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Long-term follow-up after Aortic Valve Replacement with Trifecta bioprosthesis: a single center retrospective cohort

Cândida Inês Troncho Amaral dos Reis dos Gonçalves

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FM UP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

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DISSERTAÇÃO DO MESTRADO EM

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Muito obrigada, são os melhores!

Title: Long-term follow-up after Aortic Valve Replacement with Trifecta bioprosthesis: a single center retrospective cohort

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Abbreviations:

TF	Trifecta
AVD	Aortic Valve Disease
AVR	Aortic Valve Replacement
SVD	Structural Valve Deterioration
NSVD	Non-Structural Valve Deterioration
TTE	Transthoracic echocardiogram
EOA	Effective Orifice Area
PPM	Patient-Prothesis Mismatch
LV	Left Ventricular
LVMi	Left Ventricular Mass index
LVEDD	Left Ventricular End Diastolic Diameter
IVS	Intraventricular Septum
LVWP	Posterior wall thickness
BSA	Body Surface Area
ViV	Valve-in-Valve

Abstract

Introduction: St. Jude Trifecta (TF) bioprosthesis were adopted at most centers due to their unique design and hemodynamic performance. However, concerns regarding durability have been raised and long-term follow-up studies (≥10 years) are scarce.

Aims: To report hemodynamic performance as well as early/mid and long-term results of TF valve.

Material and Methods: In this longitudinal, single-center study, consecutive patients that underwent surgical aortic valve replacement (AVR) with TF, from July 2011 to December 2019 were included. Pre-, intra- and post-operative data, including routine early and latest outpatient ambulatory postoperative transthoracic echocardiogram (TTE) (median 4 months and 4.4 years, respectively) were collected. Hospital mortality was defined as in-hospital or within the first 30 days after surgery. Survival and need for reintervention were accessed in December 2022. Median follow-up was 5 years, maximum 11,5 years. Kaplan-Meier method was used for time-to-event outcomes (all-causes mortality and aortic prosthesis related reintervention irrespective of reason, due to structural valve deterioration (SVD) and endocarditis).

Results: We included 1192 patients, 53% being male, with a mean age of 74±8 years. Surgery priority was elective in 925 (78%) of cases. Most patients received a TF prothesis of size 23 (36%), followed by size 21 (31%). There were 610 (51%) multiple procedures, mostly coronary artery bypass grafting (53% within the multiple procedures). Median European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was 2.8 (0.5;72) and hospital mortality was 6%. Excluding these patients, cumulative survival at 1-, 3-, 5- and 10-years, were, respectively, 91%, 84%, 74% and 50%. There were 55 patients who needed reintervention by AVR or Valve-in-Valve (ViV): 33 due to structural valve deterioration (SVD), 19 due to endocarditis and 3 due to non-structural valve dysfunction (NSVD). Freedom from reoperation at 1-, 3-, 5- and 10- years were of 99%, 98%, 97% and 89%, respectively. In comparison to pre-operative TTE, first and latest post-operative follow-up TTE (n=1047 and n=682, respectively), showed that mean and maximum transvalvular gradients decreased significantly and mean effective orifice area increased at early TTE and slightly decreased in latest evaluation, but this parameter was significantly higher compared with pre- TTE. Patient-prosthesis mismatch (PPM) was severe in 11 (1%) cases at early TTE and 17 (7%) patients at latest TTE.

Conclusion: Our findings confirm the satisfactory hemodynamics and safety profile of TF bioprosthesis. Long-term results are comparable with published TF series and there seems to be no particular sign of adverse valve-related events in our sample, but a continuing echocardiographic update of this cohort it´s necessary.

Keywords: Aortic Valve Replacement, bioprosthesis; Trifecta

Introduction

Due to population aging, the prevalence of aortic valve disease (AVD) is steadily increasing worldwide. Elderly quality of life and life expectancy are becoming compromise, once AVD accounts for 61% of all valvular heart disease deaths, in 2017, according to Centers for Disease Control and Prevention.[1]

Aortic valve replacement (AVR) emerged as a *gold standard* procedure for AVD such as, aortic stenosis, aortic valve regurgitation, the combination of both or endocarditis, the major pathologies requiring surgical replacement. In developed countries, aortic stenosis is the primary valve disease leading to surgery, with a global prevalence estimated in 9.4 million people in 2019 being responsible for, nearly, 127,000 deaths in the same year.[2]

Within the last decades, the popularity of biological prosthesis had increased for AVR in elderly population (patients >65 years), as recommended by AHA and ESC/EACTS[3,4], nonetheless, its use in younger patients is raising[5,6]. Besides avoiding the burden and complications regarding anticoagulation therapy, the continuous improvement of valve design and hemodynamic performance and the expectable durability enhancement of the new-generation prosthesis, are making this trend to grow.[7-11]. Despite satisfactory durability, the nature of bioprosthesis translates a greater susceptibility to structural valve deterioration (SVD) that represents its major drawback[11,12].

The Trifecta (TF) bioprosthesis (*Abbott*) is a new-generation stented valve with a unique design intended to improve hemodynamic performance and durability. This valve has a supra-annular suture and bovine pericardium leaflets, externally mounted onto a polyester-covered titanium stent, allowing a greater effective orifice area (EOA), lower pressure gradients and an acceptable percentage of patient prosthesis mismatch (PPM). Additionally, it has an ethanol-based anticalcification technology aimed to extend durability [12-14]. Despite the great hemodynamic features, several concerns in the literature have been raised about early structural degeneration of TF[9,11,15,16]. Earlier this year (February 2023) *Abbott* published a letter confirming the early/mid-term structural dysfunction of TF valves within the first five years after implantation[17]. However, as long-term follow-up results remain scarce, we aim to describe a tertiary center TF cohort including TF hemodynamic performance as well as early/mid and long-term results of this bioprosthesis. Our main outcomes are long-term survival and need for prosthesis reintervention (by surgery or Valve-in-Valve [ViV]). As secondary outcomes, we aim to

report the early postoperative complications and the early and late hemodynamic profile of the TF.

2.Methods

2.1 Study design, patients,and ethics

In this longitudinal, retrospective, single-center study, we included consecutive patients who underwent AVR with TF, excluding redo-surgeries, from July 2011 (beginning of experience with TF at our center) to December 2019, at the Cardiothoracic Surgery Department of Centro Hospitalar São João, Porto, Portugal. Both multiple and isolated AVR procedures (definitions in Table 1, supplementary material) were included and irrespective of reason for surgery (aortic valve degenerative disease, rheumatic, congenital, previous prosthesis failure or other causes).

This study was approved by the Centro Hospitalar Universitário de São João Ethics Committee (Institutional Review Board 146-16). Patient informed consent was waived due to the retrospective nature of the study.

2.2 Data collection and Variables

Clinical and surgical data from pre-; intra- and post-operative periods were collected throughout paper patient's files, from clinical databases and electronic health records (EHR). National registries were consulted for survival data.

Preoperative variables definitions are described at Supplementary Table 2 and European System for Cardiac Operative Risk Evaluation (EuroSCOREII) definitions were used as appropriate.

Data from all-causes mortality and need for prosthesis-related reintervention were accessed in December of 2022 (censored on 31st December 2022).

Both reoperation and ViV were considered for the need for prosthesis-related reintervention outcome. This variable was then categorized in SVD, non-structural valve deterioration (NSVD) or endocarditis according to the consensus definitions published in 2021 by Valve Academic Research Consortium 3 (VARC): SVD is defined as intrinsic permanent changes in the valve (as calcification; leaflet tear, strut deformation, etc) while, NSVD is known as any deficiency not intrinsic to the valve itself (as leak; intra-prosthetic

regurgitation not attributable to SVD; PPM; coronary ischemia from ostial coronary obstruction, etc), both leading to valve dysfunction.

The immediate postoperative events registered were as follows: new atrial fibrillation (AF) episodes; definitive pacemaker implantation, renal impairment (requiring renal replacement with dialysis); stroke or transient ischemic attack (TIA); prolonged invasive mechanical ventilation; severe thrombocytopenia (minimum platelets count <30.000μl); hospital mortality (Table 3, supplementary material) and reoperation in the same episode due to coronary artery bypass grafting; bleeding/tamponade or sternal re-suturing due to wound dehiscence/mediastinitis.

