits

All patients were assessed postoperatively by clinical examination, echocardiography, and blood tests. Laboratory parameters evaluated at each visit included: blood tests (platelet count, hemoglobin, hematocrit, aminotransferases, lactic dehydrogenase). When we had the suspicion of heart failure with preserved systolic function, brain natriuretic peptide (BNP) dosing was done. Diastolic heart failure was considered unlikely if the BNP was less than 35 pg/mL and possible for values higher than 100 pg/mL.

In order to evaluate the global quality of life, a self-reported questionnaire was used for both the mental component (MCS) and the physical one (PCS). The scores ranged from 0 (lower) to 10 (higher quality of life). Patients evaluated their change in quality of life at the 30-day follow-up by answering the question: "How would you rate your quality of life now?". The answers they had to choose from were: "Worse than before your surgical procedure", "The same as before your surgical procedure", and "Better than before your surgical procedure".

Depending on the type of the aortic lesion, patients were divided in two groups:

- Group A—226 pts undergoing AVR for AS;
- Group B—171 pts undergoing AVR for AR.

AVR was performed with a bileaflet mechanical valve in 70.35% of patients from the AS group and in 71.93% of patients from the AR group. For the rest of the patients, valve replacement was done with a bioprosthetic valve.

2.4. Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences 23 (SPSS 23) software.

For comparison of preoperative and postoperative echocardiographic categorical variables, we used the Pearson chi-square test, likelihood ratios, and Fisher's exact test. Qualitative data were recorded as percentages. Numerical continuous variables were expressed as mean ± standard deviations. Normal distribution of all continuous variables was tested with an Independent Samples T-Test and for three groups with ANOVA. LVEF was used as a continuous and discrete variable (low-LVEF versus normal-LVEF). Baseline continuous variables were compared among the two LVEF groups (low-LVEF versus normal-LVEF) by means of paired t-tests and ANOVA. Moreover, a one-way ANOVA for repeated measures (with a Greenhouse–Geisser correction) was used for comparing preoperative, early postoperative, and late postoperative data from patients with AR and patients with AS. If the analysis showed a significant difference, the Scheffé procedure was applied.

We used univariate logistic regression analysis in order to compare the two groups. Moreover, the association between preoperative data and the magnitude of postoperative change in the LV dimensions and function was tested by linear regression analysis.

The parameters that were found statistically significant in the univariate regression analysis were entered in the multivariate regression models. In order to identify variables associated to predictive factors of mortality, we used multivariate logistic models, taking into account baseline echocardiographic characteristics. The Cox and Snell/Nagelkerke value was calculated in order to evaluate goodness of fit of the model. A $p < 0.05$ was considered statistically significant.

Overall survival and freedom-from-events (death, NYHA class, and quality of life) after the AVR were estimated by use of the Kaplan–Meier method. Multivariate Cox proportional hazards models were fit to identify variables associated with long-term outcome. Relative risks/odds ratios, hazard ratios, and 95% CIs were reported.

The main null hypotheses tested were:

1. Is the restrictive flow pattern reversible mostly after AVR for AS than AR, both in the early postoperative period and on medium-term?
2. Are early and medium-term prognosis and LV remodeling after AVR in preoperative restrictive LVDFP patients better in those with AS compared to those with AR?
3. Are severe AR, restrictive LVDFP, and severe pulmonary hypertension (PHT) independent predictors for unfavorable postoperative evolution in patients undergoing AVR?

The testing of the statistical hypotheses was done with the help of univariate and multivariate logistic regression analysis and the calculation of the correlation coefficient. Moreover, to evaluate the differences between the three moments analyzed (preoperative, early postoperative, and late-postoperative), we used the nonparametric Friedman test.

3. Results

The demographic characteristics of the two studied groups showed a higher average age and a higher percentage of men in the AS group. The percent of the patients with comorbidities and the mean LVEF was similar in the two studied groups. In the AR group, there was a significantly higher percentage of patients with NYHA class IV and with a restrictive LVDFP (Table 1).

Table 1. Baseline patients' characteristics—AS and AR patients.

	Group A—226 Pts AS	**Group B—171 Pts AR**	***p*-Value (Test)**
Mean (SD) age (years)	72 (12)	68 (11)	0.386014
Women	81 (35.84%)	68 (39.77%)	0.581801
Mean (SD) heart rate	68 (17)	81 (17)	0.645900
Diabetes mellitus, no (%)	11 (4.87%)	9 (5.26%)	0.355588
COPD, no (%)	12 (5.31%)	10 (5.85%)	0.591229
Mean (SD) LVEF (%)	52 (13)	51 (14)	0.0376032
LVEF < 50%, no (%)	89 (39.38%)	69 (40.35%)	0.432215
NYHA class I/II, no (%)	148 (65.49%)	105 (61.40%)	
NYHA class III, no (%)	64 (28.32%)	40 (23.39%)	0.001457
NYHA class IV, no (%)	14 (6.19%)	26 (36.61%)	
Restrictive LVDFP	78 (34.51%),	77 (45.03%)	0.0123004

SD—standard deviation; COPD—chronic obstructive pulmonary disease (≥Gold 2); 1 LVEF—left ventricle ejection fraction; LV—left ventricle; LVDFP—LV diastolic filling pattern; NYHA—New York Heart Association.

Patients with preoperative AR had a more severe evolution after surgery, with a higher mortality rate and more cardiovascular events than those with AS (Figure 1). At 5 years postoperatively, cardiovascular event-free survival, including hospital visits caused by heart failure symptoms and sudden cardiac death, was significantly higher, with almost 22 percent in the group of patients with preoperative AS (87.17%) compared with the AR group (64.91%), with a significant *p*-value (0.0001).

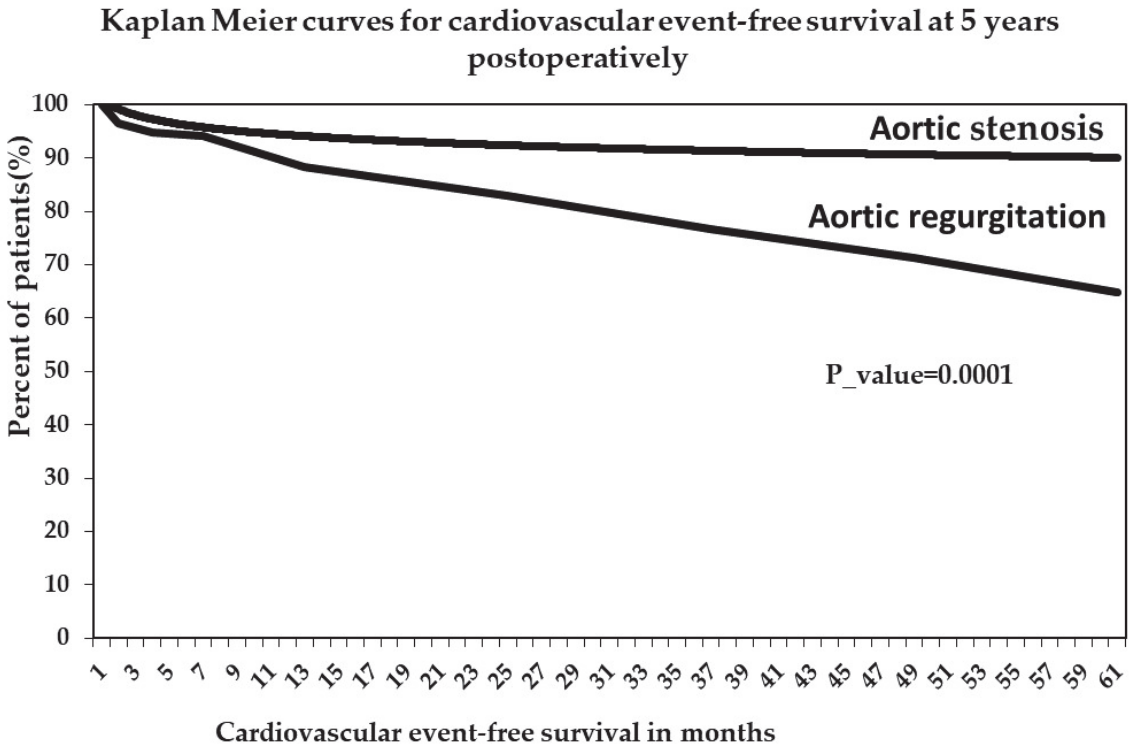

Figure 1. Kaplan–Meier curves for cardiovascular event-free survival at 5 years postoperatively.

The main independent predictors for death and hospitalization for HF at 5 years postoperatively in patients with aortic valve disease undergoing AVR revealed by univariate logistic regression analysis and the associated RR (95% CI) were: restrictive LVDFP (RR = 6.8 (5.9, 7.6), p = 0.001), preoperative AR (RR = 3.12 (2.57, 3.74), p = 0.0001), severe preoperative LV systolic dysfunction with an LVEF less than 35% (RR = 2.7, p =0.035), severe preoperative PHT with mean PAP > 50 mmHg (RR = 2. 36 (2.37, 3.29), p = 0.021), patients' age of more than 75 years (RR = 1.86 (1.74, 2.07), p = 0.032), comorbidities (RR = 1.95 (1.67, 2.79), p = 0.071), moderate LV systolic dysfunction with LVEF between 35 and 50% (RR = 2.03 (1.51, 2.73), p = 0.053), and dilated LV with preoperative LVES diameter > 55 mm (RR = 2.27 (1.65, 2.95), p = 0.059).

Moreover, univariate regression analysis showed that the preoperative AR in patients with restrictive LVDFP turned out to be an independent predictor for increasing the mortality rate (p = 0.0001), with preoperative AR being more harmful for postoperative evolution in AVR patients.

At 1 year postoperatively, the main independent prognostic predictors for the patients with aortic valve disease undergoing AVR revealed by multivariate logistic regression analysis were (Figure 2): restrictive LVDFP (RR = 9.8, p = 0.001), severe LV systolic dysfunction with a LVEF less than 35% (RR = 8.7, p = 0.002), severe PHT (PHT) with mean PAP > 50 mmHg (RR = 8.2, p = 0.021), patients' age of more than 75 years (RR = 8.1, p = 0.013), the presence of preoperative AR (RR = 6.9, p = 0.031), comorbidities (RR = 1.9, p = 0.071), moderate LV systolic dysfunction with LVEF between 35 and 50% (RR = 1.7, p = 0.074), and dilated LV with LVES diameter > 55 mm (RR = 1.8, p = 0.067). For regression analysis, in order to identify the prognostic predictors, we used baseline echocardiographic characteristics.

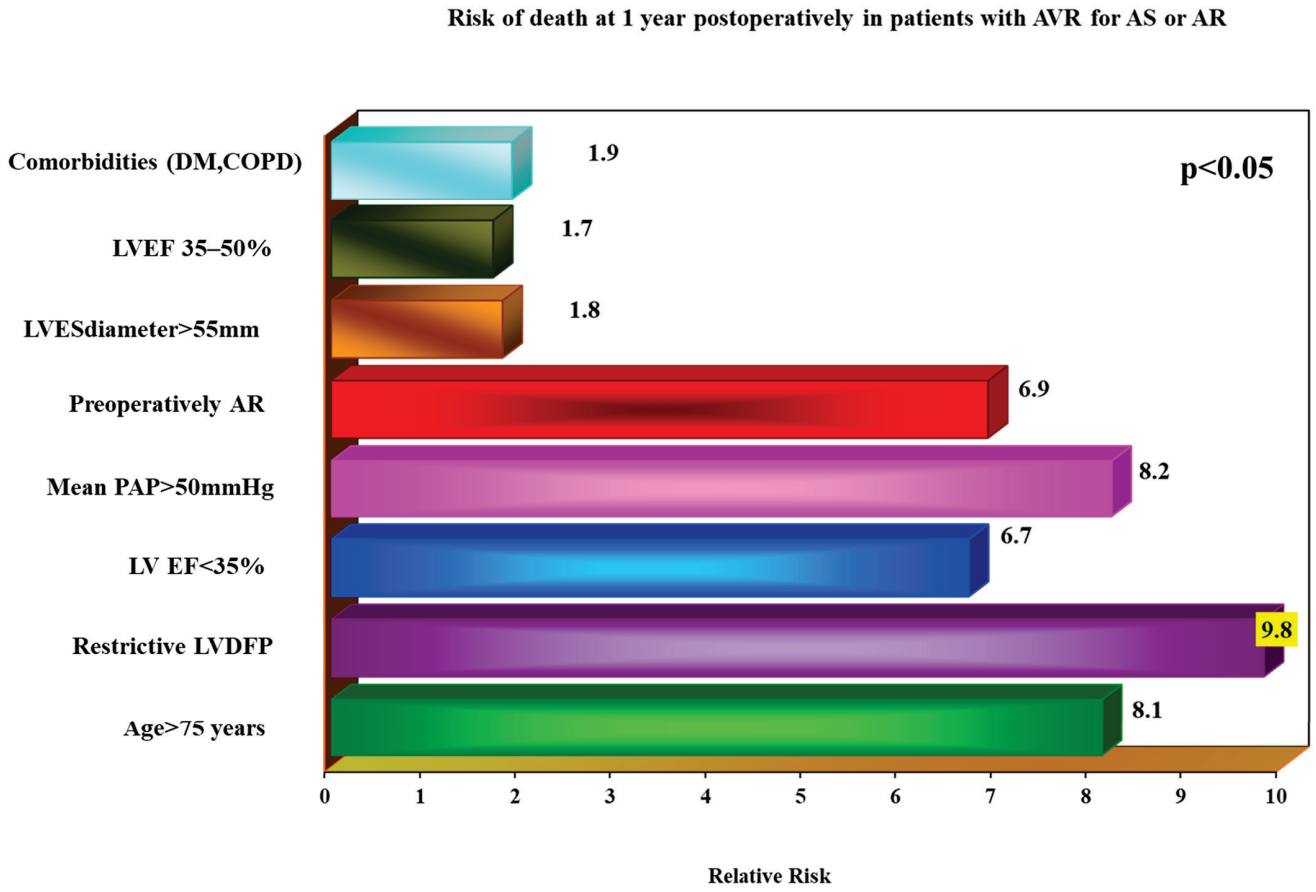

Figure 2. Risk of death at 1 year postoperatively in patients with AVR for AS or AR.

The most important preoperative predictor of early postoperative hospital course and postoperative morbidity was the presence of a restrictive LVDFP.

In the long term, the logistic regression analysis of the parameters known for increasing the mortality rates after AVR showed that the risk for cardiovascular events was higher in patients with preoperative AR. The main predictors for cardiovascular events at 5 years postoperatively in both the AS and AR groups were LV systolic performance, age, and the presence of preoperative restrictive LVDFP.

The predictive value for cardiovascular events at 5 years postoperatively of the LV systolic dysfunction, advanced age, or of the presence of a restrictive LVDFP was higher in the AR group of patients. In these patients, the risk for cardiovascular events at 5 years was significantly increased in patients with LVEF < 35% (RR = 8.8, $p < 0.05$), in patients older than 75 years (RR = 7.1, $p < 0.05$), and in patients with restrictive LVDFP (RR = 8.1, $p < 0.05$).

In patients with preoperative AS, the relative risk values for cardiovascular events at 5 years postoperatively associated to LV systolic dysfunction, elderly age, and the presence of restrictive LVDFP were smaller and more homogenous than in those with AR. The main independent predictors for increasing the risk for cardiovascular events were age > 75 years (RR = 6.5, $p < 0.05$), restrictive LVDFP (RR = 3.5, $p = 0.062$), and LVEF < 35% (RR = 3.2, $p = 0.078$) (Figure 3).

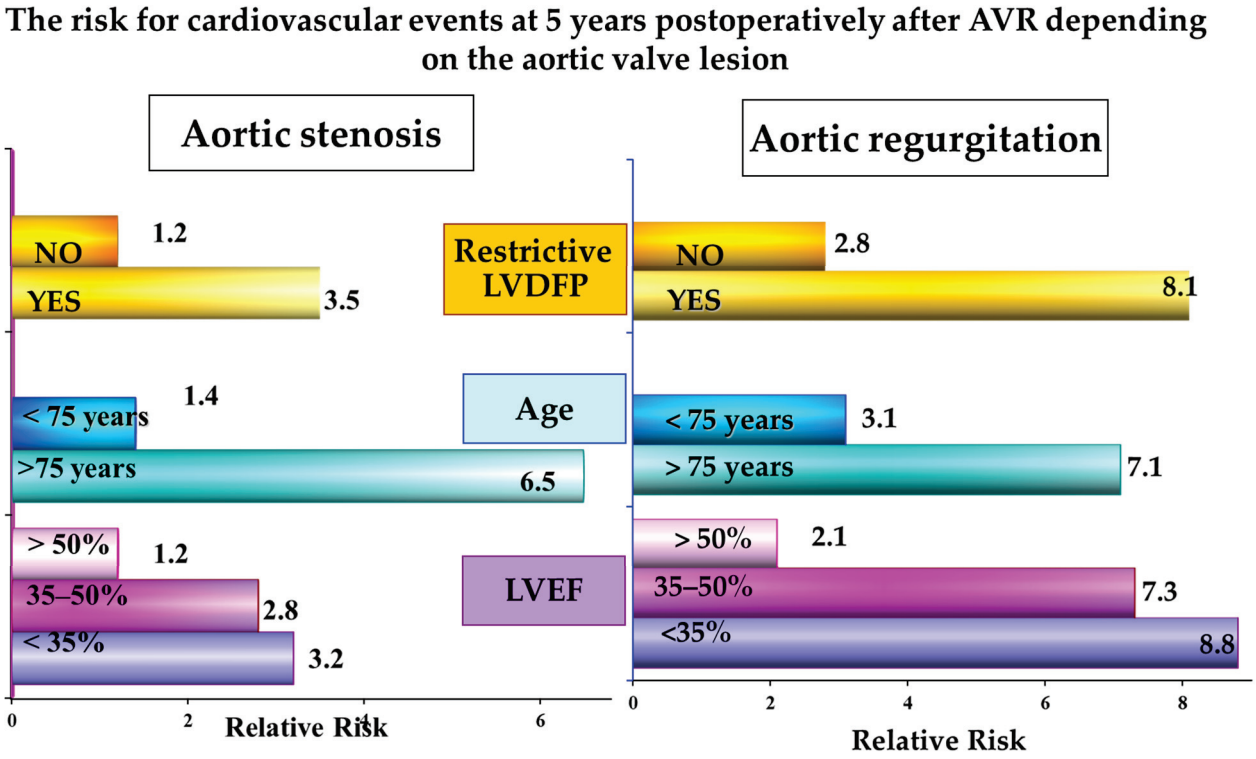

Figure 3. Risk for cardiovascular events at 5 years postoperatively after AVR depending on the type of aortic valve lesion.

From clinical point of view, in the medium and long term, the percentage of patients with a more favorable evolution regarding the NYHA class and quality of life was higher in patients with preoperative AS, regardless of the LV systolic performance before surgery.

The overall percentage of patients whose self-reported quality-of-life scores (SR QOL score) changed between worse/the same/better (including stratification by self-reported mental, physical, and global) was calculated. The percentage of the patients with a preoperative self-reported quality-of-life score < 5 was similar in the two study groups (55.75% in the AS group vs. 56.72% in the AR group). However, the SR QoL evaluated at the 1-month check-up in the AS group showed an improvement in 77.88 % of the patients as opposed to the AR group, where the SR QoL improved in only 41.52% of the patients.

Moreover, at the 1-year follow-up, the percentage of patients with NYHA class 1 and 2 was almost two-fold higher in patients with AS in comparison with AR, regardless of the preoperative LVEF ($p < 0.05$) (Figure 4). At the same time, the quality-of-life score > 5 was found in almost 2.3-fold patients with AS compared to patients with AR, both at 1 and 5 years after AVR.

Postoperative echocardiography showed a trend toward improvement for LVEF in AR patients (from 48 ± 4% before surgery to 53 ± 5% 6 months after surgery to 54 ± 6% at 2 years postoperatively, $p = 0.08$) and significant improvement in AS patients (from 50 ± 5% before surgery to 52 ± 12% 6 months after surgery to 55 ± 46% at 2 years postoperatively, $p = 0.002$).

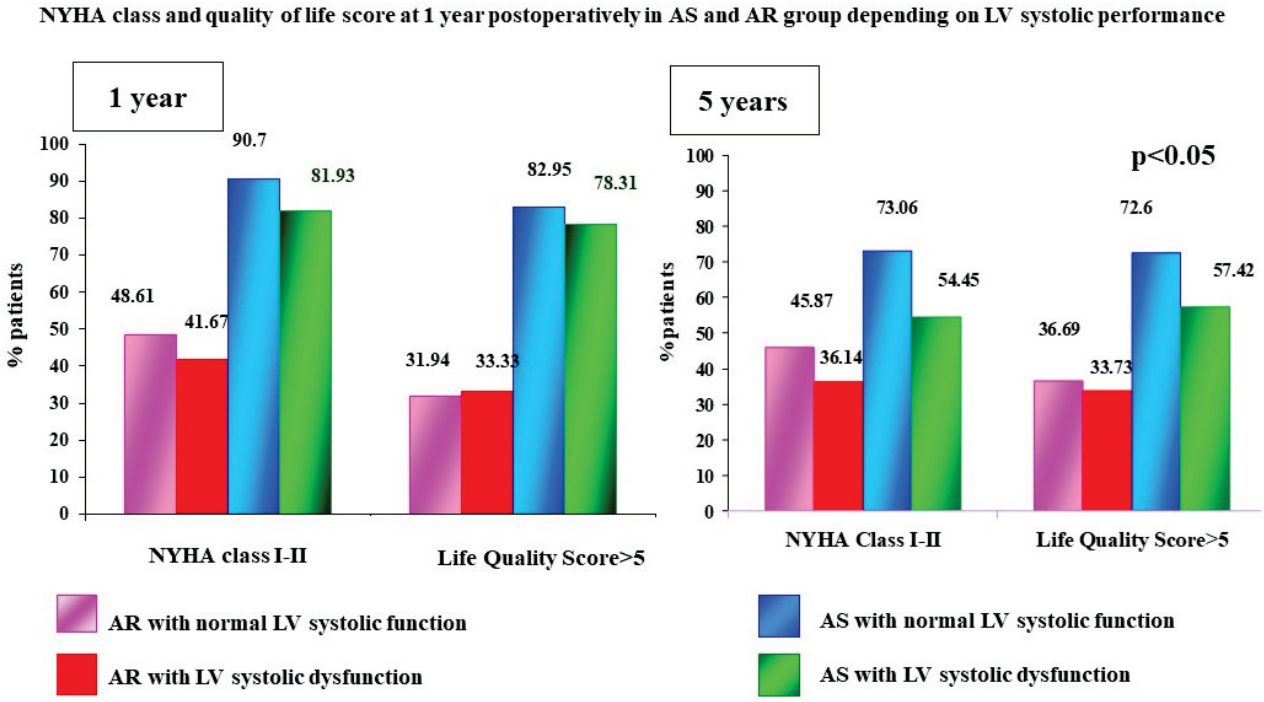

Figure 4. NYHA class and SR QOL > 5 at 1 year postoperatively in AS and AR group depending on LV systolic performance.

Postoperative end-diastolic and end-systolic dimensions decreased significantly in both groups, but was early postoperatively mostly in the AS group (Table 2).

Early postoperatively, the evolution of the LV diastolic filling was different in patients with AS rather than those with AR. After the AVR, diastolic filling improved in patients with AS, whereas patients with AR showed a smaller improvement in diastolic filling. Patients with preoperative AR had a more severe postoperative evolution, with a higher rate of persistence of the restrictive LVDFP. At 1 year postoperatively, the percentage of the patients with persistent restrictive LVDFP was 14.16% in the AS group and 36.84% in the AR group ($p = 0.001$).

The persistence of the restrictive LVDFP has increased the risk of death at 1 year postoperatively (RR = 9.2, $p < 0.05$), regardless of the presence of other known parameters that increased the mortality rate in patients with aortic valve disease undergoing surgical repair.

Thus, regression analysis revealed that the persistent restrictive LVDFP proved to be an independent predictor for increasing the mortality rate in these patients ($p = 0.001$), regardless of the patients' age, comorbidities, LV dimensions, and ejection fraction, or the presence of PHT.

After the successful AVR, the main independent predictors for the persistence of a restrictive LVDFP revealed by simple linear and multivariate regression analysis were (Figure 5):

- Preoperative AR (RR = 19.2, $p = 0.0001$);
- Severe restrictive LVDFP with an E/Ea ratio > 12 (RR = 21.1, $p = 0.0001$);
- Dilated LA with a an LA dimension index > 30 mm/m2 (RR = 8.2, $p = 0.0017$);
- Severely dilated LV with an LV endsystolic diameter (LVESD) > 55 mm (RR = 8.6, $p = 0.01$);
- Severe PHT with a mean PAP > 50 mmHg (RR = 9.7, $p = 0.002$);
- The presence of an associated second-degree mitral regurgitation (MR) (RR = 12.6, $p = 0.05$).

Table 2. Comparison of preoperative and postoperative echocardiographic variables.

Echographic Variables	Group A—226 Pts with AS				Group B—171 Pts with AR			
	Before Surgery	6 Months after Surgery	2 Years after Surgery	*p*-Value (Test)	Before Surgery	6 Months after Surgery	2 Years after Surgery	*p*-Value (Test)
LV end-diastolic diameter (mm)	54 ± 6	51 ± 9	47 ± 8	0.082321	65 ± 6	62 ± 8	59 ± 7	0.126342
LV lateral wall thickness (mm)	17 ± 0.2	15 ± 0.2	12 ± 0.2	0.043672	14 ± 0.2	13 ± 0.4	12 ± 0.2	<0.001
IVS thickness (mm)	17.0 ± 0.4	15.4 ± 0.5	12.7 ± 0.7	0.052345	13.0 ± 0.4	12.0 ± 0.2	11.4 ± 0.4	<0.001
Mean (SD) LVEF (%)	50 (5)	52 (12)	55 (10)	0.054323	48 (4)	53 (5)	54 (6)	0.082445
EDT (msec)	179.95 ± 60	184.72 ± 65	230.35 ± 74	0.051332	162 ± 6	171 ± 8	177 ± 7	0.063245
IVRT (msec)	119.5 ± 74	120 ± 44	123 ± 48	0.042812	97 ± 2	91 ± 4	83 ± 2	0.031843
E/A	1.6 ± 0.4	1.54 ± 0.5	1.47 ± 0.7	0.071254	1.9 ± 0.3	1.8 ± 0.2	1.9 ± 0.4	0.042345
Ea/Aa	1.2 ± 0.2	1.31 ± 0.3	1.38 ± 0.2	0.084728	1.1 ± 0.3	1.2 ± 0.3	1.3 ± 0.4	0.072672
E/Ea	8.9 ± 1.2	8.41 ± 0.9	7.92 ± 0.4	0.064319	9.7 ± 1.3	9.5 ± 1.3	8.9 ± 1.4	0.062531

LV—left ventricle; IVS—interventricular septum; LVEF—left ventricle ejection fraction; EDT—E-wave deceleration time; IVRT—isovolumetric relaxing time.