Medical observation and first transthoracic echocardiograms (TTE) assessment post-surgery are performed at our center as a routine post-operative procedure at a median of 4 months after surgery. After that, most patients are discharged from our center and are followed-up locally by their general assistance physician or local cardiologist. The latest TTE data available in the national electronic health records were also collected.
From the TTEs, LV (left ventricular) systolic function, LV mass index (LVMi), presence of leak or intraprosthetic aortic regurgitation; aortic valve effective orifice area (EOA), aortic transprosthetic mean and maximum gradients and PPM were recorded. LVMi was calculated using the following formula: {0.8 x [1.04 x (LV end-diastolic diameter (LVEDD) + intraventricular septum thickness (IVS) at end diastole + Posterior wall thickness at end-diastole (LVPW))^3 – LVEDD^3] + 0.6} / Body surface area (BSA). PPM was defined as moderate (0.65 cm^2/m^2 ≤ indexed EOA< 0.85 cm^2/m^2) or severe (indexed EOA<0.65 cm^2/m^2).

2.3 Surgical Technique

Prosthesis selection was based on surgical team preference. TF was implanted in a supra-annular position, through full median sternotomy or with L-shaped mini-sternotomy incision, using standard cardiopulmonary bypass (CPB) under mild hypothermia conditions. Myocardial protection was provided with cold crystalloid or blood cardioplegia. Interrupted polyester suture with pledgetes were used to perform AVR and aortotomy was closed with polypropylene running suture.

2.4 Statistics

Data processing and analysis were done using Statistical Package for the Social Sciences version 28.0 (SPSS) Software, IBM Corporation, Armonk, NY, USA, for Windows and R version 4.1.2 and RStudio version 2021.09.2. The "survival" packages were used for time to event analysis[18].

Visual inspection of histograms was used for checking data distribution. Continuous variables were presented as mean ± standard deviation or median (minimum-maximum) or interquartile range (IQR), as appropriate. Categorical variables are presented as absolute and relative frequencies (valid percentage, excluding missings).

Comparisons of continuous variables between patients with multiple versus isolated procedures were done using independent t test or Mann-Whitney test. Comparisons between pre-, early post and latest post-operative periods were done using one-way repeated measures ANOVA or Wilcoxon paired test for paired samples, according to number of evaluations.

Kaplan-Meier curves and cumulative incidence function curves were used to describe time-to-event data, such as survival and need for aortic prosthesis reintervention.

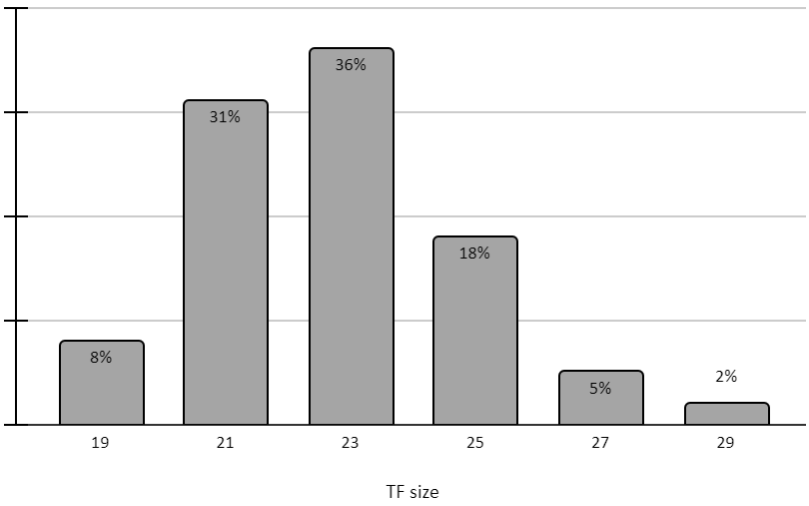
Results

Patient Characteristics

We included 1192 patients, 53% being male, with a mean age of 74±8 years. Demographic data and preoperative characteristics are presented in Table 1. The median European System for Cardiac Operative Risk Evaluation (EuroSCORE II) was 2.8 (min.: 0.5 and max.:72). Most patients (93%) had native aortic valve disease, mainly due to degenerative process (78%). The principal indication to perform AVR was stenosis (77%) followed by aortic regurgitation (10%). Furthermore, 7 (1%) patients had previous endocarditis and 52 (4%) active endocarditis (34 in native aortic valve and 18 in previous aortic prosthesis) (Table 2).

Surgical Data

Surgery priority was elective in 925 (78%) of cases. Most patients received a TF prosthesis of size 23 (36%), followed by size 21 (31%) (Graph 1). There were 610 (51%) multiple procedures, mostly Coronary Artery Bypass Grafting (CABG) (53%) and ascending aortic intervention (33%), within multiple procedures. Moreover, 38% of the patients underwent AVR and other valves intervention.



Graph 1. Trifecta prosthesis sizes

Bypass and clamping time were significantly lower in isolated procedure [82 (64,103) mmHg and 60 (47, 75) mmHg, respectively], than in multiple procedures [130 (99,173) mmHg and 92 (68, 120) mmHg, respectively], p<0.01 for both comparisons. (Table 3).

Early Post-operative results

Early post-procedure outcomes are listed in Table 4.

Intra-operative deaths occurred in 5 cases (median and mean EuroSCORE II: 2.8 and 5.1). Hospital mortality was 6%, mostly due to cardiac causes (42%) and to infection in 35% of the patients. Median length of stay was 7 (6-12) days and 128 (11%) patients needed prolonged mechanical ventilation. *De novo* atrial fibrillation occurred in 335 (35%) patients and 28 patients needed to implant a permanent pacemaker during the immediate postoperative period. Post-surgery stroke or TIA occurred in 4% cases. Eleven patients (1%) needed renal replacement therapy and 22 (2%) suffered severe thrombocytopenia.

At the same episode, there were 58 (5%) patients that need a reoperation procedure, most of them due to sternal problems (21[2 %]) or due to cardiac tamponade/bleeding (15 [2%]). Percutaneous tracheostomy was performed in 10 (2 %) patients and 4 required CABG after AVR, of which 2 presented a NSVD complication leading to CABG. (Table 4)

Transthoracic echocardiogram results

Pre-, early-post and latest-post echocardiogram data are presented in Table 5, figure 1 and figure 1,2, 3 and 4 from supplementary material.

Early post-AVR echocardiogram evaluation was performed in 1050 out of 1125 patients who discharged alive from hospital (7% lost to follow-up regarding echocardiogram data) in a median time of 4 (3,7) months. These TTE data showed an EOA of 2.0±0.5cm^2 and a mean transprosthetic gradient of 10 ± 4 mmHg. PPM occurred in 80 cases, being severe in 11 (1%) patients. Residual intraprosthetic regurgitation was evidenced in 149 (14%) patients, with no moderate/severe cases. Fifty-five (5%) patients had prosthetic leak, only one leading to a moderate/severe leak who performed a percutaneous procedure (Amplatzer Vascular Plug II implanted).

The latest echocardiographic evaluation available for the primary TF prosthesis (before any reoperation surgery) was available in the national database for 682 patients and it was performed at a median of 4.4 (2.9,5.9) years. This evaluation showed a mean EOA of 1.8±0.4 cm^2 and a mean transprosthetic gradient of 12±8 mmHg. PPM was found in 60 (8%) patients, being moderate in 43 and severe in 17 individuals (Figure 1, supplementary material). At this timepoint, 182 patients revealed intraprosthetic regurgitation being

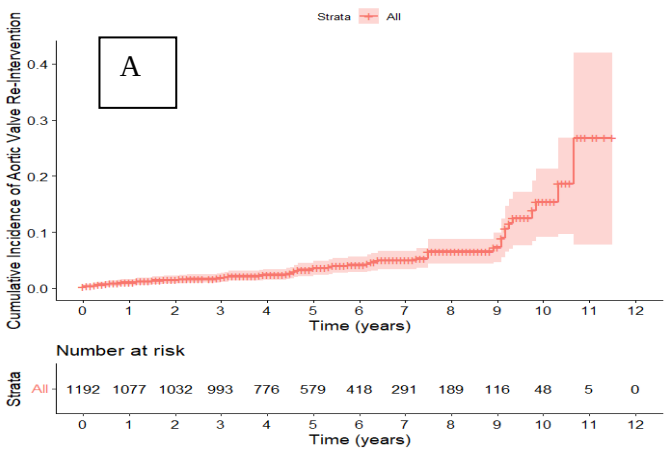
moderate to severe in 19 (3%) cases. Periprosthetic regurgitation (leak) occurred in 46 individuals, being moderate/severe in 13 (2%) (Figure 2, supplementary material).

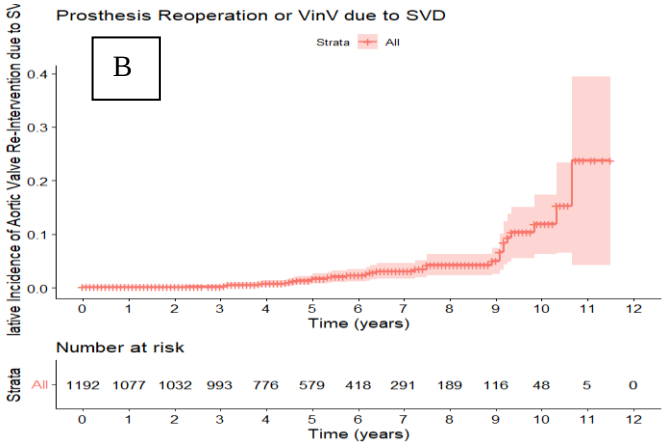
From all mid/long-term echocardiographic follow-up, 658 exams were paired with a first follow-up echocardiogram and its comparison is presented in (Figure 1). Comparing EOA, mean and maximum gradients in patients with pre-, first- and latest echocardiogram, there were a significant increase of mean EOA between pre- and early TTE [0.8 (0.2-2.6) cm^2 to 2 (0.9-3.8) cm^2] and pre- and latest TTE [0.8 (0.2-2.6) cm^2 to 1.70 (0.6-3.2)cm^2] (Figure 1. C) and a decreased median maximum/mean gradient, between pre-/first and latest echocardiogram evaluation [75 (12-201)/47 (7-125) mmHg; 18 (5-61)/10 (2-33) mmHg and 19 (6-98)/10 (4-62) mmHg, respectively in each time point] (Figure 1. A, B). LV mass underwent a significant decrease after AVR. It seems to occur a reverse remodeling leading to hypertrophy decrease after the procedure and these changes were sustained until latest TTE evaluation (median LVMi pre: 139 (9-306) g/m^2 vs median LVMi at early TTE:119 (4-411) g/m^2 vs median LVMi at latest TTE: 115 (7-259) g/m^2) (Figure 1. D).

Trifecta-related reintervention results

During a median time of 4.9 (maximum 11.5) years, there were 55 patients who underwent TF related reintervention (AVR or ViV). Reintervention was performed at median time of 4.0 (0;10) years and the cumulative incidence of prosthesis related reintervention, irrespective of reason, at 1-, 3-, 5- and 10- years were 1.1%, 1.9%, 3.7% and 15.4%, respectively (Figure 3, Panel A).

Regarding reintervention causes, most patients had SVD (n=33), 19 endocarditis and 3 NSVD (Table 6). Figure 3 Panel B reflects the cumulative incidence of aortic TF reintervention due to SVD, being 0.2%, 0.3%, 1.7%, 3.1% and 12% at -1; -3; -5, -7 and -10 years of follow-up, respectively.





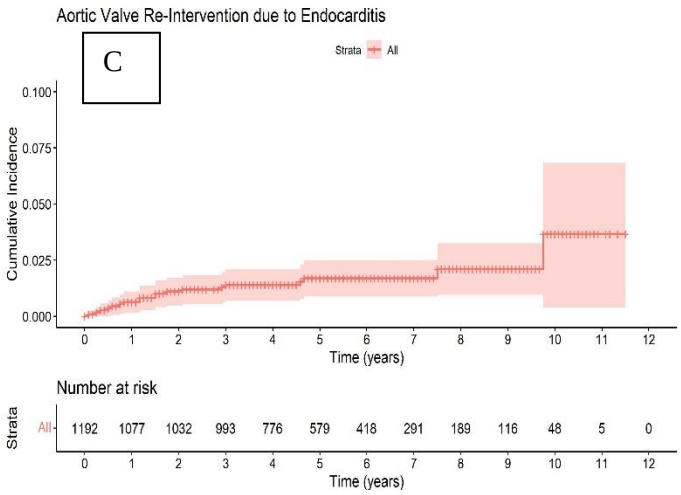


Fig.3 Panel A represents the cumulative incidence of aortic valve reintervention; Panel B represents the cumulative incidence of prosthesis related reintervention due to SVD and Panel C represents the cumulative incidence of prosthesis related reintervention due to endocarditis.

Figure 3 panel C represents cumulative incidence of TF related reintervention due to endocarditis, being 0.6%, 1.3%, 1.6% and 2%, at -1, -3, -5 and -8 years of follow-up. Nineteen patients (2%) had endocarditis as reason for the TF index surgery.

Regarding NSVD, it occurred in an early timepoint (0-6 months) after surgery and it comprised ostial coronary obstruction and leaflet(s) tear with partial dehiscence at the commissure level, leading to repeat AVR (n=1) and to CABG (n=2).

Survival

Median and maximum follow-up for all causes mortality were, respectively, 5 and 11.5 years. Excluding the hospital mortality, the cumulative survival at 1-, 3-, 5- and 10-years, were, respectively, 91%, 84%, 74% and 50% (Figure 4).

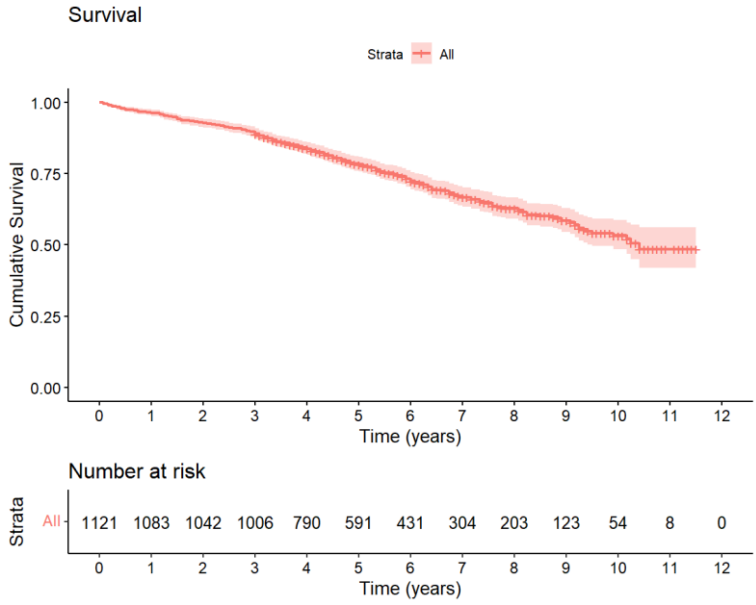


Fig.4: Cumulative Survival excluding hospital mortality (6%).

Discussion

This study outlines the experience with TF in a tertiary single center for 11.5 years. In our cohort, TF had a great hemodynamic performance even in a mid/long-term follow-up, maintaining a clinically acceptable EOA, reduced maximum and mean gradients and, consequently, low PPM percentage. Reoperation results related to prosthesis dysfunction were satisfactory: 55 patients out of 1192 required aortic valve reintervention by surgery or ViV, being SVD the main cause. We assisted to a rapid increase in reinterventions by SVD only after 9 years of follow-up (cumulative incidence until 9-years of 4.3% and 19.5% after that period), in contrast with the published literature[11,15,17], where the greater incidence of SVD cases started earlier. Cumulative survival curves depicted a predicted shape considering the characteristics of this all-comers and real-world cohort with a mean age of 74±8 years.