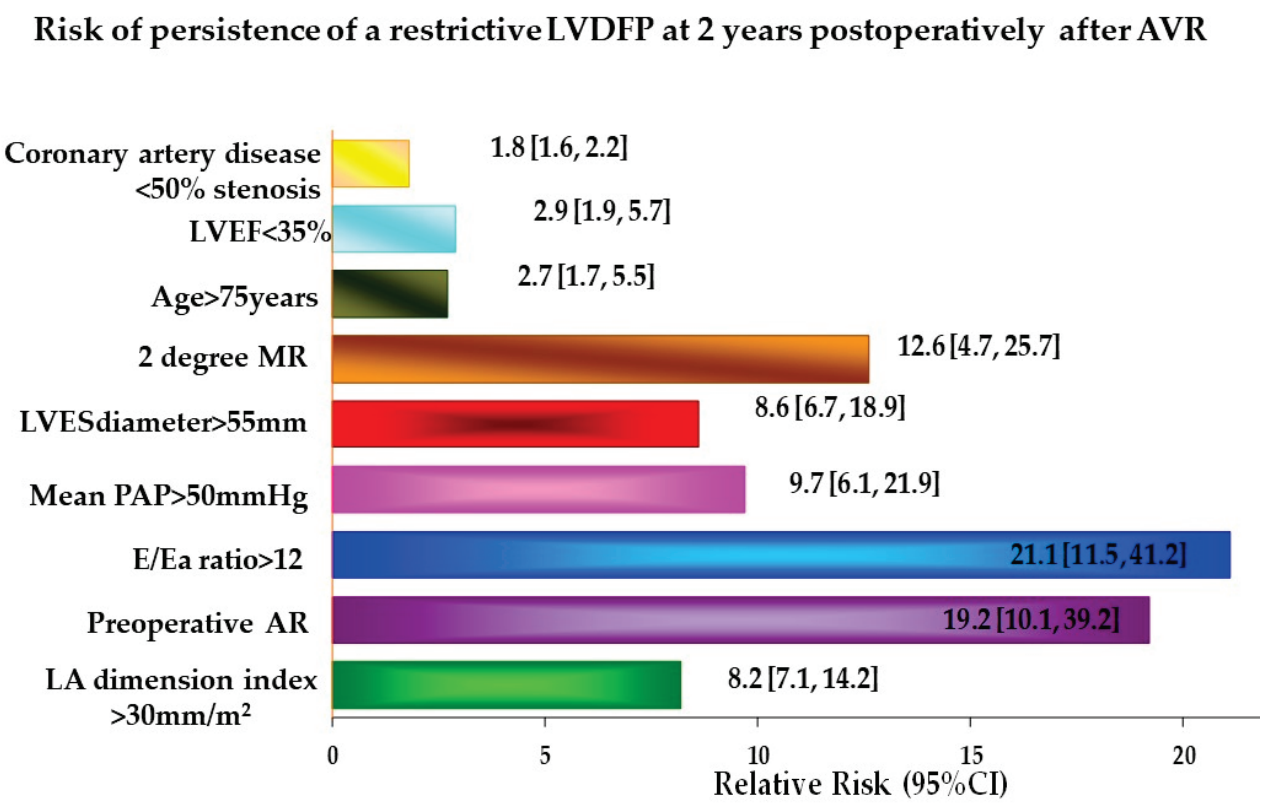

Figure 5. Risk of persistence of a restrictive LVDFP at 2 years postoperatively after AVR.

We found no correlation for the persistence of a restrictive LVDFP after the AVR in these patients for parameters of LV systolic performance, age, or coronary artery disease (Pearson r = 0.45, p = NS)

4. Discussion

After successful AVR, LV remodeling is different in patients with AS compared with AR due to the relationship between how each type of the valve lesion influences LV geometry and the LV systolic and diastolic functions [20,21]. Our study tried to evaluate how the dimensions of the heart chambers and the systolic and diastolic performance evolved in patients with AS compared to those with AR. The main conclusion was that LV remodeling decreases in postoperative end-diastolic and end-systolic dimensions and improvements in LV systolic and diastolic performance after AVR were earlier in patients with AS compared to AR.

As in our study, other researchers have shown that the early postoperative evolution of patients with AR is usually more unfavorable [7,8]. Moreover, at 1 year postoperatively, the NYHA class and self-reported quality of life in our study groups was found better after the AVR for AS compared to AR, as was reported in other previous studies [22].

Regarding systolic performance, the LVEF showed a tendency to improve both in patients with AS and in those with AR after the AVR [22,23]. In most patients with severe chronic AR, there is an important reversal of LV dilatation, associated with a significant increase in LV systolic performance during the first few months after the AVR. These changes correlate with survival in the next 4–5 years. Thus, patients with normal early postoperative systolic and diastolic performance have an excellent prognosis, while survival rates are reduced in patients with persistent LV dysfunction [22].

Regarding the evolution of the diastolic function postoperatively, the situation is different and depends on the type of valvular lesion (AS or AR) and on the time from surgery. Most studies have shown that, in the majority of patients with AS, LV diastolic function returned to normal after the valve replacement [24–26]. In contrast, in AR, diastolic

dysfunction with abnormal filling is maintained in a significant percentage of patients after surgical correction, being normalized late after surgery [27–29].

However, the presence of a restrictive diastolic pattern determined a more unfavorable postoperative evolution both in patients with AS and in patients with AR. Severe diastolic dysfunction was identified by regression analysis as an independent risk factor for death and hospitalization for heart failure, as other studies have shown [1,5,10,28] [30,31]. Therefore, we also sought to assess whether preoperative restrictive diastolic filling precluded postoperative LV remodeling and improved function, and thus might prove useful in identifying patients who benefit less from AVR. One of the most common problems is that pure diastolic dysfunction is rare before surgery, often occurring together with some degree of systolic dysfunction.

We reviewed the current literature in search for criteria that could be applied to help the preoperative assessment and to improve the postoperative management. In patients with preserved LVEF, restrictive filling usually indicates severe myocardial disease. In clinical practice, restrictive filling is strongly predictive of mortality, especially if it is not reversible after treatment [27,32]. Diastolic dysfunction proved to be a more important predictor of mortality and unfavorable postoperative evolution compared to LV dilation and severe systolic dysfunction both in patients with AS and in those with AR [30–32].

The question remains: are the early and medium-term prognoses and LV remodeling after AVR in preoperative restrictive LVDFP patients better in those with AS compared to those with AR? Our study concludes that the improvement of the diastolic performance after surgery was better in AS patients compared to AR patients. In patients with severe AR, diastolic dysfunction persists late after successful AVR, despite recovery of LV systolic performance.

On the other hand, the relevance of LV systolic and diastolic performance as predictors of prognosis and postoperative evolution is different in AR [33]. The importance of diastolic dysfunction for the postoperative evolution in patients with AR is still underestimated; therefore, it is not included in the preoperative risk scores. Moreover, in patients with HF, restrictive diastolic dysfunction is a stronger predictor of mortality than LVEF, and the severity of diastolic dysfunction correlates better than systolic performance with exercise capacity limitation, morbidity, and mortality. Kim et al. also showed that the E/e' ratio was significantly associated with adverse outcomes in patients with chronic severe AR undergoing AVR and may be useful as a prognostic marker in such patients [34]. These data are consistent with our findings and support the importance of a preoperative assessment of LV diastolic function by TDI [35]. Future, randomized studies on larger groups of patients may clarify this issue and determine if it is appropriate to introduce the restrictive diastolic pattern as a severity parameter in the calculation of the preoperative risk score.

Moreover, knowledge is still limited regarding immediate and long-term postoperative outcome in patients with restrictive LVDFP [26–28]. That is why another important question we tried to answer in our study was: does the reversibility of the restrictive flow pattern after AVR depend on the type of the aortic lesion? We concluded that restrictive LVDFP is reversible especially after AVR for AS and not for AR.

In order to answer this question, we assessed the independent predictors for the persistence of the restrictive LV diastolic filling pattern after an isolated AVR. There are few studies evaluating the influence and reversibility of the impaired diastolic function in the early and medium-term postoperatively when comparing AS with AR [8,9]. In our study, we found that LVEF had only a limited predictive value in multivariate models, which included ultrasound parameters for the assessment of diastolic function and PHT. This may highlight the finding that the prognostic information obtained from the assessment of systolic function is insufficient and many other covariates included in the multivariate model are needed. Moreover, we found that the main predictors for the persistence of a restrictive LVDFP in the medium term were E/Ea ratio > 12, preoperative AR, LA dimension index > 30 mm/m^2, severely dilated LV, severe PHT, and the presence of an associated second-degree MR.

We also tried to establish the main independent predictors for unfavorable postoperative evolution after AVR. The most important predictors were severe AR, restrictive LVDFP, and severe PHT. In the long term, the evolution in AS was significantly influenced only by age, while in those with AR were influenced by age, restrictive pattern, and severe LV systolic dysfunction.

As with other studies, our research showed that early and late results after AVR are affected by the presence of PHT, which is also an important risk factor when we talk about the preoperative evaluation [35,36]. In patients with severe PHT, postoperative mortality after AVR was significantly increased, representing an independent risk factor for reduced quality of life and long-term survival. However, although the postoperative mortality of patients with aortic valve injury and severe PHT is higher, other studies demonstrate that the prognosis of conservatively treated patients is very poor, and AVR improves this prognosis [36]. Thus, the indication for surgical intervention is maintained even in the presence of PHT, but its value should be taken into account in the preoperative evaluation. In our study, a pulmonary artery pressure greater than 50 mmHg was an independent predictor for early postoperative mortality.

Our study only evaluated the short- and medium-term evolution of patients with surgical AVR without taking into account the increasingly important population of those who benefit from transcatheter valve implantation (TAVI). Taking into account that multiple hospitalizations after TAVI are common and are often caused by HF, there are few studies trying to evaluate predictors and prognostic implications of new hospitalizations in the long term after TAVI [37,38]. However, substantial work is needed to obtain a standardized score that includes a limited number of variables that can be easily assessed during routine preoperative assessment and to test the predictive value of the models.

Our study attempts to formulate an update of the concept of preoperative evaluation in surgical aortic valve lesion, but an update of the current knowledge regarding the impact of these factors on functional capacity, morbidity and mortality is still needed. Severe diastolic dysfunction proved to be a better and more sensitive predictor of unfavorable postoperative evolution and mortality than LVEF in both AS and AR.

Since the treatment of postoperative diastolic HF remains difficult and often unsatisfactory, and the postoperative evolution of patients with a restrictive diastolic pattern is often unfavorable, the preoperative recognition of severe diastolic dysfunction is an important prognostic sign and should be incorporated into the calculation of the preoperative risk score. Thus, for the better management of patients with surgical AS or AR, future studies are needed to establish an updated preoperative algorithm that takes into account multiple risk factors, including complete echocardiographic evaluation, which would be useful to be incorporated into current guidelines.

Study Limitations

Although this is one of the largest studies to date dealing with the TDI evaluation of diastolic filling in surgical aortic valve disease, the number of the patients was still average.

Moreover, the AVR was done by surgery in all of the patients included in the present study. Therefore, we did not have a comparison group with transcatheter aortic valve implantation.

5. Conclusions

1. Postoperative LV remodeling, improvement in systolic and diastolic performance, NYHA class, and quality of life after AVR was faster in patients with AS compared with those with AR.
2. The independent predictors for increased mortality and hospitalization for HF in the medium term in patients with AVR were: restrictive diastolic filling, preoperative AR, advanced age, LVEF < 35%, severe PHT, and the presence of comorbidities.

3. The persistence of the restrictive diastolic pattern in the medium term after the AVR was more frequent in patients with AR, severe LV or LA dilatation, severe PHT, and associated second-degree MR.

Preoperative stratification of the patients undergoing AVR needs to take into account the diastolic function, presence of the PHT, the dimensions of the LV, and the systolic performance of the LV.

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Abbreviations

AS	aortic stenosis
AVR	aortic valve replacement
LV	left ventricle
LVDFP	left ventricle diastolic filling pattern
LA	left atrium
LVEF	left ventricle ejection fraction
LVESD	left ventricle end-systolic diameter
NYHA	New York Heart Association
TDI	tissue doppler imaging
LVEDV	left ventricle end-diastolic volume
LVEDD	left ventricle end-diastolic diameter
EDt	deceleration time
IVRT	isovolumetric relaxation time
LVOT	left ventricle outflow tract
Sa	peak annular systolic velocity
Ea	early diastolic velocity
Aa	late diastolic velocity
BNP	brain natriuretic peptide
ANOVA	analysis of variance
COPD	chronic obstructive pulmonary disease
SR QOL	self-reported quality of life
IVS	interventricular septum
ROC	receiver operating curve
PAP	pulmonary arterial pressure

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Age-Specific Outcomes of Bioprosthetic vs. Mechanical Aortic Valve Replacement: Balancing Reoperation Risk with Anticoagulation Burden

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Abstract: Background: The choice of prosthesis for aortic valve replacement (AVR) remains challenging. The risk of anticoagulation complications vs. the risk of aortic valve reintervention should be weighed. This study compared the outcomes of bioprosthetic vs. mechanical AVR in patients older and younger than 50. Methods: This retrospective study was conducted from 2009 to 2019 and involved 292 adult patients who underwent isolated AVR. The patients were divided according to their age (above 50 years or 50 years and younger) and the type of valves used in each age group. The outcomes of bioprosthetic valves (Groups 1a (>50 years) and 1b ($\leq$50 years)) were compared with those of mechanical valves (Groups 2a (>50 years) and 2b ($\leq$50 years)) in each age group. Results: The groups had nearly equal rates of preexisting comorbidities except for Group 1b, in which the rate of hypertension was greater (32.6% vs. 14.7%; $p = 0.025$). This group also had higher rates of old stroke (8.7% vs. 0%, $p = 0.011$) and higher creatinine clearance (127.62 (108.82–150.23) vs. 110.02 (84.87–144.49) mL/min; $p = 0.026$) than Group 1b. Patients in Group 1a were significantly older than Group 2a (64 (58–71) vs. 58 (54–67) years; $p = 0.002$). There was no significant difference in the NYHA class between the groups. The preoperative ejection fraction and other echocardiographic parameters did not differ significantly between the groups. Re-exploration for bleeding was more common in patients older than 50 years who underwent mechanical valve replacement ($p = 0.021$). There was no difference in other postoperative complications between the groups. The groups had no differences in survival, stroke, or bleeding rates. Aortic valve reintervention was significantly greater in patients $\leq$ 50 years old with bioprosthetic valves. There were no differences between groups in the changes in left ventricular mass, ejection fraction, or peak aortic valve pressure during the 5-year follow-up. Conclusions: The outcomes of mechanical and bioprosthetic valve replacement were comparable in patients older than 50 years. Using bioprosthetic valves in patients younger than 50 years was associated with a greater rate of valve reintervention, with no beneficial effect on the risk of bleeding or stroke.

Keywords: aortic valve replacement; bioprosthetic valves; mechanical valves; valve surgery

1. Introduction

Although several studies have evaluated aortic valve replacement (AVR) outcomes using different valve prostheses, the valve choice remains challenging [1–6]. The risk of bleeding associated with anticoagulation therapy and possible teratogenic risk for women

of childbearing age are two obstacles to consider before deciding to implant a mechanical valve [7,8]. Mechanical aortic valves were associated with greater bleeding rates than bioprosthetic valves in patients aged 50 to 69 years [9], consistent with studies on mechanical mitral valves [9]. Regarding bioprosthetic valve selection, structural valve deterioration and lower durability requiring reoperation are among the most feared drawbacks [10] despite the acceptable five-year durability of bioprosthetic AVR [11]. Earlier studies showed similar survival rates with mechanical or bioprosthetic AVR [12].

On the other hand, recent studies reported similar risks of bleeding and stroke between mechanical and bioprosthetic valves, with better long-term survival in patients with mechanical valves [8]. Recently, the introduction of new generations of bioprosthetic aortic valves with comparable costs to mechanical valves [13] and transcatheter aortic valve interventions [14] has increased the popularity of bioprosthetic valves. Moreover, lower anticoagulation intensity in patients with mechanical aortic valves might promote mechanical valve use in older patients [15].

Despite recent advances in aortic valve interventions through transcatheter and minimally invasive surgery [14,16–18], choosing an aortic valve prosthesis is challenging in young and old patients. Patients with rheumatic valve disease might require valve replacement at a young age. Bioprosthetic valves have the advantage of preventing anticoagulation during pregnancy; however, the risk of multiple reoperations is substantial. Therefore, further studies are required to explore the long-term differences between the two types of valves, especially in our Middle Eastern population, which has a high incidence of rheumatic heart disease requiring surgery at a young age. In this study, we aimed to investigate long-term outcomes in adult patients older or younger than 50 years after AVR with mechanical or bioprosthetic valves. Furthermore, we characterized patients who received mechanical and bioprosthetic valves in patients older or younger than 50 years.

2. Methods

2.1. Study Design and Patients

We conducted a retrospective cohort study that included 292 patients who underwent isolated AVR from 2009 to 2020 at Prince Sultan Cardiac Center, Riyadh, Saudi Arabia. We grouped the patients according to their age ($\leq$50 years and >50 years) and type of implanted aortic valve (mechanical or bioprosthetic aortic valve). The groups included patients older than 50 years with either bioprosthetic (Group 1a: n = 111) or mechanical AVR (Group 2a: n = 38) and patients aged $\leq$50 years with bioprosthetic (Group 1b: n = 48) or mechanical AVR (Group 2b: n = 95). Patients who underwent AVR and concomitant coronary artery bypass grafting (CABG), mitral or tricuspid valve surgery, or other cardiac procedures were excluded from this study. Age older than 50 is the recommended age for the possibility of using bioprosthetic valves in the aortic position [19]. This study included patients with primary or redo AVR because this could be a factor that affected prostheses choice.

Approval for this study was obtained from the Institutional Review Board (IRB approval No. 1676), and the need for patient consent was waived.

2.2. Study Data and Outcomes

Demographic, clinical, laboratory, and echocardiographic data were collected from paper and electronic medical charts. Preoperative data included age, body mass index (BMI), sex, EuroSCORE II, New York Heart Association class (NYHA), hypertension, diabetes mellitus (DM), chronic lung disease, renal impairment, liver disease, previous myocardial infarction (MI), previous heart failure hospitalization within one year prior to surgery, old stroke, atrial fibrillation (AF), previous cardiac surgery, previous percutaneous coronary intervention (PCI), previous transcatheter aortic valve replacement, hemoglobin level, and creatinine clearance. Operative data included emergency status (critical aortic stenosis or stuck aortic prosthesis), cardiopulmonary bypass (CPB), and cross-clamp times. Postoperative outcomes included hospital mortality, return to the operating room for

bleeding, blood transfusion, early permanent pacemaker insertion (PPM), new-onset AF, stroke, MI, creatinine level (highest before discharge), respiratory failure, length of ICU, and length of hospital stay. The long-term outcomes were mortality, stroke, need for valve reintervention, bleeding, and cardiac rehospitalization for heart failure.

2.3. Outcomes

The primary endpoint was all-cause mortality during hospitalization or at follow-up. The secondary endpoints were major adverse events in the hospital and follow-up. Other secondary outcomes included all bleeding, stroke, and aortic valve reintervention.

2.4. Echocardiography

All patients underwent transthoracic echocardiograms before surgery and at discharge. Changes in the ejection fraction (EF), peak aortic valve pressure, and LV mass were reported and compared between the groups.

2.5. Prosthesis Types

The mechanical valves used in our study were St. Jude mechanical valves (SJM; St. Jude Medical Inc.; Minneapolis, MN, USA), ATS (Medtronic; Minneapolis, MN, USA), Carbomedics Sorin (LivaNova PLC, Sorin, Sluggia, Italy), and On-X (CryoLife, Kennesaw, GA, USA). Tissue valves were Magna valves (Edwards Lifesciences, Irvine, CA, USA), Trifecta (Abbott, Plymouth, MN, USA), Perceval sutureless valves (LivaNova Group, Milan, Italy), and Hancock (Medtronic Inc.; Minneapolis, MN, USA).

2.6. Follow-Up

All patients were clinically followed up in our outpatient clinic at 1, 6, and 12 months postoperatively and at yearly intervals thereafter. The patient's vital status was confirmed by phone in June 2021 and by reviewing the medical records for all patients in June 2023. The hospital anticoagulation protocol was the same for mechanical and bioprosthetic valves. Patients were discharged on warfarin after achieving the target INR. and followed up in the anticoagulation clinic. The target INR was 2–3 for the mechanical valves for life, and patients with bioprosthetic valves had warfarin for only three months. Patients with bioprosthetic valves and contraindications to warfarin were discharged on aspirin only.

2.7. Definitions

Hospital outcomes were defined as those occurring 30 days after surgery or within the same hospital admission. Preoperative variables were collected according to EuroSCORE II definitions [20].

2.8. Statistical Analysis

We used Stata 18 (Stata Corp, College Station, TX, USA) to perform all the statistical analyses. The Shapiro–Wilk test was used to test the distribution of the continuous variables. Normally distributed data are expressed as the mean and standard deviation and were compared with Student's t-test. Nonnormal data are expressed as medians (25th–75th percentiles) and were compared with the Mann–Whitney test. Categorical data are presented as frequencies and percentages and were compared with Fisher's exact test if the expected frequency was less than five. Survival distribution was plotted using Kaplan–Meier curves and compared with the log-rank test. The random effect model was used to compare the repeated measures among groups. A two-sided p-value of less than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Baseline and Operative Characteristics

A greater proportion of male participants were in Group 2b ($p = 0.018$). The groups had no significant difference in body mass index (BMI). The EuroSCORE II was significantly

greater in Group 2a than in Group 2b (0.94% vs. 0.87%, $p = 0.049$). The prevalence of hypertension and old stroke was significantly greater in Group 2a than in Group 2b. The groups had nearly equal rates of other preexisting comorbidities, with no significant differences observed between the groups in terms of smoking status, renal impairment status, diabetes status, liver disease status, chronic lung disease status, previous MI status, previous heart failure hospitalization status, AF status, previous cardiac surgery status, previous PCI status or previous transcatheter aortic valve intervention (TAVI) status. Patients in Group 1a had significantly lower hemoglobin levels and creatinine clearance levels than those in Group 2b.

Moreover, the groups had similar presentations, with no significant difference in the NYHA class (Table 1). There was no difference in the operative status between patients who underwent AVR tissue or mechanical surgery, regardless of their age group. The groups had no difference in cardiopulmonary bypass and ischemic times (Table 1).

Table 1. Comparison of the preoperative patients' baseline characteristics between aortic valve replacement using bioprosthetic and mechanical valves in patients aged >50 years and ≤50 years.

Variables	Group 1a (n = 111)	Group 2a (n = 38)	*p*-Value	Group 1b (n = 48)	Group 2b (n = 95)	*p*-Value
Male	81 (72.97%)	24 (63.16%)	0.304	28 (58.33%)	85 (89.47%)	0.018 *
Age, years	64 (58, 71)	58 (54, 67)	0.002 *	38.5 (28, 47.5)	31 (20, 43)	<0.001 *
BMI, kg/m^2	29.30 (24.13, 3.73)	30.75 (26.50, 34.40)	0.150	25.42 (20.50, 32.26)	25.60 (19.46, 29.65)	0.891
EuroSCORE II, %	1.19 (0.87, 2.08)	1.2 (0.69, 2.05)	0.883	0.94 (0.69, 2.03)	0.87 (0.67, 1.52)	0.049 *
Risk factors						
Smoking	11 (10.58%)	6 (16.22%)	0.358	6 (13.33%)	12 (12.90%)	>0.99
Renal impairment	10 (9.35%)	7 (20%)	0.130	6 (13.4%)	3 (3.16%)	0.058
Hypertension, n	73 (66.97)	29 (78.38)	0.219	15 (32.61%)	14 (14.74%)	0.025 *
Diabetes	55 (50.46)	25 (67.57)	0.086	10 (21.74%)	10 (10.64%)	0.121
Liver disease	2 (1.90%)	1 (2.78%)	>0.99	1 (2.17%)	1 (1.06%)	0.551
Chronic lung disease	14 (13.08%)	4 (11.6%)	>0.99	2 (4.55%)	1 (1.06%)	0.238
Previous MI	2 (1.85%)	0	>0.99	0	1 (1.09%)	>0.99
Previous Heart Failure	1 (1.04%)	0	>0.99	1 (2.27%)	1 (1.14%)	>0.99
Old Stroke	6 (5.88%)	1 (2.78%)	0.676	4 (8.70%)	0	0.011
Atrial fibrillation	10 (9.52%)	3 (8.33%)	>0.99	1(2.17%)	5 (5.38%)	0.663
Previous Cardiac surgery	10 (9.26%)	8 (21.62%)	0.079	8 (17.02%)	22 (23.66%)	0.394
Previous PCI	6 (5.56%)	2 (5.41%)	>0.99	2 (4.26%)	0	0.110
Previous TAVI	4 (3.70%)	0	0.572	0	0	>0.99
Laboratory findings						
Hemoglobin (mg/dL)	13.5 (12, 14.7)	13.7 (11.8, 15)	0.858	13.1 (11.65, 14.75)	14.2 (13, 15.3)	0.016
Creatinine clearance (mL/min)	90.36 (62.90, 108.49)	101.45 (47.56, 124.45)	0.773	110.02 (84.87, 144.49)	127.62 (108.82, 150.23)	0.026 *
Symptoms						
NYHA class I II III IV	 2 (1.98%) 22 (20.95%) 72 (68.57%) 9 (8.57%)	 3 (7.89%) 7 (18.42%) 24 (63.16%) 4 (10.53%)	0.359	 4 (8.33%) 12 (25%) 28 (58.33%) 3 (6.25%)	 7 (7.37%) 34 (35.79%) 50 (52.63%) 4 (4.21%)	0.436
Emergency/urgent surgery	4 (3.88%)	2 (5.88%)	0.638	3 (6.38%)	4 (4.44%)	0.691

Table 1. *Cont.*

Variables	Group 1a (n = 111)	Group 2a (n = 38)	*p*-Value	Group 1b (n = 48)	Group 2b (n = 95)	*p*-Value
Cardiopulmonary bypass time, min	95 (79, 126)	94 (80, 122)	0.923	97 (84, 115)	98 (75, 115.5)	0.693
Cross clamp time, min	76 (61, 101)	75 (63, 101)	0.688	79 (65, 94)	74 (60, 98)	0.688

Continuous data are expressed as the mean and standard deviation if normally distributed or as the median and (Q1–Q3) if nonnormally distributed. Categorical data are expressed as numbers and percentages. Group 1a (bioprosthetic valve and age > 50 years), Group 2a (mechanical valve and age > 50 years), Group 1b (bioprosthetic valve and age $\leq$ 50 years), Group 2b (mechanical valve and age $\leq$ 50 years); BMI: body mass index; MI: myocardial infarction; NYHA: New York Heart Association. * Indicates a significant *p*-value (<0.05).

3.2. Echocardiographic Characteristics

There was no difference in the preoperative ejection fraction between the groups. Ventricular mass and peak velocity did not vary significantly among the presented groups. Patients had similar end-diastolic and end-systolic diameters. There was no significant difference between participants regarding pulmonary artery systolic pressure, the severity of aortic valve regurgitation, or the severity of aortic valve stenosis (Table 2).

Table 2. Comparison of the preoperative echocardiographic data between aortic valve replacement using bioprosthetic and mechanical valves in patients aged >50 years and $\leq$50 years.

Variables	Group 1a (n = 111)	Group 2a (n = 38)	*p*-Value	Group 1b (n = 48)	Group 2b (n = 95)	*p*-Value
EF, %	55 (50, 60)	55 (55–60)	0.363	55 (50, 60)	55 (50–60)	0.492
Ventricular Mass (g/m^2)	123.89 (98.5, 147.1)	104.85 (96.96, 139.54)	0.193	124.03 (92.9, 157.4)	133.48 (99.8, 169.86)	0.559
Peak velocity (m/s)	85.8 (69.3, 102.1)	82.55 (53.35, 115.85)	0.620	76.6 (35.8, 106.9)	69.4 (27.5, 106)	0.490
End-diastolic diameter (mm)	51 (46, 56)	50 (46, 55)	0.482	52 (47, 58)	54 (48, 62)	0.264
End-systolic diameter (mm)	34 (29, 39)	31.5 (28, 39.5)	0.418	36 (30, 43)	36 (30, 43)	0.937
Pulmonary artery systolic pressure (mmHg)	37 (30, 45)	30 (30, 40)	0.178	35 (30, 50)	30 (25, 40)	0.262
AR severity						
None	22 (22.92%)	10 (27.78%)	0.951	5 (11.36%)	9 (10.71%)	0.991
Mild	33 (34.38%)	10 (27.78%)		5 (11.36%)	8 (9.52%)	
Moderate	20 (20.83%)	8 (22.22%)		8 (18.60%)	16 (19.05%)	
Moderately severe	5 (5.21%)	2 (5.56%)		1 (2.33%)	2 (2.38%)	
Severe	16 (16.76%)	16 (16.76%)		24 (55.81%)	49 (58.33%)	
AS severity						
None	5 (5.21%)	5 (14.29%)	0.194	9 (21.95%)	21 (28.38%)	0.583
Mild	3 (3.13%)	0 (0%)		6 (14.63%)	9 (12.16%)	
Moderate	5 (5.21%)	3 (8.57%)		2 (4.88%)	8 (10.81%)	
Severe	83 (86.46%)	27 (77.14%)		24 (58.54%)	36 (48.65%)	

Continuous data are expressed as the mean and standard deviation if normally distributed or as the median and (Q1–Q3) if nonnormally distributed. Categorical data are expressed as numbers and percentages. Group 1a (bioprosthetic valve and age > 50 years), Group 2a (mechanical valve and age > 50 years), Group 1b (bioprosthetic valve and age $\leq$ 50 years), Group 2b (mechanical valve and age $\leq$ 50 years); EF: ejection fraction; AR: aortic regurgitation; AS: aortic stenosis.

3.3. Postoperative Complications

Re-exploration for bleeding was more common in patients older than 50 years who underwent mechanical AVR (Group 2a) (p = 0.045). There was no difference in other postoperative complications between the groups. The hospital mortality rate was not significantly different among the studied groups. There were 4 deaths (3.6%) in Group 1a and 2 (5.26%) in Group 2a. However, there were no deaths among patients who were 50 years of age or younger and who underwent aortic valve replacement with a tissue valve,

while there were no cases (2.11%) of deaths among patients who underwent mechanical valve replacement ($p = 0.551$) (Table 3).

Table 3. Comparison of postoperative data between aortic valve replacement using bioprosthetic and mechanical valves in patients aged >50 years or ≤50 years.

Variables	Group 1a (n = 111)	Group 2a (n = 38)	*p*-Value	Group 1b (n = 48)	Group 2b (n = 95)	*p*-Value
In-hospital mortality	4 (3.6%)	2 (5.26%)	0.645	0	2 (2.11%)	0.551
Re-exploration for bleeding	7 (6.73%)	7 (20%)	0.045 *	1 (2.13%)	5 (5.38%)	0.664
Blood transfusion	49 (50.52)	12 (37.50%)	0.226	18 (40.91%)	32 (36.36%)	0.704
Number of PRBCs	0 (0, 2)	0 (0, 2)	0.757	0 (0, 1)	0 (0, 1)	0.444
Early PPM	3 (2.88%)	1 (2.78%)	>0.99	0 (0%)	0 (0%)	>0.99
AF	13 (12.38%)	2(5.41%)	0.354	1 (2.17%)	1 (1.08%)	>0.99
Stroke	0 (0%)	0 (0%)	>0.99	0 (0%)	1 (1.15%)	>0.99
MI	0 (0%)	0 (0%)	>0.99	0 (0%)	0 (0%)	>0.99
Highest creatinine, mmol/L	86 (74, 112)	83 (75, 124)	0.788	70 (53.5, 93.5)	74 (66.5, 88.5)	0.272
Respiratory failure	0 (0%)	1 (2.94%)	0.254	0 (0%)	0 (0%)	>0.99
ICU stay (d)	2 (1, 4)	1.5 (1, 4)	0.963	1(1, 2)	1 (1, 3)	0.297
Hospital stay duration (days)	8 (6, 13)	9 (6, 15)	0.572	7 (6, 9)	7 (6, 11)	0.905

Continuous data are expressed as the mean and standard deviation if normally distributed or as the median and (Q1–Q3) if nonnormally distributed. Categorical data are expressed as numbers and percentages. Group 1a (bioprosthetic valve and age > 50 years), Group 2a (mechanical valve and age > 50 years); Group 1b (bioprosthetic valve and age ≤ 50 years), Group 2b (mechanical valve and age ≤ 50 years); AF: atrial fibrillation; ICU: intensive care unit; MI: myocardial infarction; PPM: permanent pacemaker; PRBCs: packed red blood cells. * Indicates a significant *p*-value (<0.05).

3.4. Survival Rates

The median follow-up time was 45 months (22–72) for patients > 50 years. Survival at 5 and 10 years was 88% and 81% in Group 1a and 89% and 89%, respectively, in Group 2b. The total mortality rate was 9% (10 patients) in Group 1a and 10.5% (4 patients) in Group 2a. The median follow-up in patients ≤ 50 years was 56 (19–85) months. Survival in Group 1b was 100%, and that in Group 2b was 98% at 5 years and 95% at 10 years (Figure 1A,B).

3.5. Freedom from Reintervention

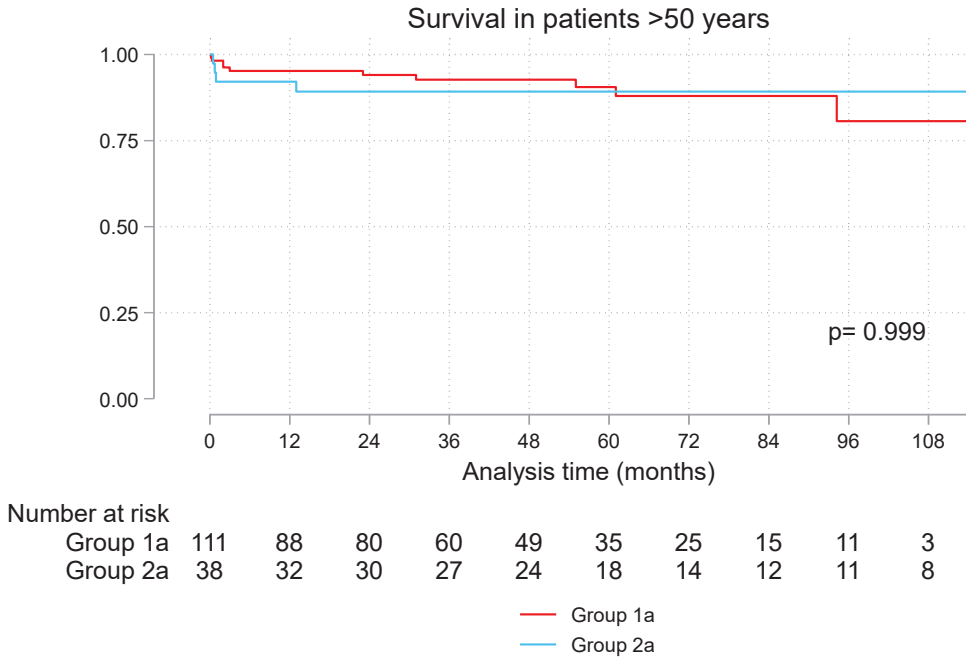
The rate of freedom from valve-related reintervention was 94% in Groups 1a and 2a after 5 years. Six patients had reintervention in Group 1a vs. three patients in Group 2a. At 5 years, 92% of the patients in Group 1b and 98% of the patients in Group 2b were free from reintervention (Figure 2A,B). Reintervention occurred in seven patients in Group 1b vs. four patients in Group 2b. Reintervention was performed surgically in 16 patients and transcatheter aortic valve replacement was performed in 4 cases. The causes of reinterventions were infective endocarditis (n = 4), degenerated prosthesis (n = 11), paravalvular leak (n = 3), and patient-prosthesis mismatch (n = 2).

3.6. Freedom from Stroke

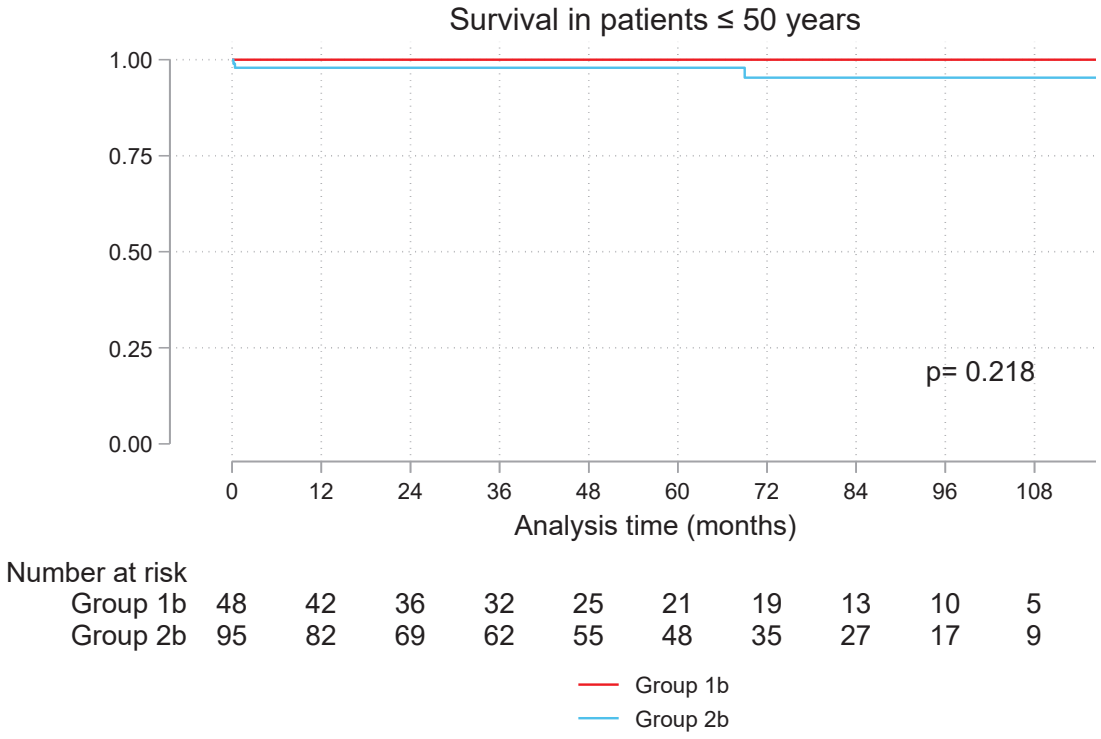
There were five strokes in Group 1a and one stroke in Group 2a. The prevalence of freedom stroke was 87% at 10 years in Group 1a and 94% in Group 2a. Stroke occurred in one patient in Group 1b and two in Group 2b. In both groups, the rate of freedom from stroke was 98% at 10 years (Figure 3A,B).

3.7. Freedom from Bleeding

There were seven bleeding episodes in Group 1a and 3 in Group 2a. There was 85% freedom from bleeding at 10 years in Group 1a and 77% in Group 2a. Four bleeding episodes occurred in Group 1b, and 12 occurred in Group 2b. The rate of freedom from bleeding was 86% at 10 years in both groups (Figure 4A,B).

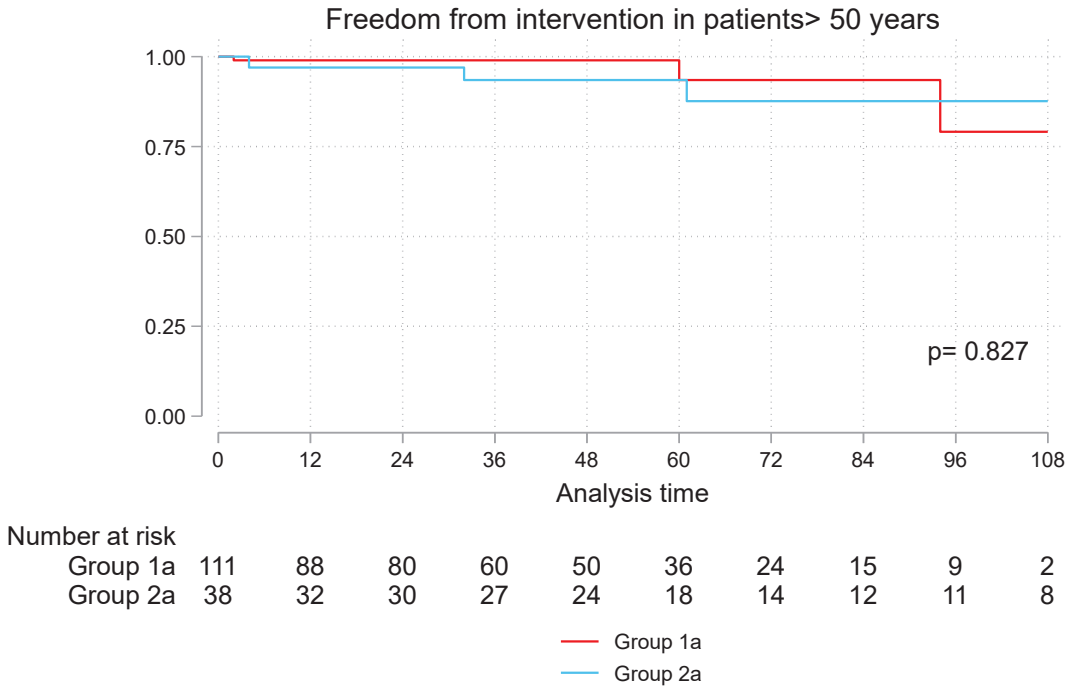


(**A**)



(**B**)

Figure 1. (**A**): Survival of patients > 50 years and (**B**): Survival of patients ≤ 50 years. Group 1a (bioprosthetic valve and age > 50 years), Group 2a (mechanical valve and age > 50 years), Group 1b (bioprosthetic valve and age ≤ 50 years), Group 2b (mechanical valve and age ≤ 50 years).



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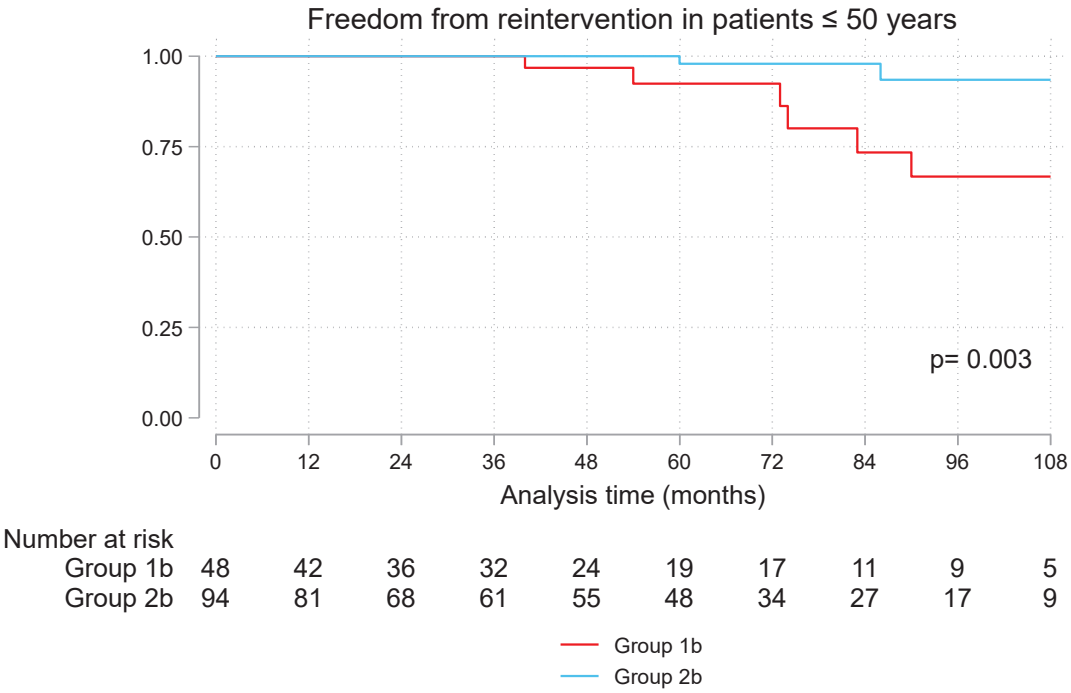
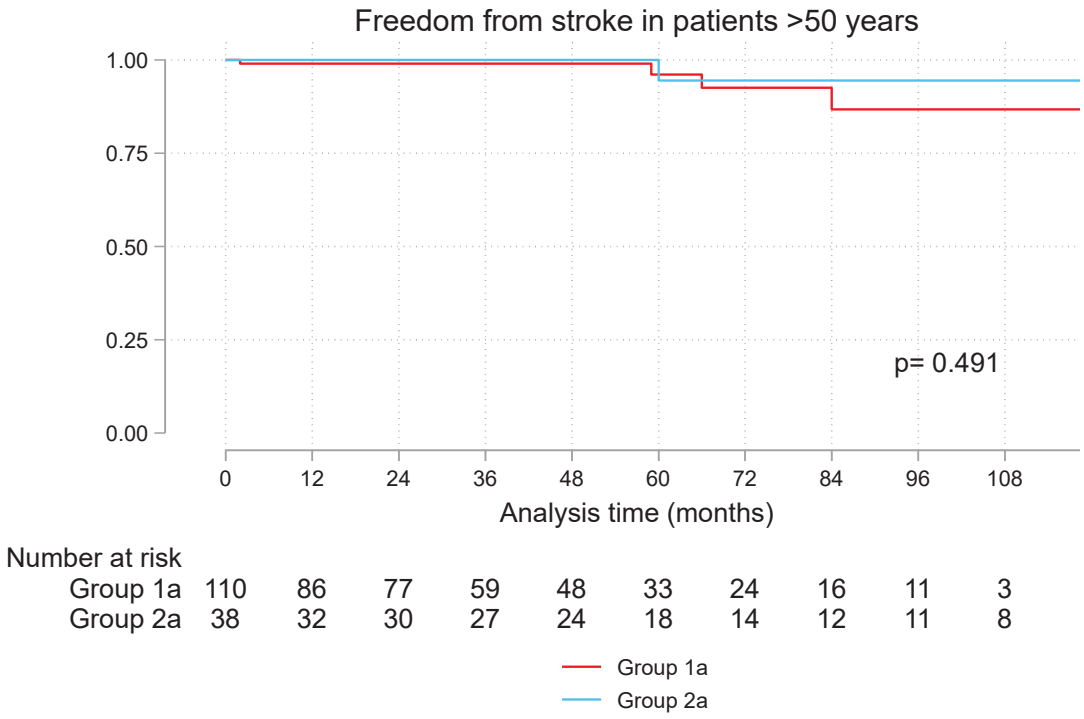


(**B**)

Figure 2. (**A**) Freedom from aortic valve reintervention in patients > 50 years and (**B**) in patients ≤ 50 years. Group 1a (bioprosthetic valve and age > 50 years), Group 2a (mechanical valve and age > 50 years), Group 1b (bioprosthetic valve and age ≤ 50 years), Group 2b (mechanical valve and age ≤ 50 years).



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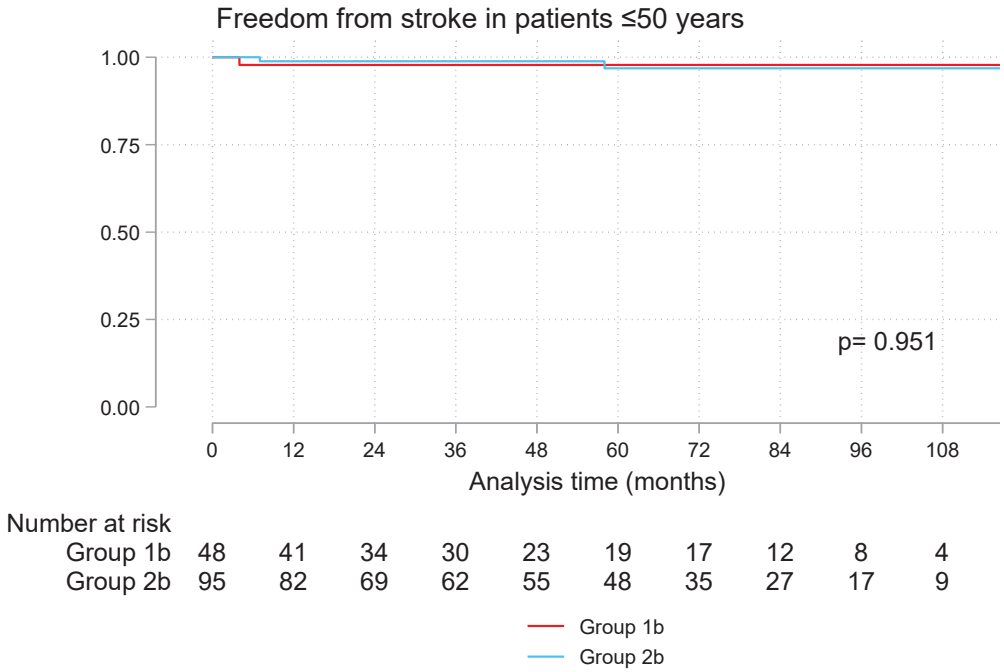
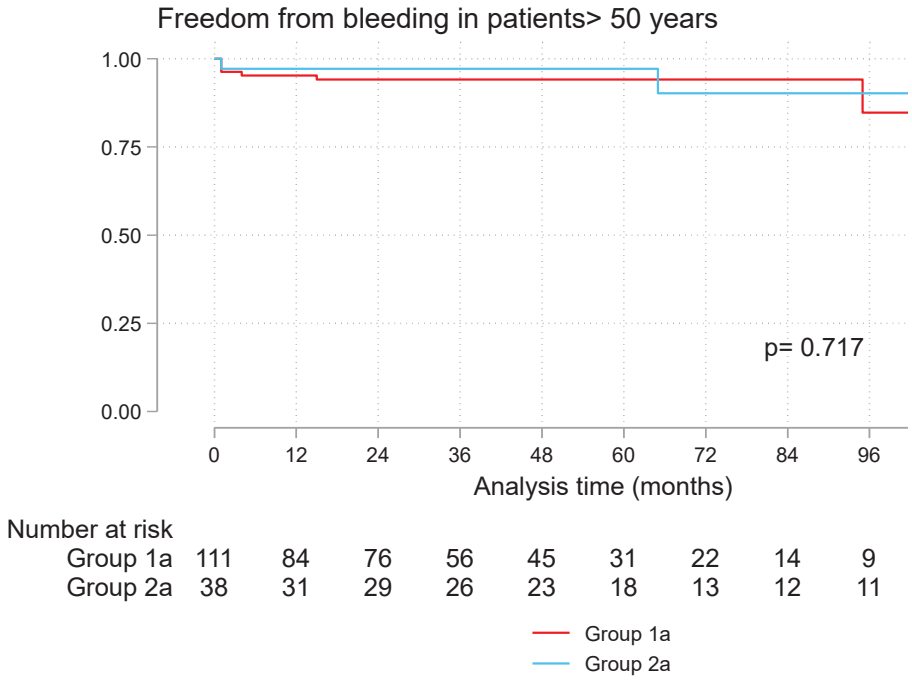


(**B**)

Figure 3. Freedom from stroke in patients > 50 years (**A**) and ≤50 years (**B**). Group 1a (bioprosthetic valve and age > 50 years), Group 2a (mechanical valve and age > 50 years), Group 1b (bioprosthetic valve and age ≤ 50 years), Group 2b (mechanical valve and age ≤ 50 years).



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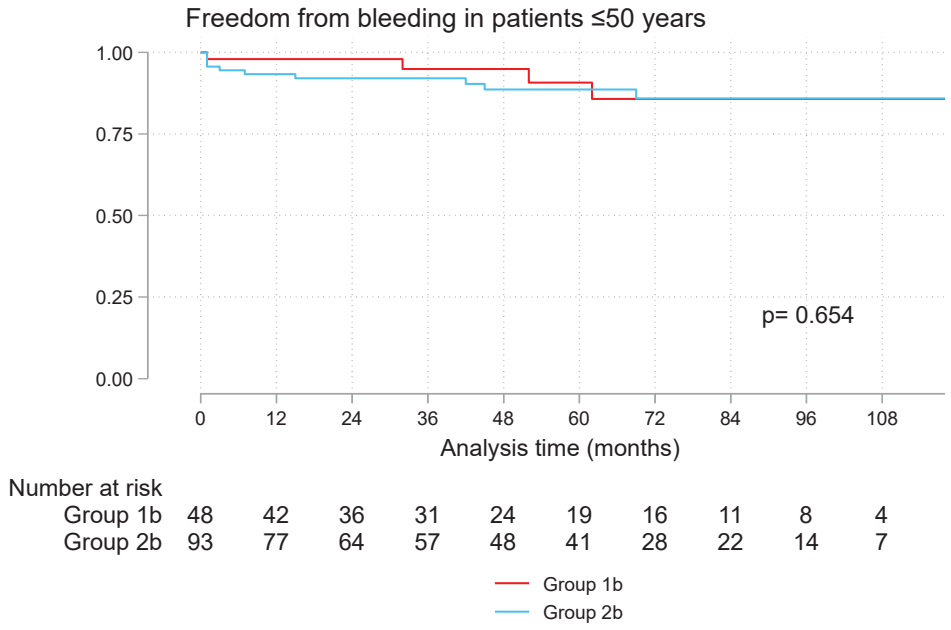


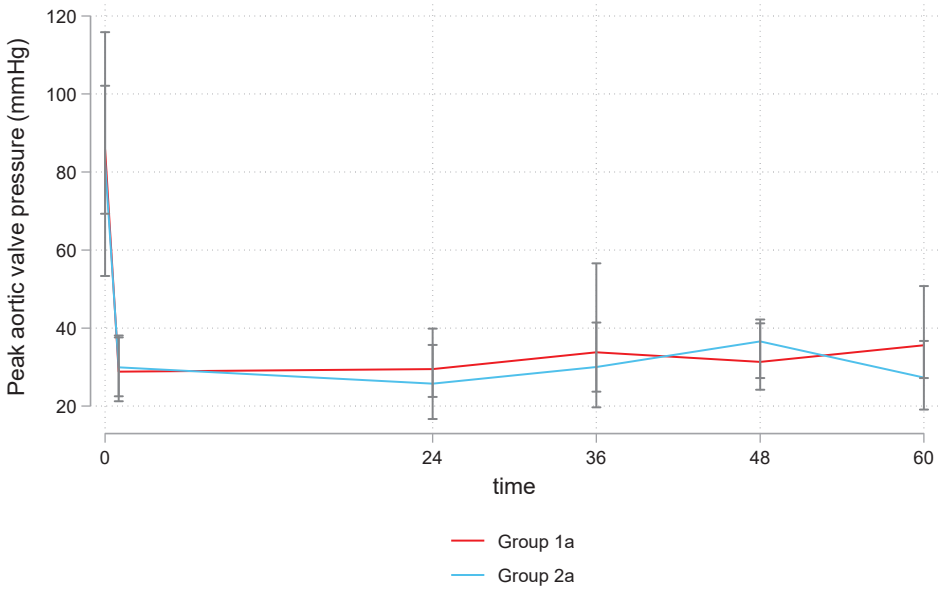
(**B**)

Figure 4. Freedom from bleeding in patients > 50 years (**A**) and ≤50 years (**B**). Group 1a (bioprosthetic valve and age > 50 years), Group 2a (mechanical valve and age > 50 years), Group 1b (bioprosthetic valve and age ≤ 50 years), Group 2b (mechanical valve and age ≤ 50 years).

3.8. Changes in Echocardiography

There was a significant reduction in the LV mass in Groups 1a and 2a over follow-up (β: −0.47 (95% CI: −0.60–−0.34), $p < 0.001$), with no difference between them (β: −6.86 (95% CI: −18.58–4.87), $p = 0.252$). The changes in ejection fraction were not significant (β: 0.02 (95% CI: −0.003–0.05), $p = 0.08$), and there was no difference between the groups (β: 2.66 (95% CI: −0.20–5.52), $p = 0.068$). The peak AV pressure significantly reduced during

follow-up (β: −0.51 (95% CI: −0.66–−0.37), $p < 0.001$), with no difference between Groups 1a and 2a (β: −0.93 (95% CI: −8.23–6.36), $p = 0.802$) (Figure 5A).



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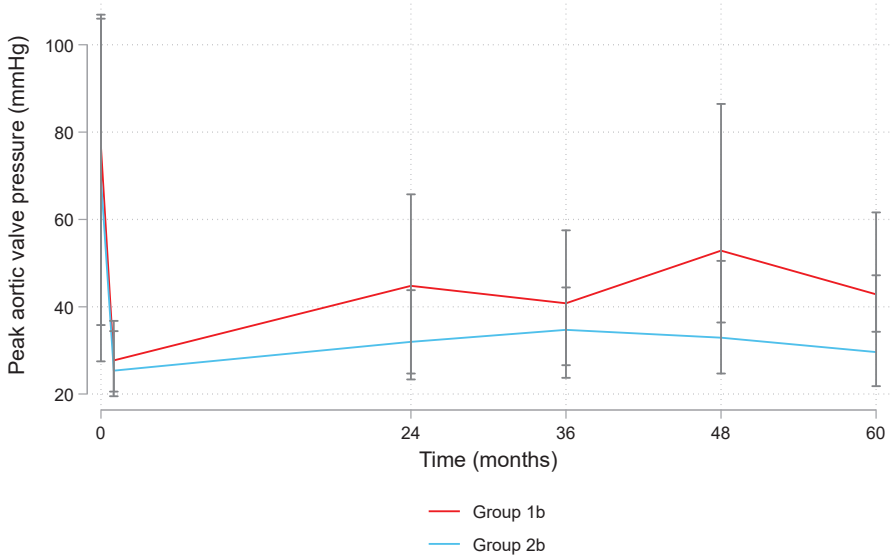

(**B**)

Figure 5. Changes in peak aortic valve pressure in patients > 50 years (**A**) and ≤50 years (**B**). Group 1a (bioprosthetic valve and age > 50 years), Group 2a (mechanical valve and age > 50 years), Group 1b (bioprosthetic valve and age ≤ 50 years), Group 2b (mechanical valve and age ≤ 50 years).