TF Hemodynamic Performance

Regarding hemodynamic performance, the outcomes were similar those presented in other studies[11,14,19,20]. For instance, Rubens and colleagues study showed a significant lower pressure gradient and a larger EOA at early follow-up of 1 year, when comparing Trifecta (n=331) with Carpentier-Edwards Perimount Magna Ease (ME) (n=360)[7]. Lehmann *et al*, in Leipzig Experience, outlined the excellent hemodynamic performance even in extended periods of follow-up up to 4 years (mean gradient 10 mmHg and EOA 1.6±0.6cm^2)[20], comparable to our 12±8 mmHg and 1.8±0.4 cm^2 at a mean time of 4.9 years. Considering the TTE longitudinal analysis, our results reinforced the TF hemodynamic profile to be consistent over a long-term follow-up time (maximum follow-up 10.6 years) with a significant and maintained cardiac reverse remodeling which is known as a relevant prognosis factor [21,22].The good hemodynamic performance observed with TF valves reduces the likelihood to develop severe PPM rates and there are several studies that revealed a minor incidence of moderate to severe PPM with this bioprosthesis compared to others [7,9,11,19]. In our cohort, at early and latest TTE evaluation reflected severe PPM rate of 1.1% and 7.2%, respectively, demonstrating favorable results even in a cohort with a reduced number of aortic enlargement procedures (1.6%) and 8% of 19mm prosthesis size implanted.

Survival

Freedom from all-cause mortality was 74%, 63% and 50% at -5, -7 and -10 years, respectively, similarly to the data published by Werner *et al* who compared TF (n = 298) with Intuity bioprosthesis (n=772) and reported a freedom from overall mortality of 72.5% and 55.7% at -5 and -8 years for the TF bioprosthesis. In their study, age, diabetes, atrial fibrillation pre-operative, log-transformed preoperative creatinine and time varying effect of the valve type emerged as significant predictors of mortality, in a median follow-up of 6.1 years (max. 9 years) [11]. Another study of 918 TF patients highlighted previous myocardial infarction and pre-operative inotropic medication, as the strongest independent predictors of mortality with no effect of TF valve at 2.7 ± 1.6 (maximum, 7.4 years) years of follow-up [20]. In contrast, Fukuhara *et al* estimated higher cumulative survival rates for TF group at 7 years (77±2.8%) which could be explained by the younger cohort of their study (mean age of 69.7±11.4, vs 74±8 years in our cohort) and lower prevalence of diabetes at baseline[15] [28.9% (Fukuhara) vs 36.9% (Werner) vs 35% (Our cohort)].

TF related reintervention – SVD

Several authors have already raised concerns about TF early dysfunction, especially due to SVD and even *Abbott* published a letter warning for this possible premature deterioration[7,9,15,17]. In our cohort, interestingly, reintervention surgery or ViV due to SVD occurred mostly after 5 years: cumulative incidence of 1.4% until 5 years of follow-up and 22.4%≥ 5 years. We assisted to a rapid increased in reintervention due to SVD events only after 9 years of follow-up (cumulative incidence until 9-years of 4.3% and 19.5% after that period). These results contrast with the ones reported by Werner *et al* and Fukuhara *et al* who underlined the quicker rate of SVD reintervention at 6 years of follow-up[11,15]. Freedom from reintervention due to SVD in our cohort was 99.8%, 99.7%,98.3% and 88%, in 1-,3-, 5- and 10- years, respectively, being comparable with Leipzig Experience, a single center cohort with 918 TF, where freedom for SVD reintervention with TF was 99.7±0.2% and 97.9±1.5% at 3- and 5- years[23]. However, most literature have been presenting worse results for TF valve. Both Biancari *et al* and Yongue and colleagues compared TF with Perimount (PM), after propensity score (PS) matching, and both reported a significant increased risk of reintervention in TF group comparing with PM [9,24]. The risk of prosthesis-related reintervention in TF valve was

1.1%, 2.0% and 4.1% versus 0.7%, 1.0% and 1.3% with the PM valve, at 1-, 3- and 5-years respectively, in 2298 pairs of patients from Yongue cohort. At 7-years, 772 PS-matched pairs of the Biancari study evidenced 6.1% TF vs. 0.4% PM[9]. These findings are in line with our results for cumulative incidence for reintervention until 5 years of follow-up, where our results are tendentially better, being 1.1%, 1.9%, 3.7% and 5% at 1-, 3-, 5- and 7- years, respectively.

In Werner *et al* cohort (TF: 298 vs Intuity: 722) cumulative incidence for reintervention due to SVD. TF valve results were 0%, 2.0% and 4.5% versus 0%, 0.3% and 1.0% in Intuity valve, at 1-, 3- and 5-years respectively[11]. Surprisingly, our results for the incidence of aortic-valve reintervention due to SVD were closer to the Intuity cohort than to their TF group, being 0.2%, 0.3% and 1.7%, at 1-; 3- and 5-years. Fukuhara *et al* work showed 13.3% TF vs 4.6% in non-TF group at 7- years of follow-up[15] and Werner cohort presented even higher cumulative incidence of reintervention due to SVD in TF group at the same time-point (23.8% TF vs 1.6% in Intuity)[11]. At 7-years of follow-up, our cumulative incidence for reintervention due to SVD was 3.1%, still closer to other bioprosthesis studied in other reports presented before, than to their same cohort TF counterparts. SVD definition from different reports could be the reason for discrepant results, however all two studies referenced had defined prosthesis-related reintervention due to SVD as open-chest reoperation or ViV procedures, without counting on SVD diagnosis by echocardiogram, without reintervention, which is the same definition we used. Of note, we only have access to the reinterventions performed at our center which could have smoothly underestimated our incidence rate of SVD, although, we are the reference center for Cardiothoracic surgery in North of Portugal that serves the great majority of patients of our cohort.

Indeed, considering the bioprosthesis failure, the surgical approach is still the preferred option of treatment in low risk and younger patients[7,12,25],but ViV emerged as a viable alternative for redo-procedure, less-invasive and likely to preserve the valve already implanted, especially in older (>75) and high risk patients[5,7,12,20]. Several studies reported great early outcomes post-ViV (≤30 days), with reduced incidence of mortality, lower incidence of major bleeding and shorter median length of stay compared to AVR, but at mid and long-term follow-up, these results are not significantly different[6,26,27].

ViV procedure has also some drawbacks such as transcatheter heart valve (THV) migration, ostial coronary obstruction, a life-threatening event, and mal positioning of the new valve, creating greater gradients and increasing the chance of PPM, being crucial to

be familiarized with the different types and sizes of valves once the diameter from the prosthesis already implanted needs to be appropriate to perform this procedure.

An article published by Shah, B. (2021) reinforces the importance of the first surgical approach to preserve the option of ViV and the procedure as a feasible method for failed TF[28].Of note, in the present cohort, 15 patients with SVD valve dysfunction were treated with ViV procedure, independently of the valve size implanted before. Nevertheless, the impossibility to fracture the rigid sewing cuff from TF with an endovascular balloon and the design with an externally mounted leaflets prone to ostial obstruction, could make a potential limitation to use ViV for reintervention in this type of bioprosthesis[9,12,13]. Further studies are needed to explore the success of ViV in TF.

TF related reintervention – NSVD

In our sample, 3 out of 55 patients who required a reintervention surgery, were due to NSVD and occurred at same day, 1- and 4 months after TF implantation. The first consisted in immediate ostial obstruction and the others occurred by partial dehiscence of leaflet(s) tears. Our NSVD prevalence was similar to the reported by Anselmi and colleagues that included 824 patients with TF bioprosthesis followed-up by 2.2 ± 1.3 years (0.3% our cohort vs 0.5% Anselmi cohort) [29]. On the other side, in Mortelé *et al* study, with 182 TF valves patients with a mean follow-up of 3.3 years, the rate of reoperation due to NSVD was 3.6%, superior to our sample (0.3%), probably due to surgeon implementation technique, once they outlined the fragility of this valves cusps and the extra careful needed when they are being implanted[14].

TF related reintervention – endocarditis

In our cohort, 19 individuals were reintervened due to TF prosthesis endocarditis during the follow-up. At 5-years, freedom from reintervention due to prosthetic endocarditis was 98.4%, whereas, in Anselmi cohort, the freedom from prosthetic endocarditis was 97.7% at the same time-point[29]. Of note, we only reported endocarditis surgically treated at our center, distinctively, Anselmi also included medically treated endocarditis. In our sample, 2 out of 19 patients who were reintervened due to endocarditis had previously active endocarditis at the time of AVR with TF.

Early post-operative outcomes

Our EuroSCORE II median and mean was 2.8 and 5.1, respectively, maximum of 72, reflected in the hospital mortality of 6%, out of this percentage, 5 (7%) patients had an intra-operatively death (two urgent surgeries, most of the patients with coronary artery disease). Lehman *et al* also presented an hospital mortality of 6%, although, their sample´s mean presented a logistic EuroSCORE of 7.8% instead of calculating EuroSCORE II.[20] Kieser and colleagues published an article comparing the logistic EuroSCORE with EuroSCORE II in a CABG sample with 1125 patients. They referred that Logistic EuroSCORE overestimates the pre-operative risk and it´s better to determine which patients are in high-risk group before surgery whereas, EuroSCORE II tendentially underestimates the pre-operative risk, particularly in high-risk patients, the group with higher impact in pre-surgery risk assessment. Therefore, the pre-operative risk could be overestimated in Lehman patients, so we can´t compare the score with our sample. In opposite, most of the literature showed a lower percentage of hospital mortality rates (Werner 4.0% and Yongue 1.2%)[11,24], compared to our cohort. This could be explained by the inclusion of all-comers in our cohort (higher percentage of urgent and emergent surgeries, including those with any type of concomitant procedures, as well as, patients with active endocarditis and patients with aortic dissection as reason to require AVR, in contrast to Werner and colleagues work, that only included patients with aortic stenosis or combined aortic disease and excluded patients with active endocarditis and aortic regurgitation as reason to perform AVR. Yongue *et al* presented a substantial lower hospital mortality of 1.2% for TF group[24] compared to our sample (6%). They included all patients that underwent AVR however, they didn´t calculated any EuroSCORE assessment, but comparing pre-operative sample characteristics with our cohort, their patients seem to have a lower pre-operative risk (younger cohort [69±11]; less percentage of patients with diabetes; they didn´t specify the urgency of the surgeries included].

In general, we had a lower incidence of early post-operative complications, comparing with the literature, such as length of stay, major bleeding requiring revision, AF *de novo*, permanent pacemaker implantation post-surgery and new onset dialysis [9,14,15,20,23]. The most common post-operative complication was *de novo* AF that occurred in 35% of cases, similarly to Yongue *et al* cohort (39%)[24]. Postoperative stroke or TIA occurred in 3.5% of our cohort and 2.7% of stroke in Biancari *et al* sample, however they excluded TIA rates from this percentage[9]. There were 28 (2%) individuals who need to implant a

permanent pacemaker at the immediate post-operative period, similarly with other studies published in the literature (Anselmi: 1.9%; Werner 2.35%; Lehnam:2.4%)[11,20,29].

Study Limitations

This study has some limitations: 1) retrospective nature and missing data due to this type of data collection; 2) being a single center and observational cohort, where the prosthesis choice is a surgical team decision, underlining the personal preferences with the inherent selection bias; 3) The observational nature also prevents the echocardiogrphic evaluation at the same exact time points for all patients and by the same group of operators bringing not only a wide range of echo time intervals, but also a wider operator variability; 4) unavailability of mortality causes information; 5) unavailability of other long-term outcomes such as major cardiovascular and cerebrovascular events which are of utmost relevance in a cardiac surgery cohort; 6) survival bias of our national system of electronic health records: information from other centers, including transthoracic echocardiograms, is only accessible if the patient is still alive: the latest transthoracic echocardiogram we used for deceased patients was the one performed at our center and that might have not been the latest performed; 7) although we have one of the longest follow-up period published until now with TF bioprostheses, it should be noticed that after 10-years of follow-up we have only <50 patients at risk which limits the cumulative incidences estimated.

Conclusion

In conclusion, our results confirm the satisfactory hemodynamic and safety profile of TF valves at early follow-up, reinforcing our previous publication 525 implanted TF until 2016)[8] now counting on 1192 TF. Additionally, we verified appropriate performance and durability at mid and long-term follow-up (median follow-up: 5 years; maximum: 11.5 years). Further investigation is needed once our results are distinct from the majority of studies published in the literature about reintervention in TF due to SVD. Our cohort had lower percentage of reintervention due to SVD cases and, interestingly, showed a higher incidence of reintervention due to SVD only after -9 years of follow-up. It is necessary the update of the echocardiographic data to ensure results from TF bioprosthesis performance along the years. It was also possible to observe the growing use of ViV for

reintervention procedure, however studies about ViV results are scarce, especially in TF valves.

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TrifectaTM Valve and TrifectaTM Valve with Glide Technology

Model: TF-19A, TF-21A, TF23A, TF25A, TF-27A, TF-29A, TFGT-19A, TFGT-21A, TFGT-23A, TFGT-25A, TFGT-27A, and TFGT-29A, 2023).
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Variable	Value (n =1192)
Age (y), mean±SD	74 ± 8
Male sex, n (%)	630 (53)
NYHA ≥III, n (%)	383 (33)
CCS≥III, n (%)	160 (14)
Hypertension, n (%)	1003 (85)
Dyslipidemia, n (%)	812 (69)
Diabetes *mellitus*, n (%)	414 (35)
Obesity, n (%)	356 (30)
History of smoking, n (%)	255 (12)
Chronic renal failure, n (%)	
Moderate (clearance creatinine ≥50->85mL/min)	568 (48)
Severe (clereance creatinine <50mL/min or Dialysis)	249 (21)
Extracardiac arteriopathy, n (%)	
Cerebro-vascular disease	159 (15)
Peripheral-vascular disease	20 (2)
Both diseases	7 (1)
Previous cardiac surgery, n (%)	67 (6)
EuroSCORE II, %, median (IQR)	2.8 (1.5–5.5)
Preoperative cardiac rhythm, n (%)	
Sinus rhythm	935 (79)
Atrial fibrillation	213 (18)
Pacemaker	31 (3)
Surgery urgency, n (%)	
Elective	925 (78)
Urgent	255 (21)
Emergent	8 (1)

NYHA:New York Heart Association functional classification; CCS: Canadian Cardiovascular Society angina score; IQR: interquartile range

Table 1. Patient Characteristics, values presented as n (%) or median (IQR).

Variable	Value (n=1192)
Aortic native valve, n (%)	1149 (96)
Previous aortic prosthesis, n (%)	47 (4)
-Dysfunction	26 (55)
- Active Endocarditis	18 (38)
-Previous Endocarditis	3 (6)
Native aortic valve pathology, n (%)	
Degenerative	955 (80)
Congenital	109 (9)
Rheumatic	34 (3)
Endocarditis	41 (3)
Active	34 (3)
Previous AVR	7 (1)
Predominant stenosis, n (%)	919 (77)
Predominant aortic regurgitation, n (%)	114 (10)
Stenosis and aortic regurgitation, n (%)	104 (9)

AVR: aortic valve replacement

Table 2. Aortic etiology and pathology, values are presented as n (%)

Variable	Value (n =1192)
Multiple procedures, n (%)	610 (51)
Concomitant procedures, n (%)	(n=610)
Mitral valve intervention	115 (19)
Tricuspid valve intervention	115 (19)
CABG	326 (53)
Aorta intervention	202 (33)
Bentall operation	22 (4)
AF ablation (unipolar and bipolar)	15 (2)
Permanent pacemaker implantation	10 (2)
Cardiopulmonary bypass time, minutes, median (IQR)	
Isolated procedure	82 (64,103)
Multiple procedure	130 (99,173)
Aortic cross-clamp time, minutes, median (IQR)	
Isolated procedure	60 (47,75)
Multiple procedure	92 (68,120)

CABG: coronary artery bypass graft; AF: atrial fibrillation; IQR: interquartile range

Table 3. Peri-operative data, values are presented as n (%) and median (IQR).