Left ventricular mass decreased significantly over time (β: −0.72 (95% CI: −0.99–−0.44), $p < 0.001$), with no difference between Groups 1b and 2b (β: 2.39 (95% CI: −9.27–14.04), $p = 0.688$). There was a significant improvement in EF over time (β: 0.05 (95% CI: 0.02–0.08), $p < 0.001$), while there was no difference between Groups 1b and 2b (β: −0.73 (95% CI: −3.41–1.97), $p = 0.597$). There was a reduction in the peak AV pressure, but it did not reach a significant level (β: −0.15 (95% CI: −0.31–0.004), $p = 0.056$), and there was no difference between Groups 1b and 2b (β: −6.80 (95% CI: −14.58–0.98), $p = 0.087$) (Figure 5B).

4. Discussion

The challenges of choosing an aortic valve prosthesis are continuously debated. This study explored the differences in short- and long-term outcomes after AVR between patients who received bioprosthetic and those who received mechanical valves stratified by age. There was no difference in postoperative complications between groups apart from greater re-exploration for bleeding in patients > 50 years old with mechanical valves. The groups had no differences in survival, stroke, or bleeding rates. Aortic valve reintervention was significantly greater in patients $\leq$ 50 with bioprosthetic valves. There were no differences between groups in the changes in left ventricular mass, ejection fraction, or peak aortic valve pressure during the 5-year follow-up.

Male patients constituted the vast majority of the participants in all groups; however, the proportion of males was lower in patients $\leq$ 50 years of age who received bioprosthetic valves. This finding could be attributed to the increased use of bioprosthetic valves in women of childbearing age [21]. A meta-analysis conducted by Grashuis and colleagues showed that bioprosthetic valves for females of childbearing age with plans for future pregnancies were preferred over mechanical valves even when considering the possibility of receiving safe continuous low-dose oral anticoagulation during pregnancy [22]. In this study, the rate of preoperative comorbidities did not vary between the groups except for the rates of hypertension and old stroke, which were greater in patients $\leq$ 50 years old and who underwent bioprosthetic AVR. This finding could be attributed to the tendency to avoid the risk of anticoagulation in those patients. There were no differences in hospital complications among groups; however, re-exploration for bleeding was higher in older patients with mechanical valves. Not all patients with bioprosthetic valves had warfarin postoperatively, which could explain the higher bleeding rate in older patients with mechanical valves.

The long-term use of aortic valve bioprostheses at a young age is controversial. Malvindi and colleagues conducted research comparing bioprosthetic and mechanical AVR in patients between 50 and 69 years old. They reported similar survival, greater bleeding with mechanical valves, and greater reintervention with bioprosthetic valves [23]. Chiang and colleagues reported a greater cumulative incidence of bleeding following mechanical valve replacement than following bioprosthetic valve replacement in patients aged 50–69 years, with greater reintervention with bioprosthetic valves and similar survival and stroke rates [24]. Traxler and associates compared the long-term outcomes of patients aged between 50 and 69 years with bioprosthetic and mechanical valves. They reported a lower risk of bleeding, better survival, and a lower risk of myocardial infarction in patients with mechanical valves [25]. On the other hand, the risk of stroke was similar between the two valves. Kyto and colleagues matched patients with mechanical and bioprosthetic valves aged 50 to 70. They reported lower mortality, reoperation, and infective endocarditis in patients with mechanical valves [26]. Zhao and colleagues performed a meta-analysis of studies comparing mechanical and bioprosthetic AVR in patients aged >50 years [27]. They reported similar survival rates but reduced bleeding and greater structural valve deterioration with bioprosthetic valves. These studies indicate that expanding the indications for bioprosthetic valves in patients aged >50 years should be performed with caution. The risk of reoperation is still high; however, the advancement of transcatheter aortic valve replacement has mitigated the risk of surgical reoperation [28]. Our study demonstrated comparable reintervention and survival rates between both prostheses in patients > 50 years; moreover, there was no increased risk of bleeding or stroke in patients with mechanical valves.

Few studies have reported data on aortic valve prostheses in patients $\leq$ 50 years. Hirji and colleagues reported comparable mid-term and long-term bleeding and survival in patients with mechanical and bioprosthetic AVR aged 50 years and younger; however, the risk of reoperation was greater with bioprosthetic valves [29]. Similar findings were reported in other studies [10,30]. A study by Corona and colleagues reported similar structural bioprosthetic aortic valve deterioration in young and old patients [31]. Our study

reported comparable survival, bleeding, and stroke rates in patients aged 50 years and younger; however, aortic valve reintervention remains an issue with bioprosthetic valves.

In summary, our study demonstrated that bioprosthetic and mechanical valves could be viable options for patients older than 50 years; however, bioprosthetic valves should be used with caution in younger patients because of the greater risk of reintervention.

Study Limitations

This study has limitations. First, the sample size was relatively small, with an uneven distribution across the different groups. These differences could be attributed to the current recommendations for aortic valve prostheses. Second, this was a single-center study, and using anticoagulation protocols and follow-up could affect the outcomes. Third, the study is retrospective, with inherent referral and selection biases. Fourth, the valve type could have affected the outcomes, which were not evaluated in this study. Finally, the long-term follow-up is limited. Most reinterventions for bioprosthetic valve degeneration occur after 10 years and not all patients in our study completed 10 years. Studies with longer follow-ups beyond 10 years are recommended.

5. Conclusions

Aortic valve replacement can be performed safely in adult patients using both biological and prosthetic valves, as they showed similar early survival rates. The outcomes of mechanical and bioprosthetic valves were comparable in patients older than 50 years. Using bioprosthetic valves in patients younger than 50 years was associated with a greater rate of valve reintervention, with no beneficial effect on the risk of bleeding or stroke.

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Review

Prosthesis–Patient Mismatch and Aortic Root Enlargement: Indications, Techniques and Outcomes

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Abstract: Prosthesis–patient mismatch (PPM) is defined as implanting a prosthetic that is insufficiently sized for the patient receiving it. PPM leads to high residual transvalvular gradients post-aortic valve replacement and consequently results in left ventricular dysfunction, morbidity and mortality in both the short and long term. Younger patients and patients with poor preoperative left ventricular function are more vulnerable to increased mortality secondary to PPM. There is debate over the measurement of valvular effective orifice area (EOA) and variation exists in how manufacturers report the EOA. The most reliable technique is using in vivo echocardiographic measurements to create tables of predicted EOAs for different valve sizes. PPM can be prevented surgically in patients at risk through aortic root enlargement (ARE). Established techniques include the posterior enlargement through Nicks and Manouguian procedures, and aortico-ventriculoplasty with the Konno–Rastan procedure, which allows for a greater enlargement but carries increased surgical risk. A contemporary development is the Yang procedure, which uses a Y-shaped incision created through the non- and left-coronary cusp commissure, undermining the nadirs of the non- and left-coronary cusps. Early results are promising and demonstrate an ability to safely increase the aortic root by up to two to three sizes. Aortic root enlargement thus remains a valuable and safe tool in addressing PPM, and should be considered during surgical planning.

Keywords: aortic root enlargement; prosthesis–patient mismatch; aortic stenosis; aortic valve surgery; adult cardiac surgery

1. Introduction and Definition of Prosthesis–Patient Mismatch

Aortic valve replacement is one of the most performed procedures in adult cardiac surgical practice. Prosthesis–patient mismatch (PPM) was first described in 1978 as a complication of aortic valve replacement [1]. It is defined as occurring when a prosthetic valve effective orifice area (EOA) is too small relative to the size of the patient it is being implanted in. When indexed relative to a patient's body surface area (BSA), it is expressed as the indexed EOA (iEOA). The degree of PPM can be expressed using the iEOA as follows: $\leq$0.85 cm^2/m^2—moderate PPM and $\leq$0.65 cm^2/m^2—severe PPM [2]. The definition has been recently updated by the valve academic research consortium 3 (VARC 3) criteria to also account for body mass index (BMI), as a high BSA would lead to the over-indexing of the iEOA and the overestimation of PPM. Thus, when BMI > 30 kg/m^2, mild PPM is present; moderate PPM is present when iEOA < 0.70 cm^2/m^2 and severe PPM is present when iEOA is <0.55 cm^2/m^2 [3,4] (Table 1). The incidence of PPM shows variation across different studies and patient cohorts, but a recent meta-analysis demonstrated an incidence of 53.7% (with a range of 6.1–93.8% in included studies), highlighting that it is a common phenomenon [5]. It impacts the prostheses used in both surgical (SAVR) as well as transcatheter (TAVR) aortic valve replacement. Therefore, it is important for heart teams to understand PPM, its clinical impact, and strategies to account for and mitigate PPM, which include aortic root enlargement (ARE).

Table 1. Definitions of PPM based on iEOA. Adjustments according to BMI are also included. PPM—prosthesis–patient mismatch, iEOA—indexed effective orifice area, BMI—body mass index.

Definition	iEOA	BMI Adjustment (>30 kg/m^2)
Moderate PPM	$\leq$0.85 cm^2/m^2	<0.70 cm^2/m^2
Severe PPM	$\leq$0.65 cm^2/m^2	<0.55 cm^2/m^2

2. Measuring and Predicting PPM

The measurement of prosthesis–patient mismatch (PPM) holds significant importance in various stages of both surgical and transcatheter intervention, including preoperative, intraoperative, and postoperative phases. Preoperatively, the assessment of PPM serves to guide the selection of appropriate valve choices. It aids in determining the optimal valve size that would mitigate the occurrence of PPM in potentially high-risk patients, such as those with a high BMI or poor LVEF. In some cases, it might highlight the necessity of performing root enlargement. In Tables 2 and 3, an example is highlighted using the Medtronic Hancock II and Carpentier–Edwards Perimount Magna prosthetic valve, simulating predicted iEOA for a variety of patient BSA values and valve sizes taken from the literature [6]. Using this table, we can see that a patient with a BSA of 2 m^2 will require a minimum size 27 Hancock II or size 21 Perimount Magna valve to avoid PPM. Furthermore, intraoperative PPM measurements facilitate a comprehensive evaluation of the implanted valve, thereby predicting the likelihood of PPM in the specific patient. Therefore, PPM assessment serves as a vital component in risk stratification, enabling the identification of patients who require closer follow-up and monitoring.

Table 2. Simulation of predicted iEOA for a range of patient BSA values and Medtronic Hancock II valve sizes. Moderate PPM values are highlighted in yellow, severe in red. BSA—body surface area, EOA—effective orifice area, PPM—prosthesis–patient mismatch.

Valve Size (mm)	EOA (cm^2)	Indexed EOA (cm^2/m^2)			
21	1.20	0.80	0.69	0.60	0.53
23	1.40	0.93	0.80	0.70	0.62
25	1.60	1.07	0.91	0.80	0.71
27	1.80	1.20	1.03	0.90	0.80
29	2.00	1.33	1.14	1.00	0.89
		1.50	**1.75**	**2.00**	**2.25**
		Patient BSA (m^2)			

Table 3. Simulation of predicted iEOA for a range of patient BSA values and Carpentier–Edwards Perimount Magna valve sizes. Moderate PPM values are highlighted in yellow. BSA—body surface area, EOA—effective orifice area, PPM—prosthesis–patient mismatch.

Valve Size (mm)	EOA (cm^2)	Indexed EOA (cm^2/m^2)			
19	1.58	1.05	0.90	0.79	0.70
21	1.90	1.27	1.09	0.95	0.84
23	2.07	1.38	1.18	1.04	0.92
25	2.33	1.55	1.33	1.17	1.04
27	2.38	1.59	1.36	1.19	1.06
29	2.84	1.89	1.62	1.42	1.26
		1.50	**1.75**	**2.00**	**2.25**
		Patient BSA (m^2)			

There are several methods that can be used to predict the iEOA prior to intervention. These are evaluated in a study by Bleiziffer et al. [7] who compared four different methods and calculated the correlation with postoperative in vivo transthoracic echocardiographic (TTE) measurements:

- Method 1—Using in house TTE data obtained from patients 6 months postoperatively to create "home-grown" iEOA charts (r = 0.62);
- Method 2—Using the geometric orifice area based on static parameters (the valve internal diameter specified by the manufacturer) (r = 0.27);
- Method 3—Using commercial iEOA charts, which are produced by using data obtained through various methods but can include in vitro measurements (varies based on manufacturer; r = 0.27–0.59 for four different valve types);
- Method 4—Using published EOA data from the literature (r = 0.53).

The authors concluded that the best methods were methods 1 and 4. The most reliable sources of data to make preoperative predictions about iEOA are echocardiographic studies involving large numbers of patients for each valve size. In the absence of data in in the literature, for example, in new valves, "Method 1" of creating an institutional database of TTE-measured EOA values should be used. Furthermore, use of in vitro data should be cautioned against. This is supported by a recent meta-analysis [5], which observed that regardless of whether predicted (by manufacturer or published in vivo data) or measured iEOA is used, the same correlation with outcomes (perioperative mortality) is found. Furthermore, each different method of preoperatively predicting iEOA showed different degrees of statistical heterogeneity when compared across the studies included in the meta-analysis, with Doppler echocardiography being the most reliable.

Counterarguments, however, have emerged. Two studies by Ternacle et al. showed that TTE-derived iEOA values demonstrate high variability, and suggest that this method overestimates PPM, compared with using predicted iEOA derived from manufacturer reference values [8,9]. Furthermore, they found that predicted iEOA correlated better with hemodynamic parameters (trans-prosthetic gradients and high residual gradients), whilst neither predicted nor measured iEOA correlated with clinical outcomes. The authors suggest that drawbacks of TTE measurements include inter-operator variability and the susceptibility of TTE to underestimate EOA in low-flow states [8,9]. However, a major drawback in the generalisability of these studies is that they looked at TAVR prosthetics as opposed to SAVR.

Another argument highlighting the limitations of TTE measurements is put forward by Vriesendorp et al. [10], who analyzed the predictive value of iEOA charts in a homogenous cohort of patients. They constructed "train" and "test" subgroups, wherein they measured EOA in the "train" cohort and tested the predictive value by comparing with the post-implant EOA in the "test" cohort. They demonstrated a large variation in measured EOA for each size of valve and a high degree of misclassification of PPM in the test cohort. Nonetheless, even using in vitro measurements, the correlation between projected iEOA (derived from iEOA charts created using TTE data from the train subset) and measured iEOA (in the test subset) was poor (r = 0.50) [10].

3. Clinical Impact of PPM

The impact of PPM on patients is profound. It can lead to higher morbidity and mortality and persistent symptoms, and accelerates the degeneration of bioprosthetic valves [2,11,12]. The most recently published large-scale clinical study involved 16,423 patients and demonstrated that severe PPM (adjudicated based on published EOA data and VARC3 criteria) impacted long-term (10 year) mortality, as well as leading to increased readmissions with heart failure [13]. However, the same study suggested that moderate PPM had a negligible effect. Therefore, some groups suggest that we may be too aggressive in taking steps to avoid moderate PPM, conducting more extensive surgeries for limited prognostic benefit [4].

There have been five meta-analyses looking at patient outcomes related to PPM. Sa et al. [5] included 108,182 patients with moderate and severe PPM, and demonstrated increased peri-operative mortality, and also mortality 1, 5, and 10 years after surgery. In a subgroup analysis, the mortality impact was worse in the severe PPM group compared to the moderate PPM group. Dayan et al. [14] assessed 40,381 patients (of which 813 had TAVR), and showed perioperative mortality was 56% higher and overall mortality 26%

higher in the PPM group. PPM also has an increased effect of worsening mortality in patients aged <70 or with concomitant coronary artery bypass grafting (CABG). When divided into subsets of severe and moderate PPM, severe PPM caused increased mortality in the perioperative period and in the long-term, but moderate PPM only did so in the perioperative period, indicating perhaps a vulnerability of the myocardium to increased afterload immediately post-surgery. Chen et al. [15] included 14,874 patients and showed that PPM increased mid-term (5-year) and long-term (10-year) mortalities by 42% and 52%, respectively. They showed that this was the case for all patient sub-populations with severe PPM, but not those with moderate PPM. Younger patients, women, and patients with poor preoperative left-ventricular ejection fraction (LVEF) showed worse long-term outcomes in the presence of any degree of PPM. In patients with impaired LVEF, both moderate and severe PPM increased both perioperative and long-term mortality. Takagi et al. [16] included 16,021 patients and demonstrated a 31% increased risk of late mortality in PPM. However, when stratifying patients according to severe or moderate PPM, only those with severe PPM showed an increase in hazard ratio for mortality. Head et al. [17] included 27,186 patients and demonstrated a 34% increase in all-cause, long term mortality for all definitions of PPM. Additionally, when stratified by degree of PPM, both moderate and severe PPM were associated with increased all-cause and cardiac mortality. Therefore, PPM is associated with increased morbidity and mortality, with severe PPM being strongly associated with worse outcomes, although the impact of moderate PPM is not consistent across the published literature.

A particular subgroup of patients who are at significant risk of poor outcomes due to PPM are those with poor LVEF. Blais et al. [18] showed that in patients with LVEF $\geq$ 40%, early mortality was relatively low with non-severe or moderate PPM (mortality rate 2–5%). However, for patients with LVEF < 40%, mortality was 16%, and it was 77% for both those with moderate and those with severe PPM. The authors suggest that this is because an impaired LV is more vulnerable to increased afterload. This will have implications for the management of potential PPM when deciding to treat these patients, as a poor LVEF will be a strong indication to undertake strategies to mitigate potential PPM.

4. Management of PPM by Aortic Root Enlargement

Given the consequences of PPM, efforts to address it must be considered—as per the 2021 ESC/EACTS Guidelines for the management of valvular heart disease, "*Efforts to prevent PPM should receive more emphasis to improve long-term survival after either SAVR or TAVI*" [19]. A proposed management scheme for PPM is described in a review by Bilkhu et al. [20], as shown below.

Preoperatively predict the iEOA of a chosen prosthesis for a patient, and then:

1. Proceed with the selected prosthesis if the predicted iEOA is >0.85.
2. If the predicted iEOA is $\leq$0.85 then:
   - Accept PPM in certain clinical contexts;
   - Choose a prosthetic with larger EOA;
   - Carry out an aortic root enlargement.

In terms of choosing a prosthetic with a larger EOA, some valve designs have larger EOA values for the same size of valve. This is demonstrated in Tables 2 and 3 above, which show that for the same label size, a Carpentier–Edwards Perimount Magna has a larger EOA than a Medtronic Hancock II prosthesis. Additionally, newer-generation prosthetic valves are being produced, which have larger EOAs with the same external diameter. Stentless valves such as the Corcym Perceval valves also have larger EOAs [21], as do TAVR prostheses. Sutureless aortic valves [22] and TAVR valves [23] both offer larger EOAs due to the lack of a sewing ring [24]. Certainly, TAVR appears to confer advantages over SAVR in terms of a reduced incidence of PPM. Studies show that in TAVR, the incidence of moderate PPM is around 6–46%, and for severe PPM the incidence ranges from 0 to 15% [25]. A meta-analysis demonstrated a 77% relative risk reduction in TAVR patients of developing PPM [26], and a recent analysis of the PARTNER 2 trial data showed that

there was a decreased incidence of PPM in the TAVR group (9.3%) vs. the SAVR group (27.9%) [9]. TAVR valves were advantageous in terms of having reduced transvalvular gradients, greater EOAs and reduced risk of PPM compared to SAVR [25]. However, newer-generation TAVR devices seem to have diminished advantages (i.e., higher rates of PPM) due to a reduction in EOA on account of external skirts designed to mitigate paravalvular leak [27]. Therefore, a variety of patient- and operation-related factors must be considered on a case-by-case basis and after undertaking a heart team multidisciplinary discussion before counselling patients and obtaining informed consent to proceed with an aortic root enlargement.

Indications for aortic root enlargement are risk of postoperative PPM, as defined above. Severe PPM would be a strong indication, with moderate PPM being a more controversial indication due to the conflicting evidence relating to its impact on clinical outcomes, with some studies suggesting a negligible effect of moderate PPM on morbidity and mortality [13]. Certainly, some authors urge caution with being too aggressive in prospectively avoiding PPM, as the operative risk of a root enlargement will outweigh the benefit in treating a moderate PPM [4]. Some patient-related factors will also influence this decision. For example, patients with a poor LVEF will be at high risk of early mortality if there is PPM post-AVR [18]. Demographic factors are also important. Sa et al. discuss this from a global health perspective in their recent meta-analysis [5]: in developed countries, a common scenario is deciding to implant a small, 21 mm prosthesis in a short, obese, frail elderly female patient with calcific aortic stenosis and a low functional baseline. A degree of PPM would be acceptable in this case [5]. In a developing country, a possible scenario would be having to replace rheumatic aortic valves in younger, more active patients wherein avoiding PPM would be a higher priority [5]. A further dimension to consider is that patients in developed countries will be implanted with newer prosthetics with better hemodynamic profiles [5]. Finally, the choice of a mechanical versus bioprosthetic valve should also be considered. Although calcific aortic stenosis predominantly affects older patients, younger patients with diseases such as bicuspid aortic valves are suitable candidates for mechanical valve prostheses, which, due to their construction, tend to have larger EOAs and better hemodynamic performance compared to similarly sized bioprosthetic valves [6,28].

5. Established Techniques of Aortic Root Enlargement

Aortic root enlargement techniques have traditionally been considered in two categories: posterior enlargement techniques (the Nicks and Manouguian techniques, Figure 1) and complex, less-commonly performed, anterior enlargement with aorto-ventriculoplasty (the Konno–Rastan procedure, Figure 1) [29–31]. ARE accounts for less than 1 in 10 of all aortic valve replacement procedures in the STS database [32] and for around 3% of all aortic valve surgeries in a recent meta-analysis of 213,134 patients [33], although it is increasingly being advocated for as PPM is being increasingly recognised as an Important issue to address [5,33–35].

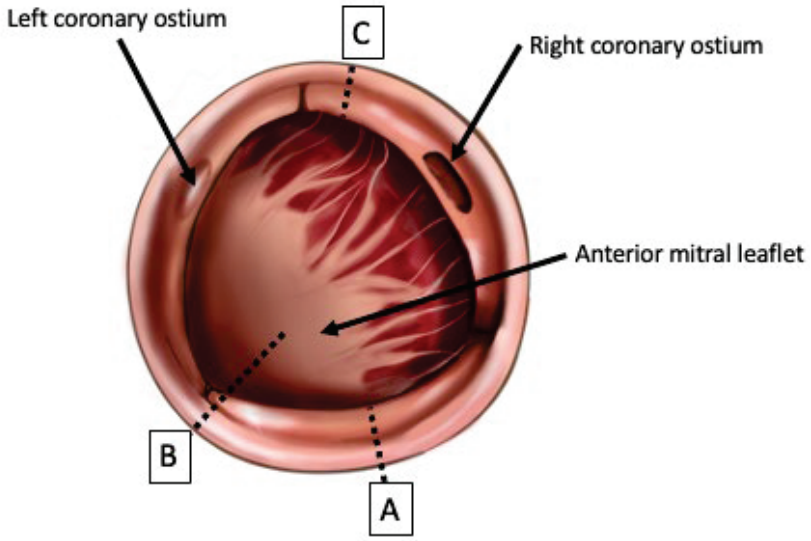

Figure 1. Surgical anatomy of the aortic root, with valve leaflets excised, with incision lines for the Nicks procedure ((**A**): through the non-coronary cuspJ); the Manouguian procedure ((**B**): through the commissure between the non- and left-coronary cusps and extending into the anterior mitral leaflet), and the Konno–Rastan procedure ((**C**): through the right coronary cusp and (not drawn) continuing into the interventricular septum via the aortic annulus). Informed by [29,31,36–38].

5.1. Techniques of Aortic Root Enlargement

The Nicks procedure was first described in 1970 [36]. Briefly, it involves extending the aortotomy incision into the non-coronary sinus of the aortic root and then performing a patch repair to the defect to repair and enlarge the annulus. The Manouguian technique was first described in 1979 [37], and involves the same steps, but instead of cutting through the non-coronary sinus, the aortotomy incision is continued through the commissure between the left- and non-coronary sinuses, and may be extended to the anterior mitral curtain to allow for further up-sizing [29]. A variation of this technique is the Manouguian–Nunez procedure, whereby the incision stops short of being extended into the anterior mitral leaflet [31]. Additionally, the Manouguian technique involves opening the roof of the left atrium. Consequently, there is a degree of risk of mitral regurgitation with the Manouguian procedure [39].

The Konno–Rastan procedure, first described in 1975 [40], is a more complex operation and involves an anterior incision and aortoventriculoplasty. The aorta is transected anteriorly in a longitudinal fashion, and the cardiomyotomy carried through the right coronary sinus and aortic annulus and through to the interventricular septum. The anterior surface of the right ventricle is also opened, and the right ventricular outflow tract enlarged. A double-patch repair is then used to repair the defects in the aorta, interventricular septum and RVOT [38]. Care must be taken during this procedure to avoid injuring important structures: the initial incision through the right coronary cusp must pass near the commissure between the right and left coronary sinuses to avoid damaging the cardiac conduction system, and when incising the right ventricular free wall, care must be taken to avoid damaging the right coronary artery [31,38]. There is an additional risk of the formation of intracardiac fistulae between the chambers [31].

Although it carries an increased operative risk due to the complexity of the enlargement and repair, the Konno–Rastan procedure allows for more enlargement than the Nicks and Manouguian techniques. The Nicks procedure generally allows for enlargement by one size, the Manouguian by two sizes [31]; the Konno–Rastan procedure allows for greater enlargement than either, with up to three to four sizes of increase [41]. However, the Nicks procedure remains the most commonly performed procedure, perhaps due to the ease of carrying it out and the short learning curve suggested by some authors [31,42].

5.2. Outcomes of Aortic Root Enlargement Procedures

The "established" (i.e., Nicks and Manouguian) procedures for ARE have been extensively studied and demonstrated to be safe in experienced centers, although there are risks that much be considered at the time of surgical planning. Yu et al. conducted a meta-analysis, which included 8561 patients of whom 2570 underwent ARE [43]. The group, which underwent ARE, had increased cross-clamp and bypass times [43], and this is consistent with a large, contemporaneously published propensity-matched retrospective cohort study, which showed increased cross-clamp, bypass and total operative times [44]. Therefore, the additional operative steps required to conduct ARE prolong the operation, and risks of perioperative complications must be considered.

Studies have also examined the postoperative complications of ARE. There appears to be no increased risk of conduction defects (complete heart block, permanent pacemaker implantation), ischemic events (myocardial infarction, stroke), or re-operation for bleeding [35,43,44]. However, one study [44] did report an increased occurrence of respiratory failure in the ARE group (18.3% vs. 9.5%). In this study, ARE was not independently correlated with risk of increased mortality; however, postoperative respiratory failure was (HR 2.84) [44]. Hence, despite the association, postoperative respiratory failure ARE can nevertheless be performed safely.

ARE is effective in treating PPM, "nd r'duces moderate and severe PPM while significantly increasing the postoperative aortic valve EOA [34,43,45]. The effect on perioperative mortality, however, is more contentious. Some studies report no increase in perioperative mortality [43,44]. Other studies report increased short-term mortality [34,35,46]. However, in two of these studies, when adjusting for confounders by matching cohorts or when excluding ARE performed concomitantly with other surgeries such as mitral valve surgery and coronary artery bypass grafting, the perioperative mortality risk was deemed not significant [34,35]. When considering long-term outcomes, Yu et al. [43] had a mean follow up of 7.8 years, and Sa et al. [33] had a median follow up of 3 years, while both show no difference in late mortality. Mehaffey et al. conducted a recent, large study including 5412 patients who underwent ARE from the Society of Thoracic Surgeons (STS) database, and demonstrated that although there was a short-term morbidity and mortality risk associated with ARE, the survival curves crossed over at the 3-year mark in favor of the ARE arm compared to 183,856 patients who underwent SAVR ± CABG without ARE [47]. Therefore, when considering the option of ARE, the short-term risk of increased complications and mortality must be weighed against the long-term advantage of addressing PPM in select patients. Decision-making will benefit from future randomized clinical trials, as all the evidence so far is derived from non-randomized studies.