Variable	Value n (%)
Reoperation at the same episode	
Bleeding/tamponade	15 (3)
Sternal wound problems	21 (3)
CABG	4 (1)
Percutaneous tracheostomy	10 (2)
IABP implantation	24 (2)
LOC	183 (17)
Severe thrombocytopenia	22 (2)
Prolonged ventilation	128 (11)
Stroke or TIA	41 (4)
AF *de novo*	335 (35)
Definitive pacemaker implantation	28 (3)
New-onset dialysis	11 (1)
Hospital mortality	71 (6)

CABG: coronary artery bypass graft; IABP: Intra-aortic balloon pump; LOC: low cardiac output; TIA: transient ischemic attack; AF: atrial fibrillation

Table 4. Early post-operative results, values presented as n (%).

	Pre-operative Echocardiogram (n=1149)	Early Echocardiogram (n=1047)	Latest Echocardiogram (n=682)
Depressed left ventricular ejection fraction, n(%)	224 (19)	225 (20)	171 (24)
LVMi, g/cm^2, mean (SD)	143.6 (37)	122.2 (31)	117.2 (32)
EOA, cm^2, mean (SD)	0.8 (0.3)	2.1 (0.5)	1.8 (0.4)
Mean gradient, mmHg, median (min-max)	47 (7-125)	10 (2-33)	10 (4-62)
Maximum gradient, mmHg, median (min-max)	75 (12-201)	18 (5-61)	19 (6-98)
Paravalvular leak≥III, n (%)	NA	1 (2)	13 (2)
Intraprosthetic regurgitation ≥III, n (%)	NA	0 (0)	19 (3)
PPM severe, n (%)	NA	11 (1)	17 (7)

LVMi: Left Ventricular Mass index; SD: Standard deviation; EOA: Effective Orifice Area; PPM: patient prothesis mismatch; NA: not applicable

Table 5. Pre, early and late echocardiogram (TTE) evaluation. Variables are presented as n (%); mean (SD) and median (IQR).

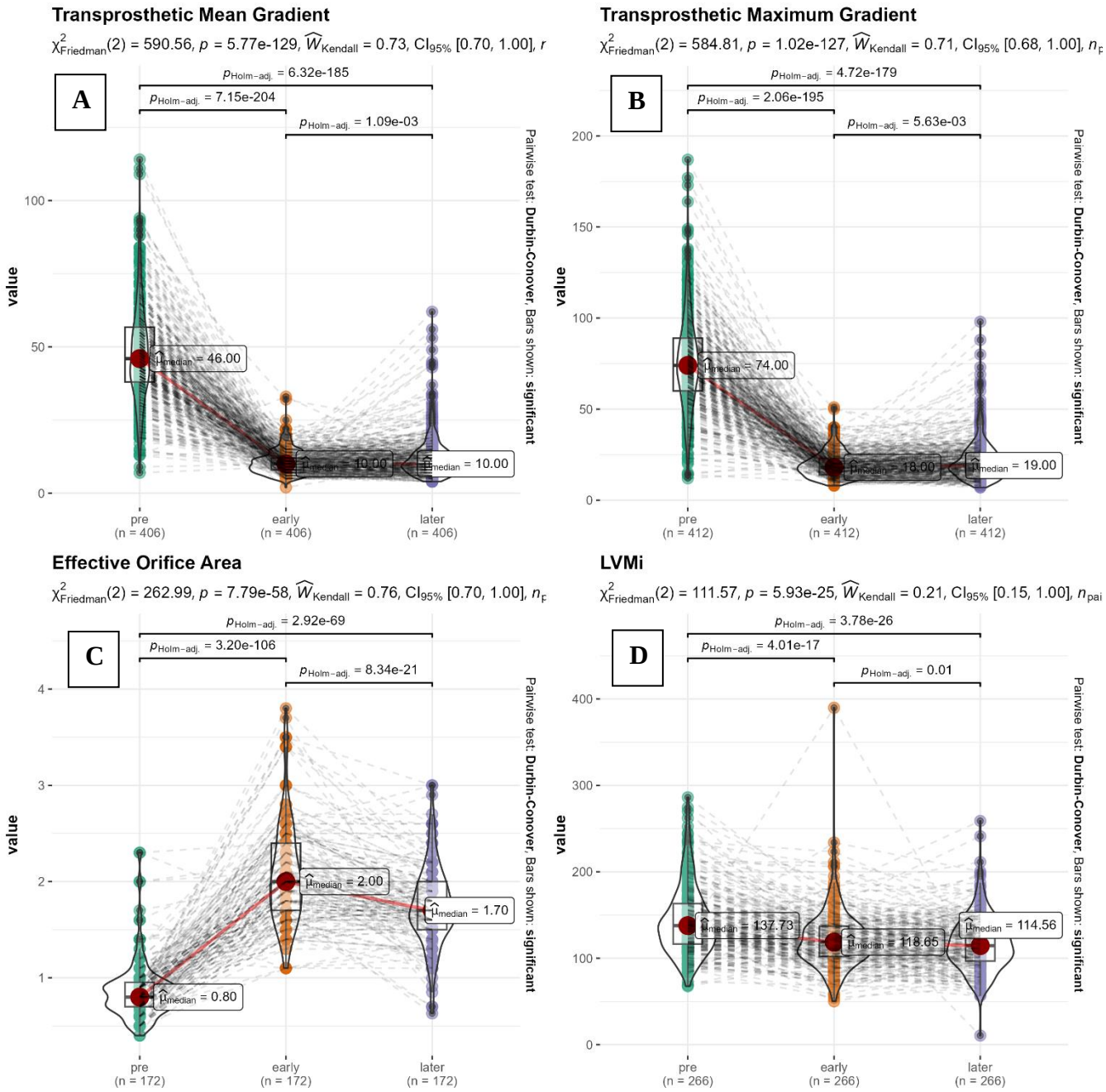


Fig.1 TTE evaluation in three time points: Pre-; early and latest compared by Friedman test with post-hoc Bonferroni test presented for multiple comparison. Dashed lines represent the variation of each patient . A- Transprosthetic mean gradient (mmHg) values; B- Transprosthetic maximum gradient (mmHg); C- Effective Orifice Area (EOA) (cm^2); D-Left Ventricular Mass indexed (LVMi) (g/m^2).

Variable	Value
Reintervention, n (%)	
SVD	33 (3%)
NSVD	3 (0.3%)
Endocarditis	19 (2%)
Time until reoperation, years, median (min-max)	4.9(0-11.5)

SVD: structural valve deterioration structural; NSVD: Non-Structural Valve Deterioration

Table 6. Causes leading to reintervention surgery n(%) and time until reintervention median in years, (min-max).

Supplementary Material

Table 1

Weights considered for additional surgical procedures

AVR considered as isolate procedure	Leaflets or aortic ring decalcification, left atrial appendage closure, IABP implantation, Aortic fistula closure, Enlargement of the aortic root, ascending aortic endarterectomy, prostatic abscess closure, excluding and cleaning of an abscess, resection of subaortic membrane
Multiple procedure, if AVR was performed at the same surgical time than one of the following:	Aortoplasty, ascending aorta resection, ascending aorta replacement, bentall surgery, mitral or tricuspid repair/replacement, aneurysm resection, AF ablation, Atrial and ventricular septal defects, carotid endarterectomy, aortic root reconstruction, aortic root replacement

AF: atrial fibrillation; AVR: aortic valve replacement; IABP: Intra-aortic balloon pump