6. Contemporary Developments in ARE: The Yang Procedure

The Y incision technique is a novel technique of aortic root enlargement that was first described in 2021 [48], and was subsequently named the "Yang procedure" [49]. It involves making an incision through the commissure between the non- and left-coronary cusps, into the aortomitral curtain, and extending it to create an inverted "Y" shape undermining the left and noncoronary cusps (Figure 2). A rectangular patch repair of the resultant defect is then carried out. The Yang procedure enlarges the fibrous part of the aortic root and thereby the annulus—similar to the Nicks and Manouguian techniques [48]. However, the Yang procedure does not enlarge the basal ring of the aortic root, in contrast to what is achieved in the Nicks, Manouguian and Konno–Rastan procedures [50].

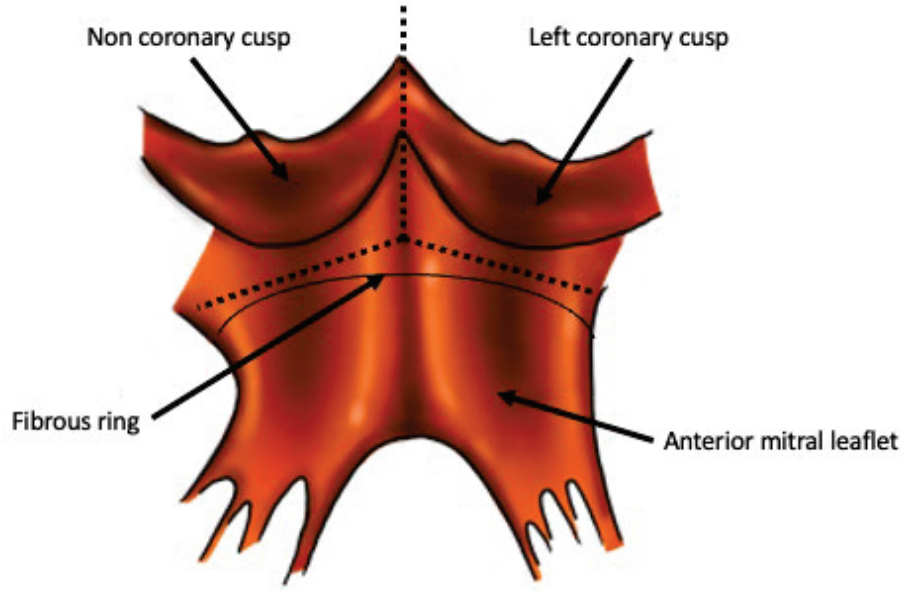

Figure 2. Incisions for the Yang procedure. The view of the aortic root is from the inside out, with excised aortic valve leaflets. The Y-shaped incision is created by incising between the non- and left-coronary cusps and extending the incision to undermine either cusp. Informed by [48].

A subsequent addition to this procedure was described in 2022, dubbed the "Roof technique"; this involves an incision and triangular-shaped patch repair of the ascending aorta above the previously described rectangular patch repair. This is undertaken via aortotomy closure, which allows for concomitant aortic enlargement in a proximal–distal fashion [51]. It enables the straightening out of any kinks between the native ascending aorta and the newly enlarged root, effacing the sinotubular junction and thus preparing the patient for a future valve-in-valve TAVR [50].

There are advantages to the Yang technique over the Nicks and Manouguian. Some surgeons may be hesitant about performing a Manouguian procedure due to the risk of mitral regurgitation, therefore stopping the incision before the anterior mitral leaflet (sometimes called a modified Manouguian or a Manouguian–Nunez procedure) [52]. This will protect the mitral valve, but will not allow for a significant up-sizing. The Yang procedure manages to create a significant upsizing while reducing risk to the mitral valve by extending the incision in an inverted Y-shape and undermining the left- and non-coronary cusps. This leaves a margin of tissue above the aortomitral curtain, reducing traction on the anterior mitral leaflet. Ultimately, the left atrium and mitral valve are not violated, and a greater degree of annular upsizing can be achieved [48]. In addition to ameliorating PPM, this will also allow for "future proofing" as the larger prosthetic will make a subsequent valve-in-valve TAVR easier to achieve [53].

There are concerns that a situation similar to subvalvular stenosis would arise as a result of the Yang procedure due to the LVOT and basal ring of the aortic root not being enlarged and the prosthesis being implanted in a supra-annular location [54]. However, the internal diameter of prosthetic valves is often smaller than the labeled diameter, due to structures such as the sewing ring and struts of the prosthesis and aortic annular tissue from the residual annulus [50]. The Yang procedure also allows for both the supra-annular and the intra-annular implantation of prosthetic valves [50]. Furthermore, not enlarging the basal ring will not have a functional consequence, since the basal ring is normally sized even with stenotic aortic valves, and is not the site of flow limitation [50]. This is supported by computed tomography imaging, which shows the implanted valve sitting on the LVOT like a "crown on a head", with satisfactory hemodynamics, further supported by the mean pressure gradient across the LVOT remaining unchanged from preoperative measurements [50].

Additionally, there are concerns regarding the distortion of the aortic root anatomy, arising due to the significant upsizing achieved by this procedure. Firstly, over-sized prostheses being implanted could increase risks of compromising the closure of the aortotomy or causing coronary ostial obstruction [54]. Secondly, the rectangular patch repair of the aortic annulus causes a rotation of the left coronary ostium, which may increase the risk of coronary obstruction due to distortion and kinking [52,55]. The left coronary ostium will rotate by approximately 90°, and caution must be exercised if there is coronary artery disease, as not properly mobilizing the ostium before rotation could lead to luminal compromise [55]. Further investigations should be undertaken, such as radiological evaluations of the anatomical implications of manipulating the aortic root and left coronary ostium in this technique [55]. Finally, due to the tilting of the prosthetic valve during implantation, turbulent periprosthetic blood flow could lead to worsening bioprosthetic degradation [24]. However, this has been addressed with the addition of the "roof procedure", which straightens out the sinotubular junction and ascending aorta, and postoperative-computed tomography shows a well aligned valve laying perpendicular to direction of blood flow [50].

The index case report [48] showed an increase of two valve sizes, with subsequent case reports showing increases of three [56], four [57] and five valve sizes [58], as the authors increased in experience with the procedure. Early outcomes of 50 consecutive patients undergoing the Yang technique have been reported. Median annular enlargement was by three valve sizes, and a reduction in mean aortic valve gradient from 40 mmHg to 7 mmHg from pre- to post-operative stages, respectively [59]. There was no operative mortality and no major complications (such as reopening for bleeding, chronic dialysis-dependent renal failure) except for one case of stroke, and there was zero mortality at 18 months follow-up [59]. However, only 25 of 50 the patients in this early outcome paper underwent the "roof technique", although there was no significant hemodynamic difference in those the "roof technique" was carried out in compared to those where it was not [50]. Thus, the Yang procedure is a promising new technique, although data on long-term outcomes will not be available before widespread adoption can take place.

7. Conclusions

PPM is increasingly recognised as a significant complication/consequence of AVR. The role of moderate PPM is unclear, but severe PPM is strongly associated with poor long-term morbidity and mortality. Strategies to address PPM include sutureless prosthetics, TAVR and the usage of new-generation valves with bigger EOAs. Aortic root enlargement is another strategy to up-size aortic roots with two well-established procedures, the Nicks and Manouguian procedures, although these are rarely performed, and data on outcomes are limited to non-randomized studies. The Yang procedure is a recent development that allows for a much larger degree of enlargement, but there are no data on long-term outcomes. The significant increase in annulus size will not only help address PPM, but will also facilitate future valve-in-valve TAVR, providing a long-term solution for younger patients.

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Mid-Term Clinical Outcomes and Hemodynamic Performances of Trifecta and Perimount Bioprostheses following Aortic Valve Replacement

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Abstract: Aims of the Study: We evaluated the clinical outcome and the hemodynamic and freedom from structural valve degeneration of two standard aortic bioprostheses. **Methods:** Clinical results, echocardiographic findings and follow-up data of patients operated for isolated or combined aortic valve replacement with the Perimount or the Trifecta bioprosthesis were prospectively collected, retrospectively analysed and compared. We weighted all the analyses by the inverse of the propensity of choosing either valves. **Results:** Between April 2015 and December 2019, 168 consecutive patients (all comers) underwent aortic valve replacement with Trifecta (n = 86) or Perimount (n = 82) bioprostheses. Mean age was 70.8 ± 8.6 and 68.8 ± 8.6 years for the Trifecta and Perimount groups, respectively ($p = 0.120$). Perimount patients presented a greater body mass index (27.6 ± 4.5 vs. 26.0 ± 4.2; $p = 0.022$), and 23% of them suffered from angina functional class 2–3 (23.2% vs. 5.8%; $p = 0.002$). Mean ejection fraction was 53.7 ± 11.9% (Trifecta) and 54.5 ± 10.4% (Perimount) ($p = 0.994$), with mean gradients of 40.4 ± 15.9 mmHg (Trifecta) and 42.3 ± 20.6 mmHg (Perimount) ($p = 0.710$). Mean EuroSCORE-II was 7 ± 11% and 6 ± 9% for the Trifecta and Perimount group, respectively ($p = 0.553$). Trifecta patients more often underwent isolated aortic valve replacement (45.3% vs. 26.8%; $p = 0.016$) and annulus enlargement (10.5% vs. 2.4%; $p = 0.058$). All-cause mortality at 30 days was 3.5% (Trifecta) and 8.5% (Perimount), ($p = 0.203$) while new pacemaker implantation (1.2% vs. 2.5%; $p = 0.609$) and stroke rate (1.2% vs. 2.5%; $p = 0.609$) were similar. Acute MACCE were observed in 5% (Trifecta) and 9% (Perimount) of patients with an unweighted OR of 2.22 (95%CI 0.64–7.66; $p = 0.196$) and a weighted OR of 1.10 (95%CI: 0.44–2.76, $p = 0.836$). Cumulative survival at 24 months was 98% (95%CI: 0.91–0.99) and 96% (95%CI: 0.85–0.99) for Trifecta and Perimount groups, respectively (log-rank test; $p = 0.555$). The 2-year freedom from MACCE was 94% (95%CI: 0.65–0.99) for Trifecta and 96% (95%CI: 0.86–0.99) for Perimount (log-rank test; $p = 0.759$, HR 1.46 (95%CI: 0.13–16.48)) in the unweighted analysis (not estimable in the weighted analysis). During the follow-up (median time: 384 vs. 593 days; $p = 0.0001$) there were no re-operations for structural valve degeneration. Mean valve gradient at discharge was lower for Trifecta across all valve sizes (7.9 ± 3.2 vs. 12.1 ± 4.7 mmHg; $p < 0.001$), but the difference did not persist during follow-up (8.2 ± 3.7 mmHg for Trifecta, 8.9 ± 3.6 mmHg for Perimount; $p = 0.224$); **Conclusions:** Postoperative outcome and mid-term follow-up were similar. An early better hemodynamic performance was detected for the Trifecta valve but did not persist over time. No difference in the reoperation rate for structural valve degeneration was found.

Keywords: aortic valve prosthesis; aortic valve replacement; perimount bioprosthesis; Trifecta bioprosthesis

1. Introduction

The current lifetime management of aortic valve disease will align the surgical and transcatheter armamentarium, with particular focus on optimized prosthetic hemodynamic and management of structural valve degeneration (SVD). Many commercially available aortic valves have undergone clear improvements over the recent years; hence, identifying optimal durable and performing surgical bioprostheses is of paramount importance. The current surgical landscape offers a multitude of bioprostheses, including the Perimount (Edwards Lifesciences, Irvine, CA, USA) and the Trifecta (Abbott Laboratories, Abbott Park, IL, USA) [1]. The Perimount is a choice supported by numerous records attesting good hemodynamic and durability, low incidence of patient–prosthesis mismatch (PPM), and rates of survival and valve-related complications comparable if not superior to other valves [2–6]. The Trifecta is a supra-annular bovine pericardial stented bioprosthesis which has demonstrated favourable hemodynamics in the short term compared to Perimount: lower mean gradient, lower maximum blood velocity, and larger orifice size at rest and during exercise [7–11]. This promising performance has increased its approval, with a resultant popularity in usage. More large studies have also proved comparable or slightly lower rates of mortality and congestive heart failure, supporting the consensus surrounding the Trifecta [9,12–14]. However, a Trifecta mid-term data analysis reports contradictory outcomes. On one side, recent studies have demonstrated Trifecta associated with higher early SVD and higher reinterventions rate, while others have reported comparable results with the Perimount [15–20]. This study aims to report our experience with Trifecta and Perimount stented pericardial aortic bioprostheses, evaluating hemodynamic performances and outcomes at discharge and mid-term follow-up, along with freedom from SVD at mid-term follow-up.

2. Materials and Methods

2.1. Study Population

The study population includes all consecutive patients who underwent aortic valve replacement (AVR) with a biological bioprostheses at Cardiocentro Ticino Institute between April 2015 and December 2019. Patients received the Trifecta (n = 86) or the Perimount Magna Ease aortic valves (n = 82) depending on surgeon's preference. We included all-comer elective and urgent patients undergoing isolated or combined AVR procedures such as surgery of the ascending aorta and/or coronary artery bypass grafting (CABG), and/or additional valve surgery, and aortic root enlargement. Patients with AVR in combination with acute type-A dissection and redo procedures were also included. During the study period, other types of aortic valve prosthesis were used, such as transcatheter prostheses, mechanical valves or sutureless prosthesis, but these are not the object of the present study. In elective surgery, all patients signed informed consents for surgery and the use of their medical records for research and quality control purposes. Ethics approval was granted by the local ethics committee (project ID number: 2016-02166-CE 3153). The present investigation abides by the principles outlined in the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). Clinical results, echocardiographic findings and follow-up data of all patients were prospectively collected, retrospectively analysed and compared. Patient demographics were tracked from medical records, and selected variables were compared between the two groups. Operative data and intraoperative variables were recorded in a prospective surgical database and retrospectively extracted and evaluated. Patients in both groups underwent clinical and echocardiographic assessment before surgery, at discharge and during follow-up. Echocardiographic measurements were acquired according to the current recommendations [21]. The incidence of PPM was calculated following standard guidelines (not clinically significant (iEOA: >1 cm^2/m^2), mild (iEOA: <1 and >0.85 cm^2/m^2), moderate (iEOA: <0.85 and >0.65 cm^2/m^2), and severe (iEOA: <0.65 cm^2/m^2)). SVD was defined according to the European Association of Cardio-Thoracic Surgery/European Association of Percutaneous Coronary Intervention, VIVID (Valve-in-Valve International Database), and VARC 3 (Valve Academic Research

Consortium–3) statements, based on the identification of morphologic and hemodynamic valve deterioration of aortic bioprosthetic valves at echocardiographic follow-up [22–24].

Follow-up was performed by contacting the patient's general practitioner or the cardiologist. Echocardiographic evaluation was performed annually or earlier based on the patient's clinical status. Patients without a cardiologist were contacted by phone or e-mail to perform an echocardiographic exam at our institution one year after the procedure. After discharge, almost all patients that had major adverse cardiac and/or cerebrovascular events were referred to our institution as the reference hospital in the Tessin Canton, and therefore, all major adverse events were captured by searching the patient's internal clinical history.

2.2. Study Endpoints

The primary endpoint was the hemodynamic performance of Trifecta and Perimount aortic valves at discharge and at mid-term follow-up together with the early and mid-term clinical outcomes. Single clinical outcomes as well as the combined endpoint of major adverse cardio-cerebral events (MACCE) were considered. The secondary endpoint was the freedom from structural valve degeneration at mid-term follow-up.

2.3. Surgical Details

A preoperative computed tomography scan was routinely performed to evaluate the ascending aorta in patients with chronic ascending aortic aneurysm and type-A dissection or in patients candidate for minimally invasive surgery. AVR was performed through full sternotomy or upper mini-sternotomy, and valve fixation was carried out using either running sutures or multiple U-fashion stitches reinforced with pledgets. If needed, an aortic annulus enlargement was performed. Prostheses type and size were intraoperatively determined. Postoperatively, all patients received anticoagulation therapy for 3 months, with an international normalized ratio therapeutic level of 2.0–3.0, followed by aspirin 100 mg per day, unless the patient required full anticoagulation.

2.4. Statistical Analysis

All the analyses were performed using the Stata software (release 16, StataCorp, College Station, TX, USA); all p values were two-sided. Propensity (PS) of choosing a Perimount rather than a Trifecta valve was estimated based on a logistic regression model that included a wide series of baseline characteristics, to enable analyses weighted by the inverse of the probability of choosing a Perimount valve and to adjust analyses for differences in clinical and echocardiographic characteristics at admission between Perimount and Trifecta patients. The lower 2.5 and upper 97.5 percentiles of the score were trimmed. The balancing properties of the propensity score were good, resulting in comparable cohorts. The common support was assessed graphically using kdensity plots, showing a good overlap (Supplementary Figure S1); 133 out of 168 patients were retained in the weighted analysis. The model included the following variables: gender, age, BMI, hypertension, smoking status, diabetes with insulin treatment, peripheral vascular disease, chronic lung disease, chronic kidney failure, New York Heart Association classes III–IV, Canadian cardiovascular society angina functional classes 2–3, critical state, active endocarditis, previous cardiac surgery, recent myocardial infarction, EuroSCORE-II value, urgent timing, aortic stenosis, mean pre-operative left ventricular ejection fraction (LVEF), pre-operative pulmonary hypertension, surgery on thoracic aorta and size of aortic prosthesis. These variables were deemed potential confounders of the relationship of type of valve and clinical outcome [25,26]. The study population was described using the mean and standard deviation (±SD) or the median and quartile for continuous variables and using counts and percent for categorical variables in the original and matched cohorts. To compare them, Student's t or the Mann–Whitney U test and Fisher's exact test were used. Logistic regression models to assess 30-day mortality by valve and Cox regression models to assess outcomes over follow-up were used. The odds ratios (OR) and hazard ratios (HR) were reported with their 95% confidence intervals (95%CI). To compare survival, the log-rank test was used. We assessed the proportional hazard assumption graphically by comparing

the observed and expected survivals. Generalized regression models to compare continuous echocardiographic characteristics were used. Both weighted and unweighted models were fitted, the latter to control for confounding by indication through the PS.

3. Results

A total of 294 isolated or combined AVR were performed between April 2015 and December 2019, including 72 transcatheter procedures, 20 AVR with mechanical valves and 34 with rapid deployment valves. During the same period, 86 Trifecta and 82 Perimount Magna Ease were implanted. Baseline characteristics and echocardiographic data are listed in Table 1. Mean age was 70.8 ± 8.6 and 68.8 ± 8.6 years for the Trifecta and Perimount group, respectively (p = 0.120). With regard to comorbidity, patients receiving a Perimount valve presented a greater body mass index (27.6 ± 4.5 vs. 26.0 ± 4.2; p = 0.022), and 23% of them were diagnosed with angina functional class 2–3 (23.2% vs. 5.8%; p = 0.002). However, when comparisons were weighted by the PS, these differences were not observed. Previous cardiac surgery (10.5% vs. 6.1% for Trifecta and Perimount, respectively; p = 0.405) and urgency (13.4% vs. 16.3%; p = 0.668) did not differ between the groups. The median EuroSCORE-II was also similar: 3.0% (IQR 2.0–8.0) for Trifecta and 3% (IQR 1.0–6.0) for Perimount. The Trifecta cohort had a smaller mean aortic valve area (0.8 ± 0.3 vs. 0.9 ± 0.3 cm^2; p = 0.046), although it vanished in the weighted analysis. The mean valve gradients did not differ: 40.4 ± 15.9 mmHg for Trifecta and 42.3 ± 20.6 mmHg for Perimount group; in the weighted analysis population, we observed a greater mean gradient in the Perimount group (47.9 ± 19.2 vs. 41.7 ± 15.2 mmHg; p = 0.042). Overall, the LVEF, the aetiology of the aortic disease and the association with pulmonary hypertension were similar between groups, for both unweighted and weighted analyses.

Table 1. Baseline and preoperative echocardiographic characteristics.

	Unweighted Population (Total 168)			**Weighted Population (Total 133)**		
	Trifecta n 86	**Perimount n 82**	***p* Value**	**Trifecta n 79**	**Perimount n 54**	***p* Value**
Age, (years) *	70.8 ± 8.6	68.8 ± 8.6	0.120	70.5 ± 8.5	69.4 ± 7.5	0.931
Male sex *	63 (73.2)	68 (82.9)	0.141	57 (72.1)	43 (79.6)	0.970
BMI (Kg/m^2) *	26.0 ± 4.2	27.6 ± 4.5	**0.022**	26.0 ± 4.1	27.1 ± 4.4	0.826
Hypertension *	62 (72.1)	65 (79.3)	0.288	57 (72.1)	42 (77.8)	0.989
Hypercholesterolemia	47 (54.6)	51 (62.2)	0.350	43 (54.4)	35 (64.8)	0.449
Smoking *	33 (38.4)	38 (46.3)	0.349	31 (39.2)	23 (42.6)	0.635
Diabetes with insulin treatment *	3 (3.5)	6 (7.3)	0.321	3 (3.8)	2 (3.7)	0.739
Peripheral vascular disease *	15 (17.4)	12 (14.6)	0.678	12 (15.2)	9 (16.7)	0.997
Chronic lung disease *	8 (9.3)	11 (13.4)	0.469	7 (8.8)	7 (12.9)	0.943
† Chronic kidney disease *	...	...	0.180	...	...	...
Severely decreased	6 (6.9)	11 (13.4)	...	6 (7.6)	8 (14.8)	0.204
Kidney failure	1 (1.2)	0 (0.0)	...	-	-	-
NYHA class III-IV *	26 (30.2)	28 (34.1)	0.623	24 (30.4)	18 (33.3)	0.732
CCS Angina score class 2–3 *	5 (5.8)	19 (23.2)	**0.002**	5 (6.3)	4 (7.4)	0.166
Critical state *	11 (12.8)	8 (9.7)	0.629	8 (10.1)	5 (9.3)	0.709
Active endocarditis *	7 (8.1)	3 (3.7)	0.330	5 (6.3)	2 (3.7)	0.434
Previous cardiac surgery *	9 (10.5)	5 (6.1)	0.405	8 (10.1)	3 (5.6)	0.339
Recent myocardial infarction *	7 (8.1)	6 (7.3)	1.000	5 (6.3)	3 (5.6)	0.622
EuroSCORE-II *	3 (IQR: 2–8) (Mean: 7 ± 11)	3 (IQR: 1–6) (Mean: 6 ± 9)	0.553	2 (IQR: 1.7) (Mean: 6 ± 9)	3 (IQR: 1–5) (Mean: 5 ± 6)	0.445
Urgent timing *	14 (16.3)	11 (13.4)	0.668	10 (12.6)	7 (12.9)	0.758
Prevalent aortic valve stenosis *	60 (69.7)	56 (68.3)	0.869	58 (73.4)	39 (72.2)	0.604
Prevalent aortic valve regurgitation	34 (39.5)	37 (45.1)	0.533	30 (37.9)	24 (44.4)	0.952
Mean left ventricular ejection fraction (%) *	53.7 ± 11.9	54.5 ± 10.4	0.994	54.3 ± 11.9	54.2 ± 11.1	0.780
Mean aortic valve area (cm^2)	0.8 ± 0.3	0.9 ± 0.3	**0.046**	0.8 ± 0.3	0.9 ± 0.4	0.792
Mean gradient (mmHg)	40.4 ± 15.9	42.3 ± 20.6	0.710	41.7 ± 15.2	47.9 ± 19.2	**0.042**
Pulmonary hypertension *	21 (24.4)	18 (21.9)	0.719	17 (21.5)	13 (24.1)	0.923

Continuous variables are presented as mean ± standard deviation or the median and quartile; categoric variables are presented as counts and percentage; p value is a Student's t test or Mann–Whitney U test for continuous variables and a Fisher's exact test for categorical variables. Abbreviations: BMI, body mass index; NYHA, New York heart association; CCS, Canadian Cardiovascular Society. † Chronic kidney disease is defined according to the KDIGO CKD Work Group clinical practice guidelines. * Variables used for propensity score.

3.1. Procedural Details

Patients receiving the Trifecta more often underwent isolated AVR procedures (45.3% vs. 26.8%; p = 0.016), more commonly associated with annulus enlargement (10.5% vs. 2.4%; p = 0.058) (Table 2). The need for aortic annulus enlargement persisted in the weighted analysis (11.4% vs. 1.8%; p = 0.001), although the isolated AVR procedures were equally distributed (46.8% vs. 38.9%; p = 0.545). The Perimount group had more combined procedures such as AVR plus mitral valve repair and CABG (4.8% vs. 0%; p = 0.05) and more often required mechanical support, such as an intra-aortic balloon pump, which became significant in the weighted analysis populations (7.4% vs. 1.2%; p = 0.026). Mean cardiopulmonary bypass time was longer for the Perimount group, although non-significant, (142 ± 67 vs. 137 ± 57 min; p = 0.962), while a longer aortic cross-clamp time became significant for the Perimount weighted analysis population (99 ± 33 vs. 95 ± 41 min; p = 0.052). Concerning the mean valve size, groups were similar: 24.1 ± 2.1 mm for Trifecta and 24.5 ± 1.9 mm for Perimount (p = 0.102) in the unweighted analysis populations; 24.0 ± 2.0 mm for Trifecta and 24.6 ± 1.9 mm for Perimount (p = 0.771) in the weighted analysis populations.

Table 2. Procedural details.

	Unweighted Population (Total 168)			Weighted Population (Total 133)		
	Trifecta n 86	**Perimount n 82**	***p* Value**	**Trifecta n 79**	**Perimount n 54**	***p* Value**
Surgical access:						
Sternotomy	55 (63.9)	55 (67.1)	0.746	49 (62.0)	33 (61.1)	0.340
Upper mini sternotomy	32 (37.2)	30 (36.6)	1.000	31 (39.2)	24 (44.4)	0.143
Conversion to sternotomy	2 (2.3)	4 (4.9)	0.435	2 (2.5)	3 (5.6)	0.221
Isolated aortic valve replacement	39 (45.3)	22 (26.8)	**0.016**	37 (46.8)	21 (38.9)	0.545
Combined procedure:						
CABG	18 (20.9)	16 (19.5)	0.850	17 (21.5)	7 (12.9)	0.313
Ascending aorta replacement *	6 (6.9)	9 (10.9)	0.424	6 (7.6)	6 (11.1)	0.933
Ascending aorta replacement plus CABG	1 (1.2)	3 (3.9)	0.359	1 (1.27)	1 (1.85)	0.983
Bentall	11 (12.8)	18 (21.9)	0.153	10 (12.6)	10 (18.5)	0.944
CABG plus mitral valve repair	0 (0)	4 (4.8)	**0.055**	0 (0)	2 (3.7)	...
Bioprosthesis mean size (mm)	24.1 ± 2.1	24.5 ± 1.9	0.102	24.0 ± 2.0	24.6 ± 1.9	0.771
Valve size distribution: *	...	...	0.050	...	...	...
19	1 (1.2)	0 (0.0)	...	1 (1.3)	0 (0.0)	-
21	10 (11.6)	8 (9.7)	...	9 (11.4)	5 (9.3)	0.664
23	36 (41.8)	24 (29.3)	...	34 (43.0)	16 (29.6)	0.380
25	23 (26.7)	30 (36.6)	...	22 (27.8)	18 (33.3)	0.421
27	12 (13.9)	20 (24.4)	...	10 (12.7)	15 (27.8)	...
29	4 (4.6)	0 (0.0)	...	3 (3.8)	0 (0.0)	-
Aortic annulus enlargement	9 (10.5)	2 (2.4)	**0.058**	9 (11.4)	1 (1.8)	**0.001**
Intraaortic balloon pump	2 (2.33)	6 (7.32)	0.161	1 (1.27)	4 (7.41)	**0.026**
Post-procedural ECMO	1 (1.2)	3 (3.7)	0.359	1 (1.3)	1 (1.8)	0.921
Mean surgical time (min)	275.2 ± 84.1	278.8 ± 96.1	0.846	272.9 ± 84.9	255.7 ± 88.6	0.085
Mean cardiopulmonary bypass time (min)	137.1 ± 57.5	141.9 ± 67.6	0.962	134.2 ± 55.8	126.7 ± 62.0	0.128
Mean aortic cross-clamp time (min)	101.0 ± 35.1	104.7 ± 45.8	0.985	95.4 ± 41.3	99.3 ± 33.6	0.052

Continuous variables are presented as mean ± standard deviation; categoric variables are presented as counts and percentage; p value is a Student's t test for continuous variables and a Fisher's exact test for categorical variables. Abbreviations: ECMO, extra-corporeal membrane oxygenator; CABG, coronary artery bypass grafting. * Variables used for propensity score.