Table 2

Preoperative characteristics' definitions

Obesity	Body Mass Index (BMI) ≥30 kg/m^2
Diabetes *mellitus*	Patients with diabetes type I or II, irrespective of treatment.
History of Smoking	Current, occasional, or ex-smoker >6months
Atrial Fibrillation	Pre-operative history of atrial fibrillation or flutter (both paroxysmal and permanent or persistent
Cerebral-vascular disease	Previous stroke, Transient Ischemic Attack (TIA) or carotid stenosis > 50%
Peripheral-vascular disease	Claudication, Previous or planned intervention in Abdominal Aortic Aneurysm (AAA) or limb arteries, intervention in AAA; limbs amputation due to artery ischemia and non-invasive arterial tests (doppler ultrasound or ankle-brachial index [ABI])
Elective surgery	Surgery planned in advanced
Urgent Surgery	Surgery required in patients that weren´t elective admitted. These patients only can be discharge after performing a definitive procedure.
Emergent surgery	Unplanned surgery performed within 24 hours, normally for patients admitted immediately in hospital, in a life-threatening state

Table 3

Intraoperative and immediate post-surgery outcomes' definitions

Prolonged mechanical ventilation	Mechanical invasive ventilation >24hours
Low cardiac output (LCO)	Need for ≥ 2 amines simultaneously or intra-aortic balloon pump (IABP) after surgery
Severe Thrombocytopenia	Minimum platelets count <30.000 μl
Sternal wound problems	Sternal re-suturing and mediastinitis
Hospital mortality	In-hospital or within the first 30 days after surgery
Intra-operative mortality	During the surgery, at the operating room

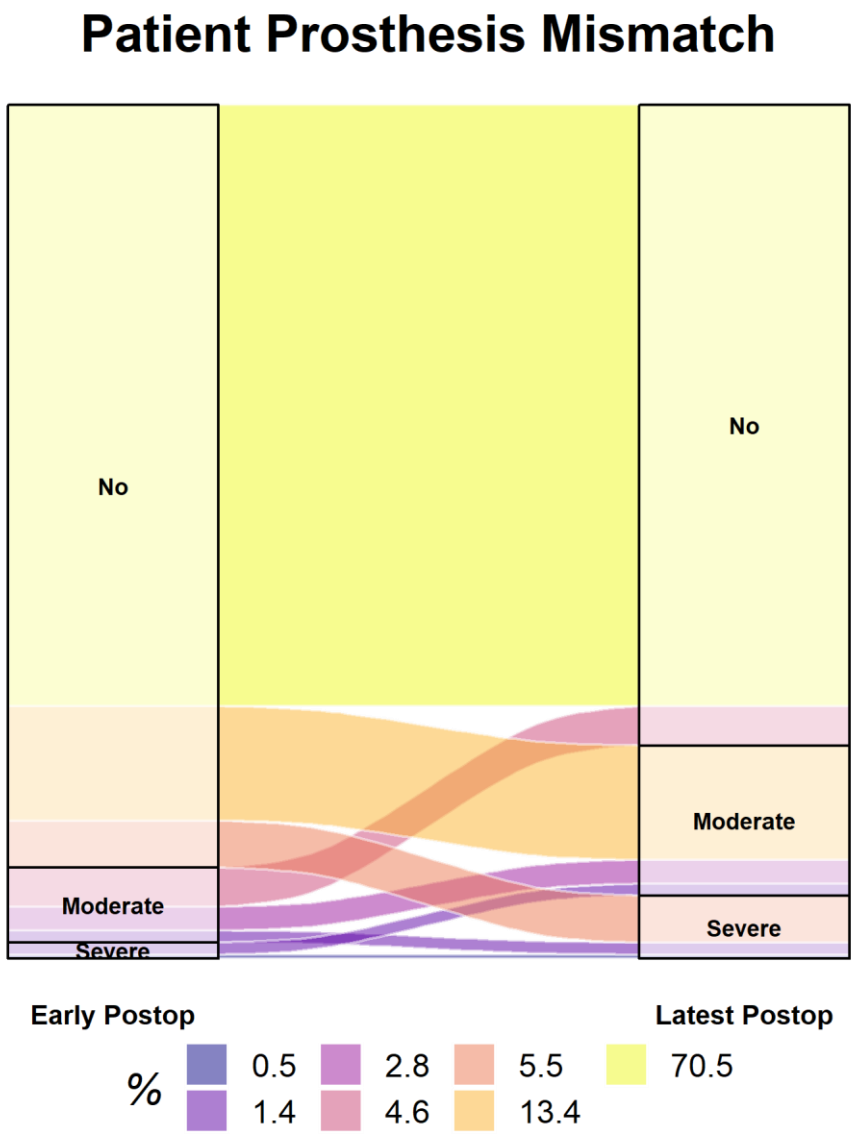


Fig.1 Patient Prothesis Mismatch (PPM) (n=217) at early and latest TTE. Lines between columns represent the percentage of patients in each transition. The majority of patients (70.5%) stayed without PPM since the early until latest follow-up TTE.

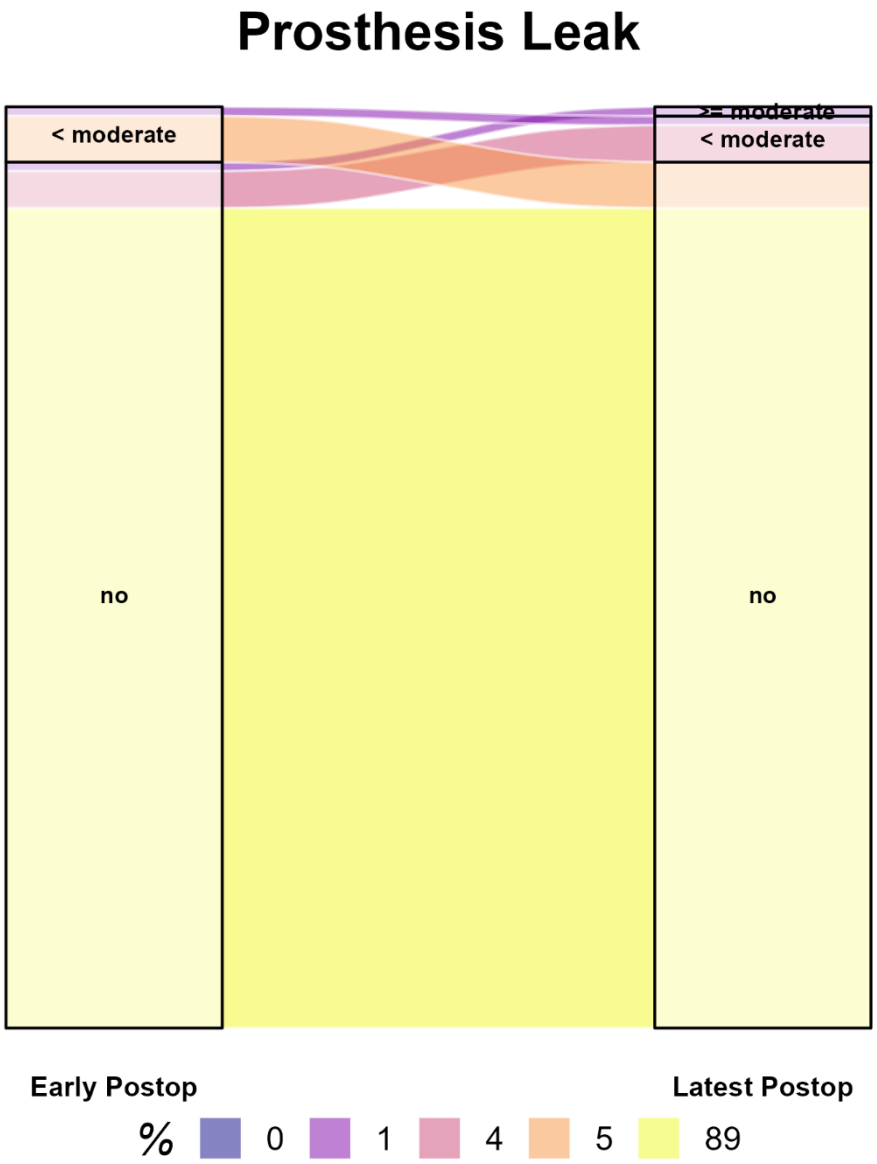


Fig.2 Prosthesis Leak (n=656) at early and latest TTE. Lines between columns represent the percentage of patients in each transition. 584 (89%) out of 656 patients remained without prosthetic leak from early to latest TTE evaluations.