3.2. Hospital Outcome

The 30-day all-cause mortality was 8.5% (seven patients) for the Perimount group, including one acute type-A aortic dissection, and 3.5% (three patients) for the Trifecta group (Table 3). The 30-day mortality rate continued to be higher, although not statistically significant, in the weighted analysis (7.4% vs. 2.5% respectively; p = 0.223). The odds of death with Perimount as compared to Trifecta was 2.68 (95%CI: 0.64–10.35) and 1.98 (95%CI: 0.77–5.07) in the unweighted and weighted analysis, respectively. Regarding the postoperative complications, the Perimount group required more surgery for bleeding (23.7% vs. 9.3%; p = 0.019), while no significant differences were found in the new pacemaker

implantation rate (2.5% for Perimount vs. 1.2% for Trifecta group; $p = 0.609$), perioperative myocardial infarction (2.5% vs. 2.3%; $p = 1.000$), and stroke (2.5% vs. 1.2%; $p = 0.609$). Patients who underwent AVR with Trifecta had a longer hospital stay (median: 10.5 (8–14) vs. 8 (8–10); $p = 0.002$) which persisted in the weighted analysis (median: 10 (8–14) vs. 8 (7–10); $p < 0.001$). MACCE were observed in 5% and 9% of patients, with an unweighted OR of 2.22 (95%CI 0.64–7.66; $p = 0.196$) and a weighted OR of 1.10 (95%CI 0.44–2.76, $p = 0.836$).

Table 3. Hospital outcome.

	Unweighted Population			Weighted Population		
	Trifecta	**Perimount**	***p* Value**	**Trifecta**	**Perimount**	***p* Value**
30-day mortality	n 86 3 (3.5)	n 82 7 (8.5)	0.203	n 79 2 (2.5)	n 54 4 (7.4)	0.223
Cause of death:						
Multi-organ failure	2	4	…	…	…	…
Heart failure	0	2	…	…	…	…
Haemorrhagic shock (TAAD)	0	1	…	…	…	…
Bowel ischemia	1	0	…	…	…	…
Perioperative myocardial infarction	n 86 2 (2.3)	n 81 2 (2.5)	1.000	n 79 1 (1.3)	n 54 1 (1.8)	0.921
New pacemaker implantation	n 86 1 (1.2)	n 80 2 (2.5)	0.609	n 79 1 (1.3)	n 53 1 (1.9)	0.933
Stroke	n 86 1 (1.2)	n 80 2 (2.5)	0.609	n 79 1 (1.3)	n 53 1 (1.9)	0.531
Reoperation for bleeding	n 86 8 (9.3)	n 80 19 (23.7)	**0.019**	n 79 7 (8.8)	n 53 9 (16.9)	0.274
† Acute kidney injury	n 86 16 (18.6)	n 80 18 (22.5)	0.568	n 79 12 (15.2)	n 53 8 (15.1)	0.598
Continuous veno-venous hemofiltration	n 86 2 (2.3)	n 80 7 (8.7)	0.090	n 79 0 (0)	n 53 3 (5.6)	-
Respiratory failure	n 86 8 (9.3)	n 80 10 (12.5)	0.620	n 79 5 (6.3)	n 53 5 (9.4)	0.645
Acute MACCE	n 86 4 (5)	n 82 8 (9)	0.196	n 79 4 (5)	n 54 5 (9)	0.836
Hospital stay (days)	n 86 10.5 (IQR: 8–14)	n 82 8 (IQR: 8–10)	**0.002**	n 79 10 (8–14)	n 54 8 (7–10)	**<0.001**
Intensive care unit stay (days)	n 86 1 (IQR: 1–2)	n 82 1 (IQR: 1–3)	0.897	n 79 1 (IQR: 1–2)	n 54 1 (IQR: 1–2)	0.415

Continuous variables are presented as mean ± standard deviation or the median and quartile; categoric variables are presented as counts and percentage; *p* value is a Student's t test or Mann–Whitney U test for continuous variables and a Fisher's exact test for categorical variables. Abbreviations: TAAD, type A aortic dissection. † Acute kidney injury is defined according to the KDIGO clinical practice guidelines.

3.3. Echocardiographic Analysis at Discharge

Echocardiographic data are shown in Table 4. Pre-discharge echocardiography demonstrated better mean trans-prosthetic gradients in the Trifecta group in all labelled sizes for both unweighted and weighted populations (7.9 ± 3.2 vs. 12.1 ± 4.7 mmHg for Trifecta and Perimount in unweighted groups, respectively, $p =< 0.001$; and 8.0 ± 3.3 vs. 12.4 ± 4.6 mmHg for Trifecta and Perimount in weighted populations, respectively, $p =< 0.001$) (Table 4) (Figure 1). Overall, the LVEF and the mean area were similar between groups. The incidence of PPM was similar between the Trifecta and the Perimount groups for both the unweighted and weighted populations (Table 4). Similarly, there were no differences regarding the rate of moderate paravalvular leaks.

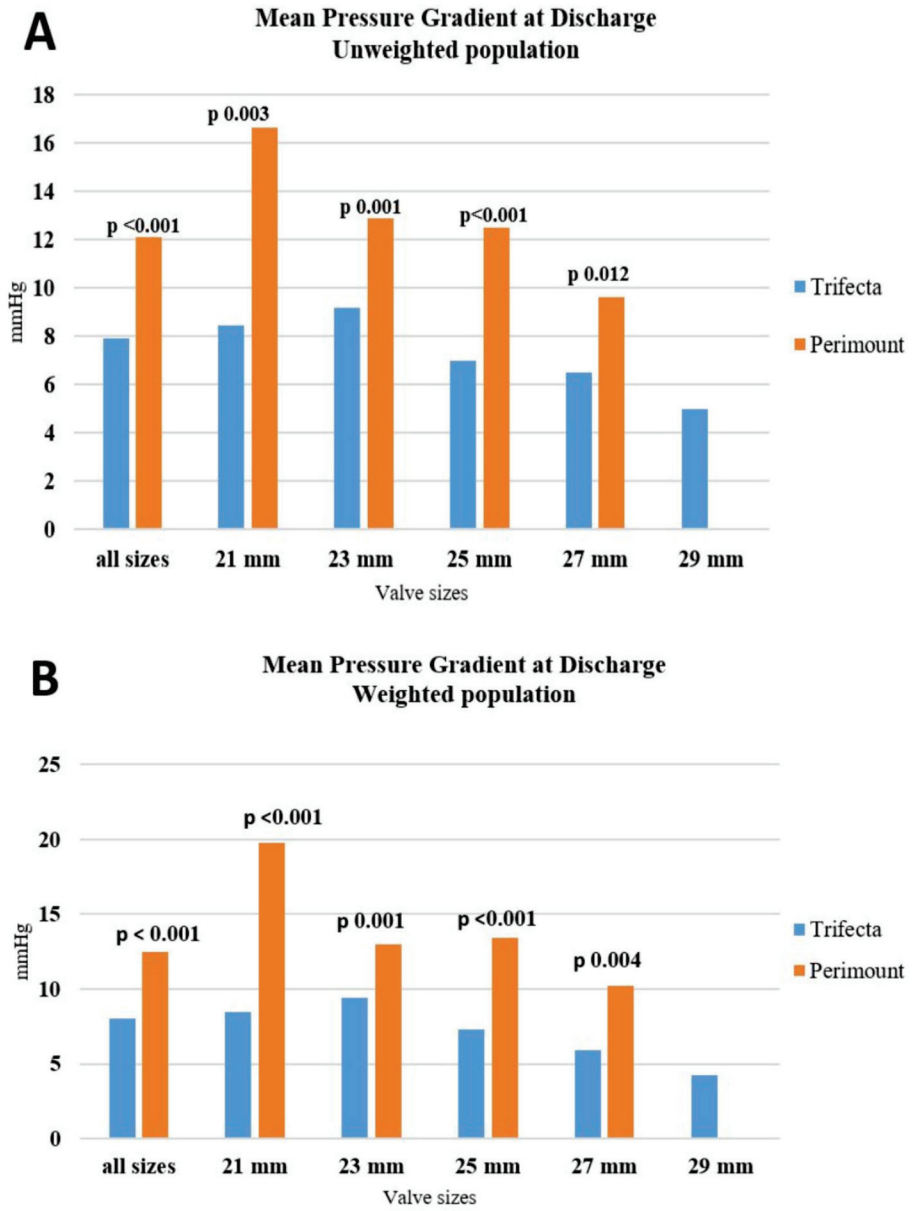

Figure 1. (**A**) Transthoracic echocardiographic assessment of the mean pressure gradient in unweighted population at discharge. (**B**) Transthoracic echocardiographic assessment of the mean pressure gradient in weighted population at discharge.

Table 4. Valve hemodynamic performance at discharge in the unweighted and weighted populations.

	Unweighted Population			Weighted Population		
	Trifecta	**Perimount**	***p* Value**	**Trifecta**	**Perimount**	***p* Value**
Mean left ventricular ejection fraction (%)	n 83 52 ± 10.6	n 76 52.6 ± 11.2	0.773	n 77 52.6 ± 10.6	n 51 52.0 ± 11.8	0.908
Mean aortic valve area (cm^2)	n 81 2.3 ± 0.7	n 67 2.4 ± 0.6	0.456	n 75 2.3 ± 0.6	n 45 2.4 ± 0.5	0.967
Aortic valve area (cm^2/m^2)	n 81 1.2 ± 0.3	n 67 1.2 ± 0.3	0.826	n 75 1.2 ± 0.3	n 45 1.2 ± 0.3	0.947
Peak pressure gradient (mmHg):	n 82 15.5 ± 6.0	n 75 21.9 ± 8.5	**<0.001**	n 76 15.6 ± 6.2	n 50 22.7 ± 8.5	**<0.001**
Size 21	n 9 16.3 ± 2.9	n 5 28.8 ± 12.2	**0.011**	n 9 16.5 ± 2.6	n 3 34.1 ± 10.9	**0.001**

Table 4. *Cont.*

	Unweighted Population			Weighted Population		
	Trifecta	**Perimount**	***p* Value**	**Trifecta**	**Perimount**	***p* Value**
Size 23	n 35 18.2 ± 6.8	n 21 23.6 ± 6.9	**0.006**	n 33 18.6 ± 6.8	n 14 23.9 ± 5.8	**0.007**
Size 25	n 22 13.4 ± 4.9	n 29 22.5 ± 9.2	**<0.001**	n 21 13.9 ± 5.5	n 18 24.6 ± 10.3	**<0.001**
Size 27	n 12 12.6 ± 4.0	n 20 17.5 ± 6.1	**0.018**	n 10 11.7 ± 4.6	n 15 18.6 ± 5.5	**0.003**
Size 29	n 4 9.7 ± 3.1	-	-	n 3 8.1 ± 1.4	-	-
Mean pressure gradient (mmHg):	n 82 7.9 ± 3.2	n 75 12.1 ± 4.7	**<0.001**	n 76 8.0 ± 3.3	n 50 12.4 ± 4.6	**<0.001**
Size 21	n 9 8.4 ± 2.0	n 5 16.6 ± 6.1	**0.003**	n 9 8.4 ± 1.9	n 3 19.7 ± 5.0	**<0.001**
Size 23	n 35 9.2 ± 3.7	n 21 12.8 ± 4.3	**0.001**	n 33 9.4 ± 3.7	n 14 13.1 ± 3.4	**0.001**
Size 25	n 22 7.0 ± 2.6	n 29 12.5 ± 4.9	**<0.001**	n 21 7.3 ± 3.0	n 18 13.3 ± 5.1	**<0.001**
Size 27	n 12 6.5 ± 2.5	n 20 9.6 ± 3.5	**0.012**	n 10 6.1 ± 2.8	n 15 10.1 ± 3.3	**0.004**
Size 29	n 4 5.0 ± 1.4	-	-	n 3 4.2 ± 0.5	-	-
Moderate paravalvular leak	n 83 2 (2.4)	n 75 2 (2.7)	1.000	n 77 2 (2.6)	n 50 2 (4.0)	0.646
Patient-prosthesis mismatch:	...	...	0.437	...	...	0.661
Mild	n 81 19 (23.5)	n 67 17 (25.4)	...	n 75 17 (22.7)	n 45 13 (28.9)	...
Moderate and severe	n 81 10 (12.3)	n 67 4 (5.9)	...	n 75 10 (13.3)	n 45 2 (4.4)	...

Continuous variables are presented as mean ± standard deviation; categoric variables are presented as counts and percentage; *p* value is a Student's t test for continuous variables and a Fisher's exact test for categorical variables.

3.4. Follow-Up

Given the later introduction of the Trifecta in our practice, the median follow-up time was longer for the Perimount group (593 days (25th–75th, 366–985 days) vs. 384 days (25th–75th, 253–525 days); $p = 0.0001$). Overall, four patients died over 36 months (one in Trifecta and three in Perimount group), corresponding to a mortality of 1.06 (95%CI: 0.15–7.5) and 2.13 (95%CI: 0.69–6.63) per 100 persons year, respectively. Cumulative survival at 24 months was 98% (95%CI: 0.91–0.99) and 96% (95%CI: 0.85–0.99) for Trifecta and Perimount, respectively (log-rank test; $p = 0.555$) (Figure 2A). The HR for Perimount vs. Trifecta was 1.98 (95%CI: 0.20–20.06) in the unweighted analysis and not estimable due to zero events in the weighted analysis.

The 36-month incidence of MACCE was 1.04 (95%CI: 0.14–7.44) and 2.78 (95%CI: 1.04–7.41) per 100 persons year in the Trifecta and Perimount groups, respectively. The 2-year freedom from MACCE was 94% (95%CI: 0.65–0.99) in the Trifecta group and 96% (95%CI: 0.86–0.99) in the Perimount cohort (log-rank test; $p = 0.759$, HR 1.46 (95%CI: 0.13–16.48) in the unweighted analysis and not estimable due to zero events in the weighted analysis) (Figure 2B). During follow-up, only three patients in the Perimount group required re-operation for endocarditis. During mid-term follow-up, no reoperation for SVD occurred in either group.

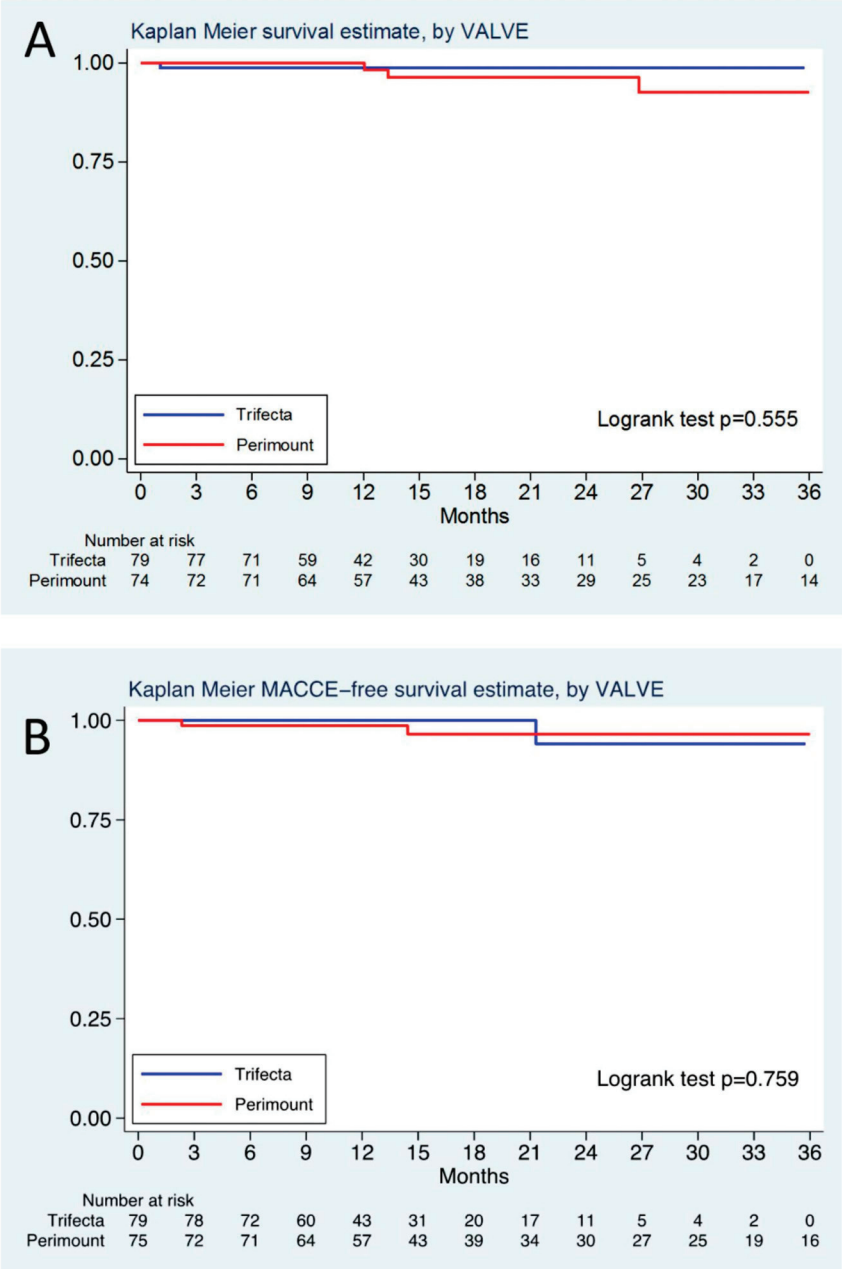

Figure 2. (**A**) Cumulative Kaplan–Meier survival curves. (**B**) Cumulative Kaplan–Meier MACCE-free survival curves. Given the very low number of events, we only present the Kaplan–Meier curves from the unweighted analysis.

3.5. Echocardiographic Analysis at Follow-Up

Echocardiographic findings at follow-up are presented in Table 5. The mean transprosthetic gradients were comparable between the groups, for the unweighted and weighted populations (8.2 ± 3.7 vs. 8.9 ± 3.6 mmHg for Trifecta and Perimount in unweighted analyses, respectively, $p = 0.224$; and 8.2 ± 3.7 vs. 8.8 ± 3.5 mmHg for Trifecta and Perimount in weighted analyses, respectively, $p = 0.121$) (Figure 3). However, the Trifecta continued to show better peak and mean gradients only for the 25 mm labelled size (7.0 ± 2.6 vs. 9.5 ± 4.0 mmHg for Trifecta and Perimount in the unweighted analyses, respectively, $p = 0.017$, and 6.9 ± 2.7 vs. 10.1 ± 3.7 mmHg for Trifecta and Perimount in the weighted analyses, respectively, $p = 0.005$). Overall, the LVEF and the mean aortic valve area were similar for both unweighted and weighted populations. Likewise, there were no differences regarding the incidence of moderate paravalvular leaks.

Table 5. Valve hemodynamic performance at follow-up in the unweighted and weighted populations.

	Unweighted Population			Weighted Population		
	Trifecta	**Perimount**	***p* Value**	**Trifecta**	**Perimount**	***p* Value**
Mean aortic valve area (cm^2)	n 14 2.1 ± 0.5	n 8 2.3 ± 0.6	0.315	n 14 2.1 ± 0.5	n 7 2.4 ± 0.5	0.517
Aortic valve area (cm^2/m^2)	n 5 1.2 ± 0.3	n 3 0.9 ± 0.1	0.166	n 5 1.2 ± 0.3	n 2 1.0 ± 0.1	0.139
Peak valve gradient (mmHg):	n 80 15.4 ± 7.3	n 73 16.7 ± 6.1	0.238	n 75 15.5 ± 7.5	n 49 16.5 ± 5.5	0.175
Size 21	n 9 14.6 ± 5.0	n 5 19.6 ± 6.1	0.120	n 9 13.6 ± 5.5	n 3 17.1 ± 2.5	0.276
Size 23	n 35 18.1 ± 9.1	n 21 16.5 ± 4.7	0.477	n 33 18.0 ± 8.5	n 14 16.5 ± 5.6	0.484
Size 25	n 21 13.6 ± 5.1	n 28 17.2 ± 6.6	**0.043**	n 20 13.5 ± 5.2	n 18 18.0 ± 6.1	**0.018**
Size 27	n 11 13.3 ± 4.6	n 19 15.4 ± 6.7	0.354	n 10 14.0 ± 4.5	n 14 15.4 ± 5.9	0.543
Size 29	n 4 9.7 ± 2.6	-	-	n 3 9.1 ± 2.7	-	-
Mean valve gradient (mmHg):	n 80 8.2 ± 3.7	n 74 8.9 ± 3.6	0.224	n 75 8.2 ± 3.7	n 49 8.8 ± 3.5	0.121
Size 21	n 9 7.9 ± 2.4	n 5 10.6 ± 2.9	0.088	n 9 7.5 ± 2.7	n 3 9.9 ± 2.2	0.158
Size 23	n 35 9.4 ± 4.5	n 21 8.4 ± 3.2	0.376	n 33 9.4 ± 4.2	n 14 8.7 ± 3.9	0.579
Size 25	n 21 7.0 ± 2.6	n 29 9.5 ± 4.0	**0.017**	n 20 6.9 ± 2.7	n 18 10.1 ± 3.7	**0.005**
Size 27	n 11 7.2 ± 2.6	n 19 7.9 ± 3.4	0.528	n 10 7.6 ± 2.8	n 14 7.9 ± 3.2	0.812
Size 29	n 4 6.2 ± 2.2	-	-	n 3 6.1 ± 2.7	-	-
Moderate paravalvular leaks	n 80 1 (1.2)	n 74 1 (1.3)	1.000	n 75 1 (1.3)	n 49 1 (2.0)	1.000

Continuous variables are presented as mean ± standard deviation; categoric variables are presented as counts and percentage; *p* value is a Student's t test for continuous variables and a Fisher's exact test for categorical variables.

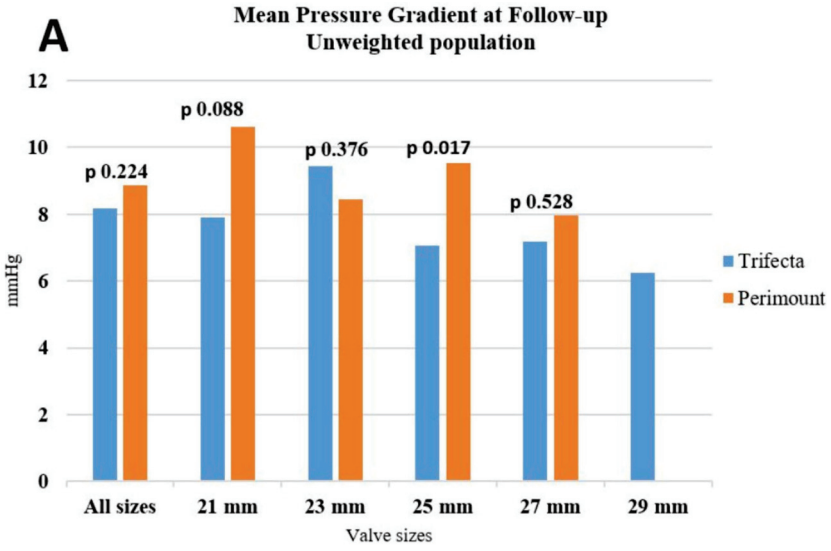

Figure 3. *Cont.*

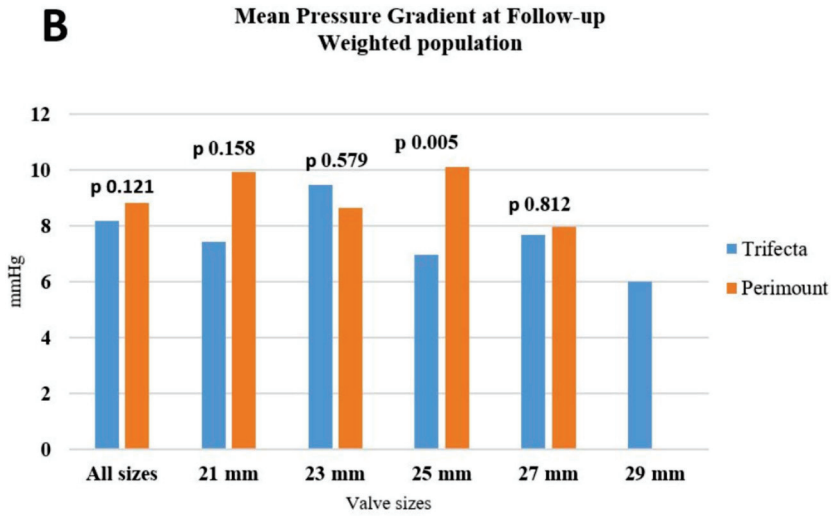

Figure 3. (**A**) Transthoracic echocardiographic assessment of the mean pressure gradient in unweighted population at follow-up. (**B**) Transthoracic echocardiographic assessment of the mean pressure gradient in weighted population at follow-up.

4. Discussion

The major findings of our analysis are the following:

(1) The peak and mean gradients across all labelled prosthetic valves were significantly lower in the Trifecta than in the Perimount cohort soon after surgery, a finding that persisted after propensity weighting. In the mid-term follow-up, the superior hemodynamic performance of the Trifecta valve decreased, both in unweighted and weighted groups.
(2) In-hospital and 36-month outcomes did not differ between the two groups.
(3) No patients in either group underwent re-operation for SVD at mid-term follow-up.

The excellent post-operative hemodynamic performance of the Trifecta valve was not a new finding: the Trifecta design with a sheet of bovine pericardium mounted outside the sewing ring optimizes the valve opening area, and prior studies have established the excellent immediate hemodynamic properties [27–29]. However, the statistically significant haemodynamic difference in terms of mean gradient did not persist over the study period. At the latest follow-up, the Trifecta valve only maintained a better mean gradient for the 25 mm valve, and for all other sizes, we observed an increasing trend which persisted in the weighted analysis populations. Tadakoro et al., in a retrospective study comparing the Trifecta valve and the Magna Ease, demonstrated that in the early postoperative period, mean pressure gradient and effective orifice area were significantly better for Trifecta, but the differences decreased over time [30]. In particular, the interaction between time and valve type was significantly different for the mean pressure gradient between the two groups ($p < 0.01$).

The 30-day all-cause mortality was higher for Perimount patients (8.5% vs. 3.5%; $p = 0.203$) although not statistically significant. Acute MACCE were observed in 5% and 9% of Trifecta and Perimount patients, respectively, with an unweighted OR of 2.22 (95%CI 0.64–7.66; $p = 0.196$) and a weighted OR of 1.10 (95%CI 0.44–2.76; $p = 0.836$). The Perimount group included more combined procedures, which may also explain the higher rate of postoperative revision surgery for bleeding (23.7% vs. 9.3% for Perimount and Trifecta, respectively; $p = 0.019$) while no differences were found in new pacemaker implantation rate (2.5% in the Perimount vs. 1.2% in the Trifecta group; $p = 0.609$), perioperative myocardial infarction (2.5% vs. 2.3%; $p = 1.000$), and stroke incidence (2.5% vs. 1.2%; $p = 0.609$). Patients who underwent AVR with the Trifecta had a longer hospital stay due to a longer wait for rehabilitation care from the hospital to a rehabilitative clinic. At 24 months, all-cause mortality (Trifecta 98% vs. Perimount 96%, log-rank test; $p = 0.555$) and freedom rates from

MACCE events (Trifecta 94% vs. Perimount 96%, log-rank test; $p = 0.759$) were comparable between the study cohorts, suggesting that both valves provide excellent clinical results.

Concerning the valve durability, three patients in the Perimount group experienced prosthetic valve endocarditis requiring re-operation for AVR. Over the study period, freedom from SVD was 100% at 36 months for both groups. In addition to the attested good durability of the Perimount valve, several studies have shown excellent mid-term results of the Trifecta valve. Goldman et al., in a multicentre, prospective, nonrandomized, observational study involving 710 patients, demonstrated that 6 years postoperatively, freedom from valve-related mortality and non-structural dysfunction were 98.3% and 98.6%, respectively [27]. Anselmi et al. reported the mid-term outcomes of 824 Trifecta implants, demonstrating freedom from SVD of 98% at 5 years [28]. Another mid-term result involving 1953 patients who underwent AVR with Trifecta showed that overall freedom from aortic valve reintervention was 96.4% at 5 years [29]. In contrast, Fukuhara et al. reported more recently a greater SVD rate of the Trifecta bioprosthesis at 7 years, while the cumulative incidence of reintervention was similar between the Trifecta and non-Trifecta groups [15]. Biancari and co-authors, using a Finnish data registry, evaluated 2216 patients of which 851 were implanted with a Trifecta valve. A rate of 3.3% reintervention for SVD at 7 years was reported in the Trifecta cohort versus 0% in the Perimount group, a finding that persisted after propensity matching [1]. In light of these conflicting data, longer-term randomized clinical trials are needed to evaluate the best bioprostheses valve choice to offer the best clinical treatment in a population where bioprostheses valve is increasingly in use even among young people.

This study has some limitations. It is a single-centre retrospective observational study including a limited number of all-comer patients including urgent and combined procedures. During the follow-up, the echocardiographic assessment was performed by different cardiologists and not always by our team. Follow-up was limited to 36 months due to the recent introduction of the Trifecta in our hospital, and therefore, it can be difficult to detect SVD or complications related to valve dysfunction within this short time frame. Although we tried to consider all potential confounders in computing the propensity score, some residual unmeasured confounding may still be present; however, the balancing properties of the propensity score were good, resulting in comparable cohorts.

5. Conclusions

The hemodynamic performance of aortic bioprosthesis was greater for the Trifecta valve in the overall population and after propensity weighting, but this difference did not persist over time. During the follow-up, both devices showed good clinical outcomes, and there were no reoperations for SVD. Longer-term randomized clinical trials are warranted to determine the rate of freedom from SVD and its influence on clinical outcome.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcdd10040139/s1, Figure S1: Distribution of the propensity score by valve.

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Conflicts of Interest: E.F. is a proctor and consultant for Edwards Lifesciences. All other authors declare no conflicts of interest related to this study.

Abbreviations

AVR, aortic valve replacement; PPM, patient-prosthesis mismatch; SVD, structural valve degeneration; LVEF, left ventricular ejection fraction; iEOA, indexed effective orifice area; CABG, coronary artery bypass grafting; IABP, intraaortic ballon pump; MACCE, major adverse cardiovascular and cerebral events; OR, odds ratio; HR, hazard ratio; CI, confidence intervals.

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Aortic Valve Repair with External Annuloplasty in Bicuspid versus Tricuspid Aortic Valve Patients

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Abstract: Surgical repair for regurgitant bicuspid aortic valve (BAV) is promising but underutilized due to perceived complexities and lack of long-term data. This study evaluated the efficacy of valve-sparing root remodeling (VSRR) or isolated valve repair combined with calibrated external ring annuloplasty in BAV versus tricuspid aortic valve (TAV) patients. All patients operated on for aortic regurgitation and/or aneurysm at our institution between 2014 and 2022 were included and entered into the Aortic Valve Insufficiency and ascending aorta Aneurysm InternATiOnal Registry (AVIATOR). Patients with successful repair at index surgery (100% in the BAV group, 93% in the TAV group, $p = 0.044$) were included in a systemic follow-up with echocardiography at regular intervals. Among 132 patients, 58 were in the BAV (44%) and 74 in the TAV group (56%). There were no inter-group differences in preoperative patient characteristics, except BAV patients being significantly younger (47 ± 18 y vs. 60 ± 14 y, $p < 0.001$) and having narrower aortic roots at the level of sinuses (41 ± 6 mm vs. 46 ± 13 mm, $p < 0.001$) and sinotubular junctions (39 ± 10 mm vs. 42 ± 11, $p = 0.032$). No perioperative deaths were recorded. At four years, there was no significant difference in terms of overall survival (96.3% BAV vs. 97.2% TAV, $p = 0.373$), freedom from valve reintervention (85.2% BAV vs. 93.4% TAV, $p = 0.905$), and freedom from severe aortic regurgitation (94.1% BAV vs. 82.9% TAV, $p = 0.222$). Surgical repair of BAV combined with extra-aortic annuloplasty can be performed with low perioperative morbidity and mortality and excellent mid-term results which are comparable to TAV repair.

Keywords: bicuspid aortic valve (BAV); tricuspid aortic valve (TAV); valve-sparing root remodeling (VSRR); aortic valve repair; external annuloplasty; AVIATOR registry

1. Introduction

With an incidence of almost 2% in the general population, bicuspid aortic valve (BAV) is the most common congenital cardiac malformation [1]. Due to its common association with abnormalities of the ascending aorta, it should be considered a disease of the entire aortic root. Even though aortic stenosis is a more common presentation of the BAV pathology [1], aortic regurgitation (AR), reported in approximately 20% of these patients, is a non-negligible clinical issue, due to its earlier presentation, most commonly in the third decade of life [2]. Although initially designed for tricuspid aortic valve (TAV), repair techniques have evolved continuously so that in the current guidelines, repair of a leaking BAV falls under the same criteria for repair as TAV—in selected patients, depending

on valve anatomy and tissue characteristics, at a comprehensive valve center [3]. Opposed to TAV, anatomical reasons for AR in BAV patients can include a combination of aneurysmal dilatation with distortion of root geometry and primary leaflet pathology, and as such may require a more complex leaflet repair. In spite of reports demonstrating excellent durability and low incidence of recurrent regurgitation [4], BAV repair has still not been widely accepted. Comparable to mitral valve repair, performing annuloplasty increases the rate of successful repairs, especially in the case of a bicuspid valve [5–7]. Calibrated external ring annuloplasty is recommended depending on the root anatomy/type of surgery at the sub- and supravalvular levels to restore and enforce the physiologic root anatomy. In this study, we analyzed the results of aortic valve repair for BAV vs. TAV patients using external ring annuloplasty. The primary endpoints of this study were the incidences of AV reintervention and postoperative AR > 2+ and cumulative survival during follow-up. Secondary endpoints were perioperative morbidity and mortality and analysis of echocardiographic parameters on follow-up.

2. Materials and Methods

2.1. Patient Selection and Study Design

An analysis of prospectively collected data of consecutive patients treated at our institution from 2014 to 2022, who had surgery involving the aortic root and/or aortic regurgitation and were enrolled in the AVIATOR database, was performed [8]. Included were patients with repair of a regurgitant bicuspid or tricuspid aortic valve with or without concomitant aortic root intervention. Excluded were patients with aortic valve/root replacement and patients with unicuspid or quadricuspid aortic valves.

2.2. AVIATOR Database

The AVIATOR database/initiative, a part of the Heart Valve Society (HVS) Aortic Valve database, is a multicentric longitudinal observational cohort study enrolling patients with ascending aorta aneurysm and/or AR [8]. It focuses on patients with disorders of the ascending aorta (including the root and supracoronary aorta) and/or isolated aortic regurgitation (including mixed congenital aortic valve disease) to gather data and experiences in order to evaluate the guidelines for surgical indication as well as the use of repair versus replacement with special focus on long-term patients' outcomes.

2.3. Ethics Statement

The local Institutional Review Board's opinion was requested. They decided that the follow-up was not a medical experiment, and therefore, their approval was not required.

2.4. Operative Technique

Valve-sparing root replacement (VSRR) by means of aortic root remodeling with external ring annuloplasty was previously described and popularized by Lansac [9]. All patients were operated on through full median sternotomy. After establishing a cardiopulmonary bypass, the heart was arrested, and the aorta was cut open with a vertical incision. The height of each cusp was measured with a dedicated caliper [10] to confirm the reparability of the valve. After confirming suitability for the valve-sparing procedure, the sinuses of Valsalva were resected, coronary buttons detached, and external dissection down to the base of the aortic annulus was performed. The size of the LVOT was measured with a Hegar dilator in order to determine the sizes of the subvalvular CORONEO Extra-Aortic ring (Coroneo, Inc., Montreal, QC, Canada) and Valsalva graft (Gelweave Valsalva; Vascutek Ltd., Renfrewshire, UK), respectively. Five pledgeted Ethibond 2-0 sutures (Ethicon Inc., Somerville, MA, USA) were placed on a circumferential plane around the LVOT, 2 mm below the lowest point of insertion of each cusp and at the base of the interleaflet triangles below each commissure. An additional non-pledgeted suture was positioned outside of the LVOT between the right and non-coronary commissure (to avoid conduction disturbances). An appropriate Valsalva graft was then prepared to re-create 2 sinuses in BAV and 3 sinuses

in TAV. In BAV patients, sinuses with raphe were merged into a single sinus. The Valsalva graft was anastomosed with a 5-0 Prolene suture (Ethicon Inc., Somerville, MA, USA). Either a flexible prosthetic CORONEO Extra-Aortic ring or a dacron ring was then placed externally and fixed by the previously placed annular Ethibond sutures. At this point, residual cusp prolapse was assessed by repeated measuring of the effective height with a caliper. When the cusp height was inadequate (less than 9 mm), additional cusp repair was performed, predominantly using the central cusp plication technique. Coronary buttons were implanted next, with a 5-0 Prolene suture in standard fashion, and distal anastomosis was performed at the appropriate level of the ascending aorta or arch, depending on the ascending aorta size.

In cases where the annulus and ascending aorta are within normal dimensions, isolated aortic insufficiency repair with external ring annuloplasty is performed. The aorta is transversely opened 1 cm above STJ, and the quality of valve leaflets, presence of calcifications, fenestrations, and/or retraction of leaflets are assessed to determine the feasibility of repair. Cusps are deemed suitable for repair if the geometric height is $\geq$17 mm in a tricuspid aortic valve and $\geq$20 mm in a bicuspid non-fused cusp. To determine the right size of the extra-aortic ring, a Hegar dilatator is used to determine the size of the native aortic annulus, and an appropriate ring size is chosen. Next, an external dissection down to the base of the aortic annulus is performed with careful dissection of the proximal portion of LM and RCA to facilitate the placement of the Dacron extra-aortic open ring. Five pledgeted Ethibond 2-0 sutures (Ethicon Inc., Somerville, MA, USA) are placed on a circumferential plane around the LVOT, with an additional non-pledgeted suture positioned outside of the LVOT between the right and non-coronary commissure in the same fashion as for valve-sparing root replacement. The Dacron extra-aortic ring is cut open and pulled under LM and RCA, then fixated at the ends with a Prolene 4-0 suture following fixation to the annulus by previously placed Ethibond sutures. Cusp prolapse is then assessed by measuring the effective height with a caliper, and if cusp height is inadequate (less than 9 mm for TAV or 10 mm for BAV), additional cusp repair is performed by placing stitches on the free edge of the culprit leaflet until an effective height of 9 mm/10 mm is obtained. For the second ring at the level of the ST junction, a CORONEO Extra-Aortic ring is used, with the same diameter as the annular Dacron ring. At this level, the ring is secured in place with a single 4-0 Prolene suture at each commissure and an additional suture above the orifice of RCA and LM. Transection of the aorta is sutured to the tubular ascending aorta with a standard running suture.

A transesophageal echo was performed to evaluate valve function and repair success.

2.5. Follow-Up

Patients with successful repair at index surgery were included in the follow-up. Since the patients were enrolled in the AVIATOR database, they required systematic follow-up with echocardiography at regular intervals. Follow-up was achieved by gathering echocardiographic data using scheduled echocardiography at our institution or from patients by phone or email if all parameters were available in outside-hospital ECHO reports. Aortic annulus measurements were obtained from transthoracic or transesophageal echocardiography using either two-dimensional or three-dimensional methods. The degree of AR was assessed in accordance with the American Society of Echocardiography (ASE) [11].

2.6. Statistical Analysis

Continuous variables are expressed as median and interquartile range (IQR). Categorical data are presented as counts and percentages throughout the manuscript. The distribution of continuous variables was controlled by means of the Shapiro–Wilk test. Continuous and discrete variables were compared using a two-sample *t*-test or Mann–Whitney test, where appropriate. Categorical and ordinal variables were compared using Pearson's Chi-squared test or Fisher's exact test, where appropriate. The probability of freedom from the event was calculated according to the Kaplan–Meier method. Freedom-from-event

curves were compared by log-rank tests. A p-value < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the IBM® SPSS® Statistics software program (version 23.0.0.0 for MS Windows, IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient Cohort

A total of 132 patients undergoing surgery for aortic regurgitation were analyzed. Fifty-eight (44%) had bicuspid aortic valve (BAV group) and seventy-four (56%) had tricuspid aortic valve (TAV group). Demographic data are presented in Table 1. Patients with BAV had a lower incidence of arterial hypertension (66% vs. 87%, $p = 0.006$) and were significantly younger (47 ± 8 years vs. 60 ± 14 years, $p < 0.001$), resulting in significantly lower EuroSCORE I and II scores.

Table 1. Preoperative patient characteristics.

Variables	Total, $n = 132$	BAV, $n = 58$	TAV, $n = 74$	p Value
Age (years)	54 ± 19	47 ± 18	60 ±14	<0.001
Gender, female	23 [17]	6 [10]	17 [23]	0.67
Height (cm)	178 ± 14	178 ± 14	178 ± 13	0.540
Weight (kg)	89 ± 22	90 ± 17	88 ± 11	0.936
BMI (kg/m^2)	28.07 ± 6	27.77 ± 5.21	28.23 ± 6.34	0.473
NYHA				0.766
I II III IV	35 [27] 82 [62] 14 [11] 1 [1]	17 [29] 35 [60] 6 [10] 0	18 [24] 47 [64] 8 [11] 1 [1]	
Creatinine (mg/dL)	0.97 ± 0.26	0.99 ± 0.23	0.96 ± 0.28	0.681
EuroSCORE I (%)	5.80 ± 3.51	4.65 ± 2.11	7.20 ± 5.64	<0.001
EuroSCORE II (%)	2.20 ± 1.12	1.83 ± 0.85	2.33 ± 1.21	0.005
Arterial hypertension	102 [77]	38 [66]	64 [87]	0.006
Diabetes mellitus	3 [2.3]	1 [1.7]	2 [2.7]	1.000
Aortic dissection	5 [3.8]	2 [3.4]	3 [4.1]	1.000
Atrial fibrillation	10 [7.6]	3 [5.2]	7 [9.5]	0.512
COPD	2 [1.5]	0	2 [2.7]	0.504
Connective tissue disease				0.531
Yes Unknown	7 [5] 19 [14]	2 [3] 10 [17]	5 [7] 9 [12]	
Previous cardiac surgery	1 [1]	0	1 [1]	1.000
Recent MI	1 [1]	0	1 [1]	1.000
Aortic regurgitation			0.279	
0 (none or trivial) 1 (mild) 2 (mild to moderate) 3 (moderate to severe) 4 (severe)	3 [2] 8 [6] 23 [18] 51 [40] 41 [33]	1 [2] 6 [11] 7 [13] 22 [40] 19 [35]	2 [3] 2 [3] 16 [23] 29 [41] 22 [31]	

Table 1. *Cont.*

Variables	Total, *n* = 132	BAV, *n* = 58	TAV, *n* = 74	*p* Value
LVEF (%)	60 ± 9	60 ±13	60 ± 9	0.814
LVEDD (mm)	61 ± 12	61 ± 10	60 ± 12	0.605
LVESD (mm)	42 ± 11	42 ± 10	42 ± 12	0.947
Aortic annulus (mm)	28 ± 6	29 ± 5	28 ± 5	0.014
Sinuses diameter (mm)	44 ± 9	41 ± 6	46 ± 13	0.001
Sinotubular junction (mm)	40 ± 11	39 ± 10	42 ± 11	0.032
Ascending aorta (mm)	47 ± 15	45 ± 15	49 ± 18	0.059

Data expressed as *n* [%] or median ± IQR; MI—myocardial infarction; LVEF—left ventricular ejection fraction; LVEDD—left ventricular end-diastolic diameter; LVESD—left ventricular end-systolic diameter.

On preoperative echo, BAV patients had a slightly larger aortic annulus (29 ± 5 mm vs. 28 ± 5 mm, $p = 0.014$), smaller sinus of Valsalva (41 ± 6 mm vs. 46 ± 13 mm, $p = 0.001$), and smaller sinotubular junction diameter (39 ± 10 mm vs. 42 ± 11 mm, $p = 0.032$). There was no significant difference in aortic regurgitation grades, left ventricular diameters, and ejection fraction between groups.

3.2. Operative Details

Operative data are summarized in Table 2. An external annuloplasty ring was used in all BAV patients and in 85% of TAV patients ($p = 0.009$). There was a higher percentage of isolated valve repair in the BAV group (22% vs. 9%, $p = 0.039$) and consequently, a higher percentage of sinotubular junction rings used in the BAV group (15% vs. 4%, $p = 0.004$). Significantly more ($p = 0.003$) valve cusp repairs were needed in the BAV group (97%) than in the TAV group (80%). The procedure was more time demanding in the TAV group than in the BAV group, with longer cardiopulmonary bypass (145 ± 46 min vs. 127 ± 40 min, $p < 0.001$) and aortic cross-clamp times (112 ± 32 min vs. 104 ± 24 min, $p = 0.004$). Valve repair success at index surgery was 100% in the BAV group and 93% in the TAV group ($p = 0.044$).

Table 2. Intraoperative patient data.

Variables	Total, *n* = 132	BAV, *n* = 58	TAV, *n* = 74	*p* Value
Type of repair				0.209
Isolated valve repair	20 [15]	13 [22]	7 [9]	
Partial root replacement (1–2 sinus) ± valve repair	4 [3]	2 [3]	2 [3]	
Tubular aorta replacement ± valve repair	22 [17]	8 [14]	14 [19]	
Valve-sparing root replacement ± valve repair	86 [65]	35 [60]	51 [69]	
Annuloplasty	124 [93.9]	58 [100]	66 [89]	0.009
External ring	121 [91.7]	58 [100]	63 [85]	0.009
Extra-aortic Coroneo Inc.	110 [91]	51 [88]	59 [94]	0.274
Dacron	11 [9]	7 [12]	4 [6]	
External ring size (mm)	27 ± 4	27 ± 3	27 ± 4	0.731
STJ ring	12 [9]	9 [15]	3 [4]	0.004
STJ ring size (mm)	29 ± 3	28 ± 3	29 ± 4	0.352
Cusp repair	115 [87]	56 [97]	59 [80]	0.003
Cabrol stitches	3 [2]	1 [2]	2 [3]	0.032
Graft size (mm)	28 ± 4	28 ± 2	28 ± 4	0.869

Table 2. *Cont.*

Variables	Total, *n* = 132	BAV, *n* = 58	TAV, *n* = 74	*p* Value
CPB (min)	138 ± 43	127 ± 40	145 ± 46	<0.001
CCT (min)	107 ± 26	104 ± 24	112 ± 32	0.004
Concomitant procedures	22 [17]	17 [23]	5 [9]	0.280
CABG	10 [8]	7 [9]	3 [5]	0.074
Aortic (hemi)arch replacement	11 [8]	9 [12]	2 [3]	0.082
Mitral valve procedure	4 [3]	1 [2]	3 [4]	0.089
Valve repair success	127 [96]	58 [100]	69 [93]	0.044

Data expressed as *n* [%] or median ± IQR; STJ—sinotubular junction; CPB—cardiopulmonary bypass; CCT—aortic cross-clamp time.

In one case, repair failed due to calcification of the non-coronary cusp (NCC), despite the fact that decalcification was performed. The second case failed because of multiple fenestrations of all three cusps. In two patients, primary cusp repair was not performed due to the normal appearance of the valve and central jet of AV regurgitation. After the proven incompetence of the aortic valve, during the second cross-clamp, plication of all three cusps was performed but without effect on the final result. Furthermore, in the last case, plication of all three cusps was primarily performed, but massive aortic regurgitation remained. Due to unsuccessful repair, aortic valve replacement was performed in these patients.

3.3. Clinical Outcomes

Both groups were analyzed for postoperative complications, which included reopening for bleeding, permanent pacemaker implantation, and cerebrovascular accident (CVA). The data are presented in Table 3. There was no difference between groups. There were no patient deaths in the perioperative period (30 days after surgery or during the same hospitalization) in either group.

Table 3. Postoperative complications.

Variables	Total, *n* = 132	BAV, *n* = 58	TAV, *n* = 74	*p* Value
Reopening for bleeding	9 [7]	3 [5]	6 [8]	0.235
Permanent pacemaker	2 [1.52]	0 [0]	2 [3]	0.207
CVA (permanent)	1 [1]	0 [0]	1 [1]	0.183
CVA (transient)	1 [1]	0 [0]	1 [1]	0.183
Perioperative mortality	0 [0]	0 [0]	0 [0]	0.999

Data expressed as *n* [%]. CVA—cerebrovascular accident.

3.4. Follow-Up

A total of 127 patients out of 132 operated patients (96%) with successful valve repair at index surgery were included in the follow-up. The median follow-up period was 483 days (IQR 946 days). The follow-up analysis contains data on mortality, freedom from valve reintervention, and echo control echocardiography from all (100%) patients included in the study (Table 4).

Table 4. Follow-up with echocardiographic data.

Variables	Total, *n* = 127	BAV, *n* = 58	TAV, *n* = 69	*p*-Value
Follow-up duration (d)	483 ± 946	479 ± 770	508 ± 946	0.527
Late mortality	3 [2]	2 [3]	1 [1]	0.435
AV reintervention	7 [6]	3 [5]	4 [6]	0.596

Table 4. *Cont.*

Variables	Total, n = 127	BAV, n = 58	TAV, n = 69	p-Value
AV mean gradient (mmHg)	8 ± 7	10 ± 9	7 ± 6	0.009
Aortic annulus (mm)	26 ± 5	26 ± 5	26 ± 6	0.710
Sinuses diameter (mm)	32 ± 5	32 ± 5	32 ± 5	0.927
Sinotubular junction (mm)	29 ± 5	30 ± 4	29 ± 5	0.290
Ascending aorta (mm)	31 ± 5	32 ± 5	32 ± 5	0.148
LVEF (%)	60 ± 12	60 ± 10	56 ± 12	0.077
LVEDD (mm)	55 ± 9	54 ± 10	56 ± 9	0.169
LVESD (mm)	36 ± 9	36 ± 10	37 ± 9	0.217
Delta EF (%)	0 ± 11	0 ± 12	−2 ± 12	0.057
Delta LVEDD (mm)	−6 ± 7	−6 ± 7	−5 ± 7	0.587
Aortic regurgitation				0.003
0 (none or trivial)	72 [57]	43 [74]	29 [42]	
1 (mild)	33 [26]	12 [21]	21 [30]	
2 (mild to moderate)	19 [15]	3 [5]	16 [23]	
3 (moderate to severe)	2 [2]	0 [0]	2 [3]	
4 (severe)	1 [1]	0 [0]	1 [1]	
Aortic regurgitation > 2+	3 [2]	0 [0]	3 [4]	0.157
Coaptation height (mm)	10 ± 4	9 ± 3	11 ± 5	0.024
Effective height (mm)	13 ± 4	13 ± 3	14 ± 4	0.145

Data expressed as n [%] or median ± IQR. LVEF—left ventricular ejection fraction; LVEDD—left ventricular end-diastolic diameter; LVESD—left ventricular end-systolic diameter.

3.5. Survival Analysis

Three patients died during follow-up, two of non-cardiac causes in the BAV group (3%) and one with sudden unexplained death in the TAV group (1%). Overall survival is depicted in Figure 1. The cumulative survival at 4 years was 96.3 ± 3.6% in the BAV group and 97.2 ± 2.7% in the TAV group (p = 0.373).

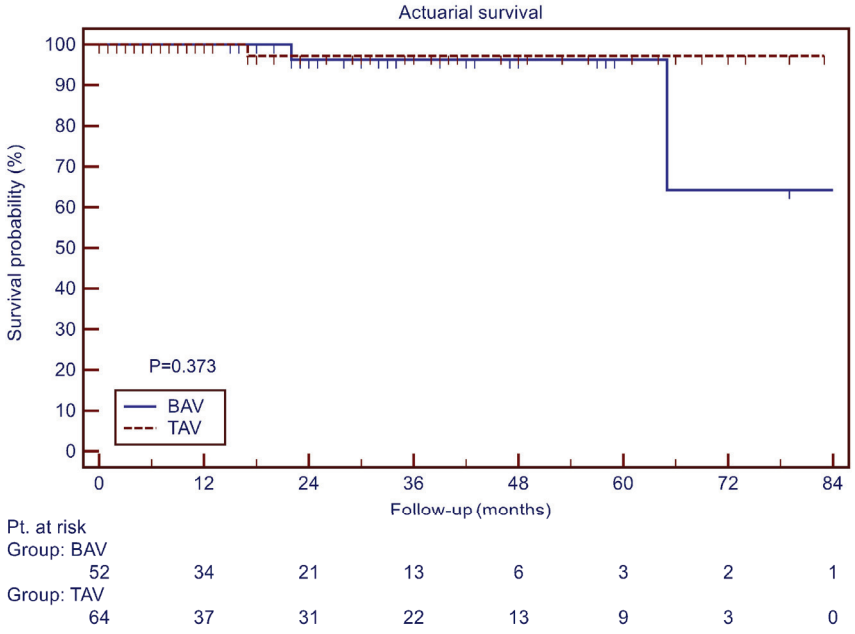

Figure 1. Overall survival.

3.6. Aortic Valve Reinterventions and Aortic Regurgitation

There was a total of seven reinterventions on the aortic valve during follow-up and three additional cases of significant aortic regurgitation (AR > 2+). The freedom from AV reintervention at 4 years was 85.2 ± 8.1% for the BAV group and 93.4 ± 3.3% for the TAV group (p = 0.905, Figure 2).

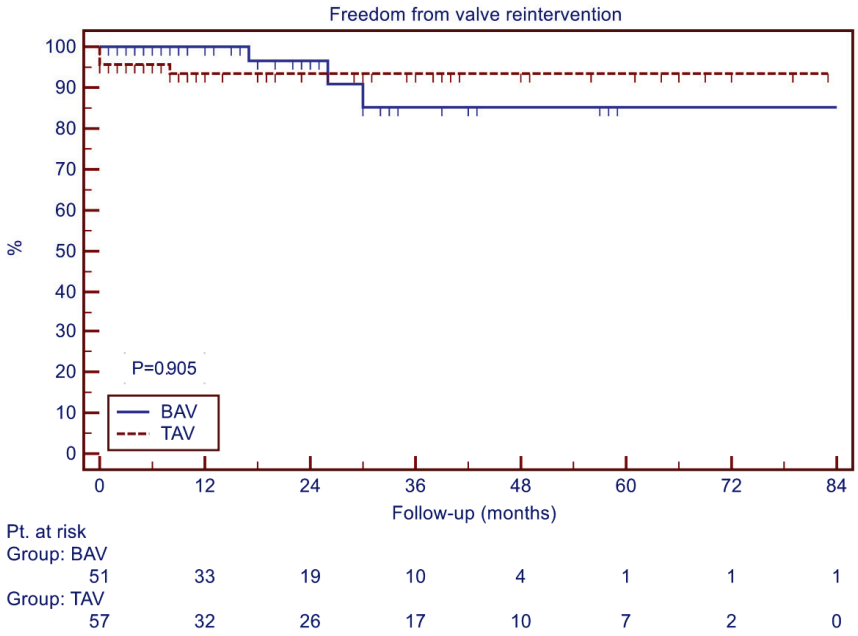

Figure 2. Freedom from AV reintervention.