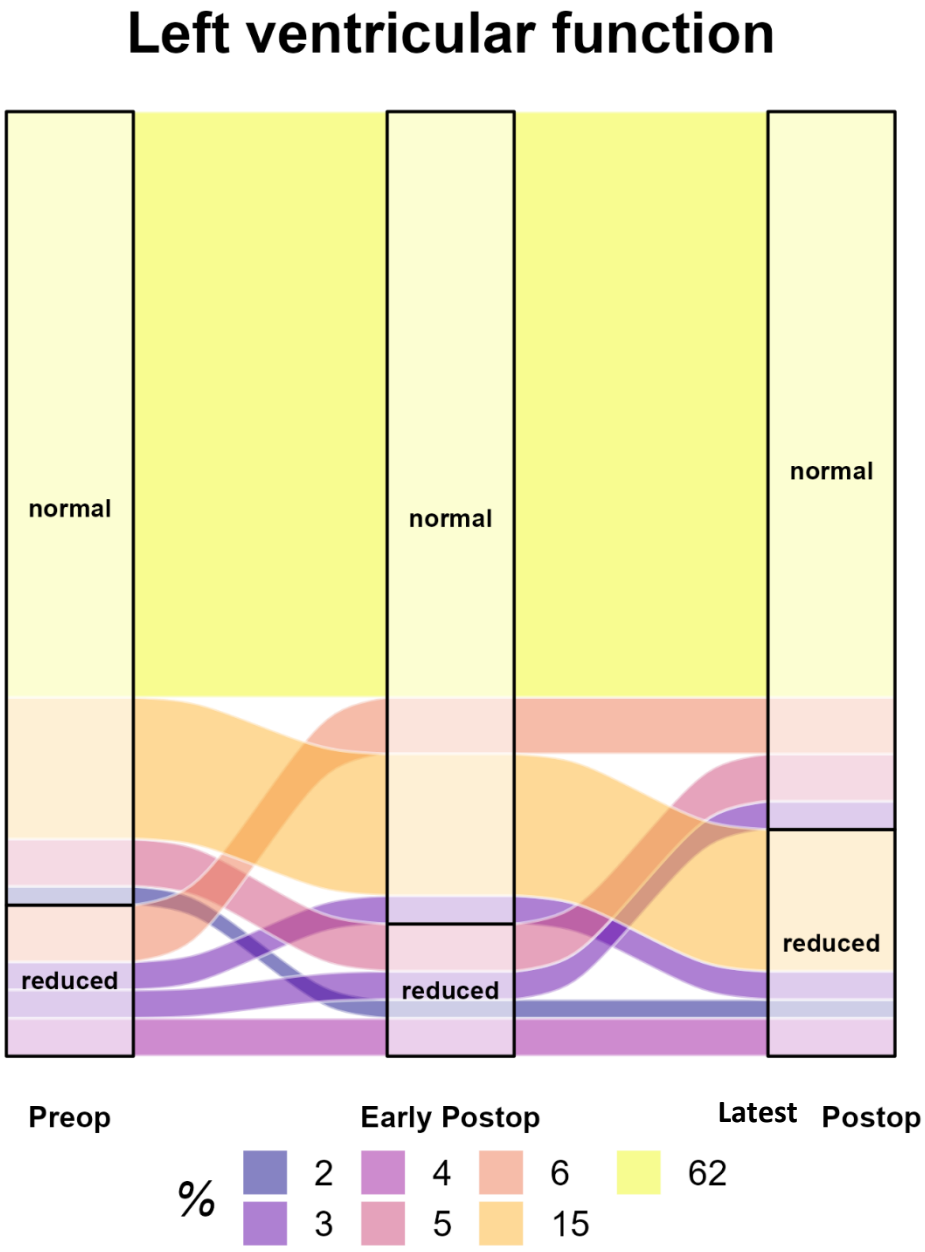


Fig.3 Left Ventricular Ejection Function (LVEF) (n=680) evaluation at pre-; early and latest TTE. Lines between columns represent the percentage of patients in each transition. The figure shows that 420 (62%) of the patients maintained a normal LVEF during the three time points (pre; early and latest TTE follow-up).

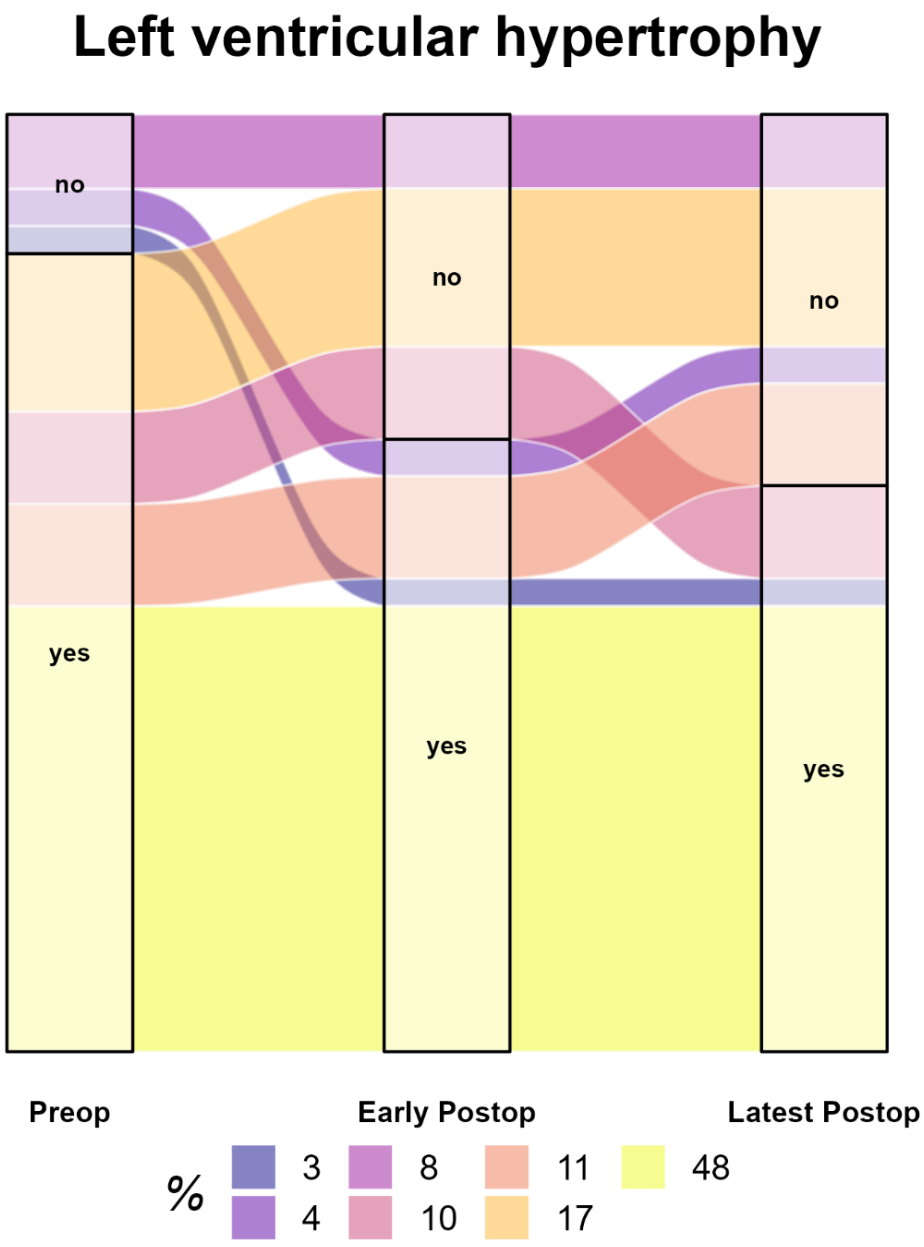


Fig.4 Left Ventricular Hypertrophy (n=266) evaluation at pre-, early and latest TTE. The figure shows the comparison between LV hypertrophy along the three time points. Lines between columns represent the percentage of patients in each transition. Most of the patients (48%) stayed with LV hypertrophy over pre-, early and latest TTE and 17% had a regression of LV hypertrophy at early and latest follow-up TTE.