Four of the AV reinterventions were in the TAV group and three were in the BAV group. Most of the patients underwent VSRR + aortic valve repair with aortic annuloplasty, except in one case, in which tubular aorta replacement and aortic valve repair without aortic annuloplasty were performed. In two cases (both TAV group, Coroneo aortic annuloplasty performed), massive aortic regurgitation was diagnosed before discharge from the hospital. Intraoperatively, in the first case, NCC–RCC commissure rupture was found. In the second case, failure was caused by RCC leaflet damage due to contact with a subannular pledget, explained by excessive leaflet motion. The third patient (TAV group, Vacutek Gelweave aortic annuloplasty performed) presented 7 days after discharge from the hospital with pseudoaneurysm of the aortic root caused by laceration of the LVOT by the annuloplasty suture. Regarding a later onset of repair failure, four cases were detected. The first case (BAV group, Coroneo aortic annuloplasty performed) presented six months after the repair and suture line dehiscence between the LCC and RCC was observed. The second case required reoperation 2 years after the repair owing to native valve endocarditis (owing to aortic root rupture due to the aortic annuloplasty ring). Also, in a similar time period, in another patient (BAV group, Coroneo aortic annuloplasty performed), failure appeared due to a laceration of the aortic valve leaflet caused by the central placating suture of a fused cusp. Finally, the last case (TAV group, no aortic annuloplasty performed) presented with massive aortic regurgitation on a regular echocardiography examination 9 months after the primary operation and underwent a TAVI procedure soon after. Even though the valve could not be observed intraoperatively, failure was explained by postoperative dilatation of the aortic annulus as a consequence of lacking aortic annuloplasty.

The freedom from severe aortic regurgitation (AR > 2+) at 4 years was 94.1 ± 5.7% for the BAV group and 82.9 ± 8.9% for the TAV group (p = 0.222, Figure 3).

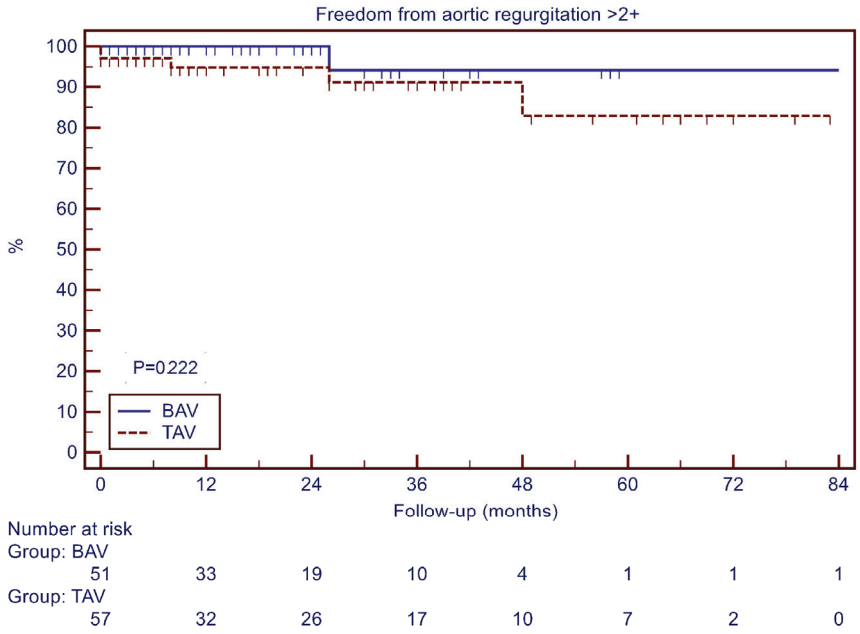

Figure 3. Freedom from aortic regurgitation > 2+.

3.7. Echocardiography

Follow-up echocardiography showed a slightly higher mean AV gradient in the BAV group (10 ± 9 mmHg vs. 7 ± 6 mmHg, $p = 0.009$) as well as a lower coaptation height (9 ± 3 mm vs. 11 ± 5 mm, $p = 0.024$). There was no difference concerning left ventricular remodeling (expressed as delta LVEDD) between groups. There were no significant differences in other echocardiography data.

4. Discussion

Our study shows that surgical repair of BAV using root remodeling or isolated valve repair combined with calibrated extra-aortic annuloplasty can be performed with high reproducibility (shown as 100% success of initial operation) and low perioperative morbidity and mortality. The mid-term results at 4 years after repair expressed as freedom from aortic valve reintervention (85% for BAV, 93% for TAV group, $p = 0.905$) or freedom from severe aortic regurgitation (94% for BAV, 83% for TAV group, $p = 0.222$) show that BAV repair is at least comparable with the results of repair in the TAV group. The cumulative survival at 4 years was excellent in both groups (96% in BAV and 97% in the TAV group, $p = 0.373$).

It seems that the slightly lower utilization of extra-aortic annuloplasty rings in the TAV group (89% vs. 100%) did not have a negative impact on the mid-term durability of repair. Although the mean postoperative gradient across the aortic valve is statistically higher in the BAV group (10 mmHg vs. 7 mmHg), it was not manifested in clinically important outcomes in the observed follow-up period.

To this day, there is scarce literature about the differences between BAV and TAV groups after valve repair and our results correspond to the results of several bigger studies with different surgical techniques applied. Aicher and colleagues showed excellent outcomes of root remodeling AV repair in a group of two hundred and forty-nine patients, with a freedom from severe AR at 5 years of 96% in the BAV group and 88% in the TAV group ($p = 0.08$), with only nine patients requiring reoperation (3.6%) [12]. Svensson et al. discovered in their cohort of 728 patients with BAV repair that at 5 years, 25% of patients had moderate (2+) and 24% severe AR (3+/4+), but the freedom from reoperation remained high (87%, 78%, and 64% at 5, 10, and 15 years, respectively) [13]. In the more recent report from the same group, the authors found that patients undergoing cusp repair combined with root procedures (mostly root reimplantation) were less likely to have a high postoperative AR grade and had a lower mean gradient and lower LV mass index

over time compared with patients with isolated cusp repair without annular support [14]. The importance of annular stabilization was further shown by Lansac et al. in a group of 232 patients with valve repair with external aortic ring annuloplasty with a high freedom from severe postoperative AR at 7 years of 90.6% and no differences between BAV and TAV [15]. Ouzounian and colleagues showed superb results of valve-sparing root replacement using a reimplantation technique in a group of 333 patients at 5 years, with no valve reoperation in either BAV or TAV propensity-matched groups, but with a higher incidence of severe AR in the BAV group (3.9% vs. 1.2%) which was not statistically significant ($p = 0.08$) [16]. Gocol and colleagues showed considerably higher 5-year survival in the BAV than in the TAV group (97% vs. 80, $p < 0.001$) [17]. Rates of reintervention and AR recurrence were similar in both groups. Their spectrum of operation included both internal and external annuloplasty, as well as both root reimplantation and remodeling techniques when root replacement was needed. Survival differences were attributed to the younger age and less comorbidity in BAV patients.

However, there are some limitations to our study that must be considered. This research is a retrospective, observational analysis of single-center results prospectively collected through the AVIATOR database. The number of patients in both groups was limited and relatively small for accurate data analysis due to the vast heterogeneity of aortic valve pathology and multiple types of surgical procedures. This was somewhat mitigated by our adherence to standardized surgical techniques, measurement, and reasoning as previously described. Furthermore, the initial echocardiography examination and follow-ups were not consistently carried out by the same person, resulting in some measurements being incomplete or inconsistent. Moreover, this study's limitations include a patient age range of 47–60 and a short follow-up period, limiting our insight into longer-term outcomes.

5. Conclusions

Based on our experience, we conclude that aortic valve repair is a safe and feasible strategy in patients with aortic regurgitation regardless of valve anatomy (BAV or TAV). Reproducible step-by-step procedure respecting individual anatomy and pathology, and especially the addition of calibrated external ring annuloplasty contributes to early and mid-term repair success. Long-term durability remains to be analyzed.

Author Contributions: Conceptualization, I.R., D.B. and D.U.; methodology, I.R., D.B. and D.U.; software, D.B.; validation D.U.; formal analysis, D.B.; investigation, Z.S.O., I.J., N.B. and D.S.; resources, G.S. and J.V.; writing—original draft preparation, N.S., G.S., S.G. and M.K.; writing—review and editing, D.B. and D.U.; visualization, D.B.; supervision, I.R. and D.B. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was previously obtained from all subjects involved in the AVIATOR database.

Data Availability Statement: Data are available on demand due to privacy protection.

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

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Aortic Valve Infective Endocarditis Complicated by Annular Abscess: Antibiotics in the Abscess Cavity

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Abstract: Objectives: Infective endocarditis of the aortic valve complicated by annular abscess is a challenging problem and often requires patch reconstruction after surgical debridement of the abscess cavity. Filling the remaining cavity with antibiotics is advocated to prevent recurrent endocarditis. This study aimed at evaluating the role of local antibiotics in patients with aortic valve infective endocarditis complicated by annular abscess. Methods: Between January 2012 and December 2021, all consecutive patients with aortic valve infective endocarditis complicated by annular abscess undergoing cardiac surgery and annular patch reconstruction were included. Patients receiving local antibiotics were compared with patients without local antibiotics. The primary endpoints were the incidence of recurrent endocarditis, re-operation, and mortality during two-year follow-up. Results: A total of 41 patients with aortic valve infective endocarditis complicated by annular abscess underwent surgical patch reconstruction after radical debridement. In total, 20 patients received local antibiotics in the abscess cavity and 21 patients were treated without local antibiotics. The most common causative microorganisms were the staphylococci species and the most common location of the abscess was the non-coronary annulus. During two-year follow-up, one patient in each group developed recurrent endocarditis ($p > 0.99$) and both patients were reoperated ($p > 0.99$). Two-year mortality was 30% in the local antibiotic group and 24% in the control group ($p = 0.65$). Conclusions: Radical debridement and patch reconstruction of the aortic annulus in patients with aortic valve infective endocarditis complicated by annular abscess is an effective surgical strategy. Filling of the remaining abscess cavity with antibiotic seems not to affect the rate of recurrent endocarditis, reoperation, and mortality during two-year follow-up.

Keywords: infective endocarditis; aortic valve; annular abscess; patch

1. Introduction

Cardiac surgery in patients with aortic valve infective endocarditis is associated with increased mortality and morbidity [1], especially in complicated cases such as annular abscess [2,3]. Radical surgical debridement of the abscess cavity is necessary to prevent recurrent endocarditis [4]. However, radical surgical debridement can result in tissue defects leading to the necessity for annular patch reconstruction to anchor a prosthetic valve. Additionally, the application of local antibiotics in the remaining abscess cavity has been proposed to prevent recurrence of infective endocarditis [5–7] and improve outcome [8]. In this study, we aimed to evaluate the effect of local antibiotic application in the remaining abscess cavity on clinical outcome in patients with aortic valve infective endocarditis complicated by annular abscess and a need for annular patch reconstruction.

2. Materials and Methods

2.1. Patients

Eligible candidates for this retrospective comparative study were patients with definitive infective endocarditis [9] of the aortic valve undergoing cardiac surgical therapy from

January 2012 to December 2021. Out of these, 71 patients were found to have annular abscess receiving annular patch reconstruction. Annular abscess was defined as paravalvular cavity with infectious or necrotic tissue in the aortic annulus or root, or as aortoventricular discontinuity. Patients undergoing replacement of the intervalvular fibrous body were excluded. The study was reviewed and approved by the institutional ethics committee (Protocol number: 23-11446-BO, approval date: 28 September 2023) and written informed consent was waived due to retrospective study design.

2.2. Surgical Technique

Standard aortic and caval cannulation techniques were applied. Cardioplegic arrest was achieved by crystalloid cardioplegia (Custodiol, Dr. Franz Koehler Chemie, Bensheim, Germany). After resection of the infected aortic valve leaflets, the aortic annulus was inspected for the presence of abscess. In cases with annular abscess, the abscess cavity was opened and all macroscopically infected tissue was removed. After irrigation with diluted povidone–iodine solution, the defect was excluded with autologous or bovine pericardial patch, respectively (Figure 1). Application of local antibiotics in the remaining abscess cavity was at the discretion of the operating surgeon. In cases with local antibiotics, the remaining cavity was filled with a mixture of antibiotic (dependent on the causative microorganism antibiogram) and fibrin glue before the closure of the defect. Finally, aortic valve replacement was performed. Concomitant procedures were performed as indicated. All instruments, synthetic material, and prostheses were soaked in vancomycin solution during operations.

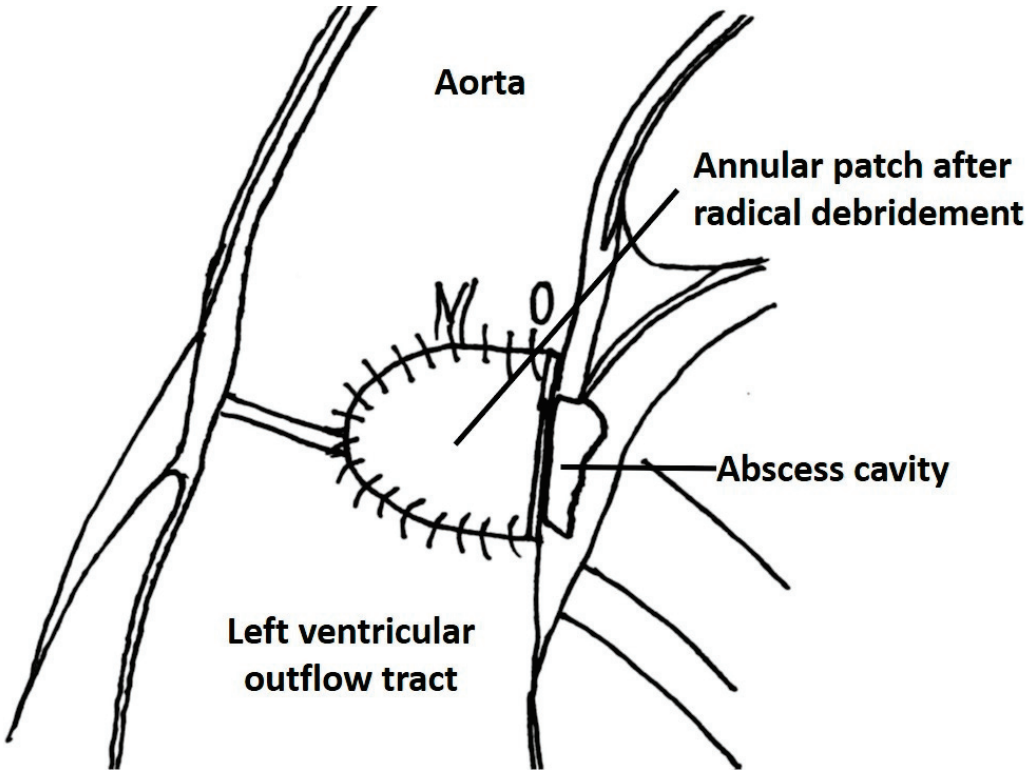

Figure 1. Patch reconstruction of the aortic annulus after radical debridement of the annular abscess cavity.

2.3. Postoperative Care

Postoperatively, all patients were transferred to the cardiac surgical intensive care unit (ICU) with invasive hemodynamic monitoring and guideline-directed antibiotic and supportive therapy. Follow-up was conducted by outpatient visits or telephone follow-up, and data on survival and valve-related complications were collected.

2.4. Endpoints

The primary endpoints of the study were the incidence of recurrent infective endocarditis, reoperation, and mortality at two-year follow-up. Recurrent infective endocarditis was defined as relapse or reinfection according to guidelines. Secondary endpoints included postoperative organ failure (circulatory, pulmonary and renal), and ICU and hospital stay.

2.5. Statistical Analysis

SPSS software version 29 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Continuous variables were reported as median and interquartile range (IQR) and compared with the Mann–Whitney test. Categorical data were expressed as number of patients and frequencies and compared using the chi-square or Fisher exact test. Kaplan–Meier curves were employed to evaluate overall survival rates and the two groups were compared using the log-rank test. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics

From January 2012 through December 2021, 211 patients underwent cardiac surgery for infective endocarditis of the aortic valve. In 79 (34%) patients, an annular abscess was found by intraoperative inspection. A patch reconstruction of the aortic annulus was performed in 41 patients. In 20 patients, a mixture of antibiotics and fibrin glue was used to fill the remaining abscess cavity. In the remaining 21 patients (control group), the abscess cavity was left empty. The preoperative demographics and clinical and inflammatory status of the two groups are given in Table 1. The most commonly identified causative microorganism for infective endocarditis (Table 2) was staphylococcus aureus. The most common location of the annular abscess was at the level of the non-coronary cusp insertion (Table 3). There were no significant differences in demographics, hemodynamic, and pulmonary status, the levels of preoperative inflammatory parameters, causative microorganism or location of the abscesses between the two groups.

Table 1. Baseline characteristics.

Variable	Local Antibiotic $N = 20$	Control $N = 21$	p
Demographics			
Age, years	72 (58–76)	68 (62–75)	0.276
Male gender	20 (100)	17 (81)	0.107
Coronary artery disease	12 (60)	7 (33)	0.087
Pulmonary disease	3 (15)	5 (10)	0.697
Dialysis	1 (5)	1 (5)	>0.999
Previous cardiac surgery	11 (55)	14 (67)	0.654
Valve surgery	11 (55)	14 (67)	0.444
Prosthetic valve IE			
Aortic valve prosthesis	10 (50)	14 (67)	0.279
Mitral valve prosthesis	-	1 (5)	0.488
EuroSCORE II	8.4 (2.7–12.2)	9.0 (6.0–20.2)	0.873

Table 1. *Cont.*

Variable	Local Antibiotic N = 20	Control N = 21	p
Preoperative clinical status			
Intubated	-	1 (5)	>0.999
Vasopressor need	-	2 (10)	0.488
Endocarditis-related stroke	7 (35)	7 (33)	0.910
Preserved left ventricular function	16 (80)	16 (76)	0.934
Inflammatory status			
C-reactive protein, mg/dL	8.80 (4.55–19.18)	6.50 (1.75–9.50)	0.276
Procalcitonin, ng/mL	0.38 (0.16–1.33)	0.12 (0.04–0.25)	0.128
White blood count, 10^9/L	7.68 (6.15–14.37)	8.28 (8.28–10.67)	0.873

Data are presented as number (%) or median (IQR); PCI, EuroSCORE, European System for Cardiac Operative Risk Evaluation.

Table 2. Microbiological profile.

Variable	Local Antibiotic N = 20	Control N = 21	p
Staphylococcus species	9 (45)	8 (38)	0.654
Staphylococcus aureus	9 (45)	7 (33)	0.444
Streptococcus species	4 (20)	4 (19)	>0.999
Enterococcus species	3 (15)	6 (29)	0.454
Others	1 (5)	1 (5)	>0.999
Negative culture	3 (15)	3 (14)	>0.999

Data are presented as number (%).

Table 3. Abscess location.

Variable	Local Antibiotic N = 20	Control N = 21
NCC	6 (30)	6 (29)
RCC	1 (5)	1 (5)
LCC	1 (5)	2 (10)
NCC-LCC-Commissure	2 (10)	2 (10)
RCC-LCC-Commissure	4 (20)	2 (10)
RCC + LCC	1 (5)	2 (10)
RCC + NCC	1 (5)	1 (5)
Circumferential	3 (15)	2 (10)
AMC	1 (5)	3 (14)

Data are presented as number (%). NCC, non-coronary cusp; RCC, right-coronary cusp; LCC, left-coronary cusp; AMC, aortic-mitral curtain.

3.2. Operative Characteristics

Table 4 presents the operative characteristics of the two groups. All patients underwent at least aortic valve replacement. In the control group, three patients underwent aortic root replacement using a conduit. Concomitant valvular procedures were performed more frequently in the control group, without statistical significance. Concomitant coronary artery bypass grafting was performed in six patients, four in the local antibiotics group,

and two in the control group ($p = 0.41$). Cardiopulmonary bypass and aortic cross-clamp times were longer in the local antibiotics group but did not reach statistical significance.

Table 4. Operative characteristics.

Variable	Local Antibiotic $N = 20$	Control $N = 21$	p
Aortic valve replacement	20 (100)	18 (86)	0.261
Biological valve	19 (95)	18 (86)	
Mechanical valve	1 (5)	-	
Aortic valve and root replacement (conduit)	-	3 (14)	0.232
Biological valve	-	2	
Mechanical valve	-	1	
Isolated AV replacement	15 (75)	12 (57)	0.228
Concomitant MV procedure	3 (15)	6 (29)	0.454
Concomitant CABG	4 (20)	2 (10)	0.410
Cardiopulmonary bypass time, minutes	171 (113–219)	130 (120–176)	0.276
Aortic cross-clamp time, minutes	109 (80–144)	101 (88–130)	0.642

Data are presented as number (%) or median (IQR); AV, aortic valve; MV, mitral valve; CABG, coronary artery bypass grafting.

3.3. Endpoints

The endpoints are summarized in Table 5. Thirty-day mortality was 12% overall, 15% in the local antibiotics group, and 10% in the control group ($p = 0.66$). The causes of early mortality were septic multiorgan failure in three cases and cardiac failure in two cases. Two-year mortality increased to 27% overall, 30% in the local antibiotics group, and 24% in the control group (Figure 2). Recurrent infective endocarditis occurred in one patient in the local antibiotics group and in one patient in the control group ($p > 0.99$). Both patients underwent reoperation. The time interval between the index operation and the recurrence of infective endocarditis in the local antibiotics group was 19 months and 40 days in the control group.

Table 5. Endpoints.

Variable	Local Antibiotic $N = 20$	Control $N = 21$	p
Primary			
Mortality			
30-Day	3 (15)	2 (10)	0.663
2-Year	6 (30)	5 (24)	0.655
Re-endocarditis (2-Year)	1 (5)	1 (5)	>0.999
Reoperation (2-Year)	1 (5)	1 (5)	>0.999
Secondary			
Postoperative MCS	3 (15)	4 (19)	>0.999
Dialysis	4 (20)	2 (10)	0.407
Reintubation	3 (15)	6 (29)	0.454
ICU-stay, days	8 (3–12)	8 (5–12)	0.860
Hospital stay, days	15 (8–22)	13 (11–17)	0.399

Data are presented as number (%) or median (IQR); MCS, mechanical circulatory support; ICU, intensive care unit.

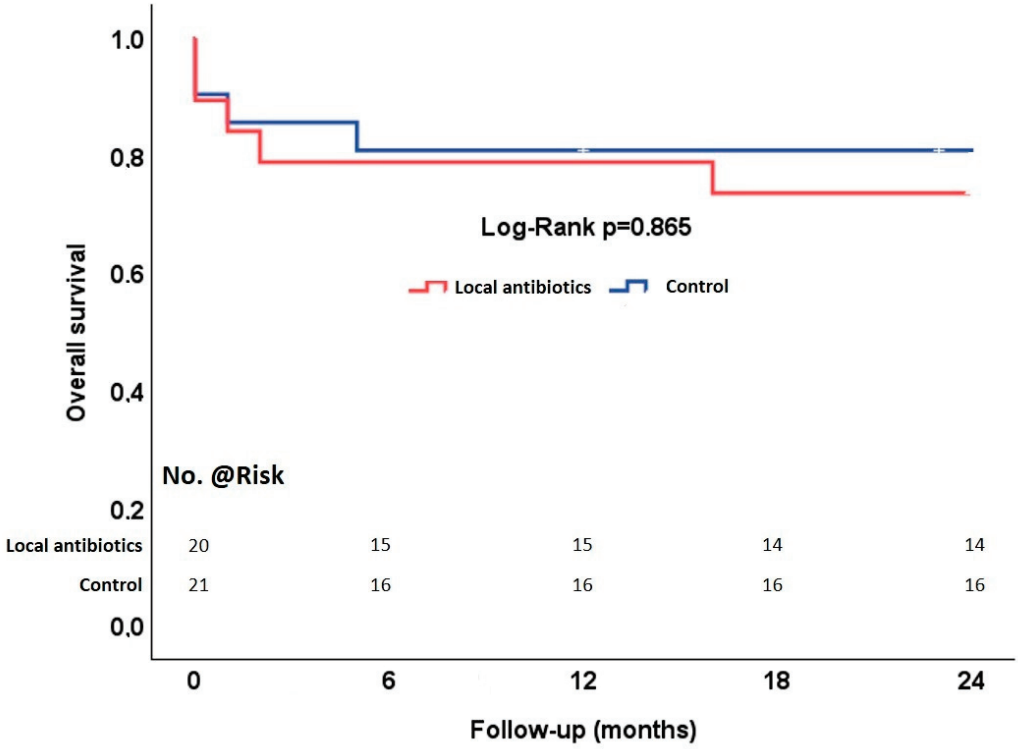

Figure 2. Overall survival of patients with aortic valve infective endocarditis complicated by annular abscess undergoing annular patch reconstruction with local antibiotics and control.

The incidence of postoperative organ failure (circulatory, respiratory and renal) requiring (temporary) support or replacement did not differ between the two groups. There were also no differences in the ICU and hospital stay between the groups.

4. Discussion

Annular abscess remains a frequent complication of aortic valve infective endocarditis and requires surgical debridement. The subsequent tissue defect often requires patch reconstruction to anchor the valve prosthesis and to exclude the remaining cavity from the circulation. In this study, we evaluated the effect of applying local antibiotics in the remaining abscess cavity on outcome, especially on the rate of recurrent infective endocarditis. We found that the rate of recurrent infective endocarditis is low after radical surgical debridement and annular patch reconstruction and that the application of local antibiotics did not affect the recurrence rate or survival during two-year follow-up.

Annular abscess is strictly a consequence of an uncontrolled infection causing a mycotic aneurysm of the sinuses of Valsalva. Uncontrolled infection can also result in fistulous communication between the aortic root and the left ventricular outflow tract (paravalvular aortic regurgitation) or to other cardiac chambers such as the right atrium and the right ventricle (Gerbode defect). Suspicion of abscess formation should rise with regards to any patient with aortic valve endocarditis on guideline-directed antibiotics and persistent fever, elevated inflammatory parameters, or cutaneous or embolic phenomena. Other signs of annular abscess include prolongation of PR interval or development of complete heart block. Multimodality imaging plays an important role when evaluating a patient with aortic valve infective endocarditis complicated by annular abscess [10].

The prevalence of aortic valve infective endocarditis complicated by annular abscess varies between 12% and 50% [11–13]. Abscess formation is an independent predictor of short-term mortality and is reported to be twice as high compared to patients without annular abscess [1]. Furthermore, recurrent infective endocarditis is higher in patients with annular abscess compared to patients without annular abscess [14]. Therefore, it is of crucial importance to eradicate infection by radical surgical debridement and exclusion

by patch reconstruction. The addition of local antibiotics in the remaining abscess cavity has been suggested to prevent recurrence. In addition, the risk of residual infected tissue seems to be low after radical surgical debridement. Furthermore, a mixture of antibiotics with fibrin glue in the remaining excluded abscess cavity may only provide temporary protection against reactivation of infection. Moreover, the presence of fibrin glue may impede the penetration of antibiotics in the surrounding tissue, mitigating the effect of such therapy. Although local antibiotics showed effectivity in the prevention of sternal wound infection [15], development of antibiotic-eluting or bacterial-resistant patches and valvular prosthesis may be a more effective strategy in the prevention of recurrent infective endocarditis in this high-risk population [16–19].

In this study, we selected only patients in whom a patch reconstruction was performed. Patients with small annular abscesses were treated by direct closure of the abscess cavity. The cohort comprises high-risk patients with large annular abscesses, who required patch reconstruction. The control group included three patients with additional aortic root replacement in which local antibiotics could not be applied. Exclusion of these patients did not change the outcome. Therefore, we decided not to exclude these patients from the analysis.

5. Limitations

To our best knowledge, this is the first study evaluating the role of local antibiotics in aortic valve infective endocarditis complicated by annular abscess. Although the baseline demographics, clinical and inflammatory status and operative characteristics of the two groups were comparable, bias cannot completely be excluded due to retrospective study design and limited sample size. Therefore, larger and randomized controlled studies are required before definitive conclusions can be drawn.

6. Conclusions

Local antibiotics in the remaining abscess cavity after radical debridement and patch reconstruction of the aortic annulus in patients with aortic valve infective endocarditis seems not to reduce the rate of recurrent endocarditis, reoperation, or mortality.

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

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