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Structural Valve Deterioration of Bioprosthetic Aortic Valves: Incidence, Risk Factors and Clinical Impact

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STRUCTURAL VALVE DETERIORATION OF BIOPROSTHETIC AORTIC VALVES: INCIDENCE, RISK FACTORS AND CLINICAL IMPACT

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Structural valve deterioration of bioprosthetic aortic valves:

Incidence, risk factors and clinical impact.

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قَالَ رَسُولَ اللَّهِ صلى الله عليه وسلم" : تَدَاوَوْا فَإِنَّ اللَّهَ عَزَّ وَجَلَّ لَمْ يَضَعْ دَاءً إِلاَّ وَضَعَ لَهُ دَوَاءً".

"Haced uso de los tratamientos médicos, porque Dios no ha creado ninguna enfermedad sin designar también un remedio para ella".

"Make use of medical treatment, for Allah has not made a disease without appointing a remedy for it".

The Prophet Muhammad (ﷺ)

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Statement:

"The author Zaid AlHamwy declares that there is no conflict of interests in relation to this Thesis."

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ABBREVIATIONS

3D	Three dimensional
AF	Atrial Fibrillation
AH	Arterial Hypertension
AS	Aortic Stenosis
AV	Aortic Valve
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BMI	Body Mass Index
BNP	Brain Natriuretic Peptides
BSA	Body Surface Area
BVF	Bioprosthetic Valve Failure
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CHF	Congestive Heart Failure
CIF	Cumulative Incidence Function
CMR	Cardiovascular Magnetic Resonance
COPD	Chronic Obstructive Pulmonary Disease
CR	Competing Risks
CRF	Chronic Renal Failure
CSH	Cause-Specific Cox Regression Model
CT	Computerized Tomography
EACTS	European Association for Cardio-Thoracic Surgery
EAPCI	European Association of Percutaneous Cardiovascular Interventions
ECG	Electrocardiogram
EOA	Effective Orifice Area
EOAI	Effective Orifice Area Indexed
ESC	European Society of Cardiology
ESR	Erythrocyte Sedimentation Rate

ESRD	Sewing ring Diameter
FDR	False Discovery Ratio
FiO2	Fraction of Inspired Oxygen
INR	International Normalized Ratio
IOD	Internal Orifice Diameter
LMICs	Low- and Middle- Income Countries
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricle Hypertrophy
LVOT	Left Ventricular Outflow Tract
MSCT	Multislice Computed Tomography
PEEP	Positive End-Expiratory Pressure
PPM	Prosthesis-Patient Mismatch
RHD	Rheumatic heart disease
SAVR	Surgical Aortic Valve Replacement
SIMV	Synchronized Intermittent Mandatory Ventilation
SVD	Structural Valve Deterioration
SVi	Stroke Volume Index
SVI	Systolic Volume Index
SVR	Surgical Valve Replacement
TAD	Tissue Annulus Diameter
TAVI	Transcatheter Aortic Valve Implantation
TAVR	Transcatheter Aortic Valve Replacement
TOE	Transesophageal Echocardiography
TSVI	Diameter of the left ventricular outflow tract
TVI_{AO}	Velocity time integral calculated through the prosthesis
TVI_{LVOT}	Velocity time integral calculated using pulsed in the LVOT
VHD	Valvular Heart Disease

VHD	Valve Hemodynamic Deterioration
VIVID	Valve in Valve International Data
WHO	The World Health Organization
ΔP	Pressure Gradient

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SUMMARY

Galego

Introdución e obxectivos

A substitución da válvula aórtica por bioprótese, ben mediante catéter ou cirurxía, segue a ser a única ferramenta eficaz para o tratamento da estenose dexenerativa da aorta e que, debido ao envellecemento da poboación, esta técnica expandirase notablemente nos próximos anos.

Por outra banda, o deterioro estrutural das biopróteses de válvulas é un fenómeno constante a pesar dos continuos avances e melloras no deseño e fabricación de materiais, e por este motivo constitúe o principal factor limitante para o uso destes substitutos de válvulas na poboación.

Identificáronse varios factores relacionados coa deterioración estrutural, como o tipo de prótese, a desproporción entre o tamaño da válvula e o corpo e outras características como a idade e certos trastornos metabólicos dos pacientes, sen descartar unha predisposición individual cuxa etiopatoxénese sexa descoñecida.

O envellecemento da poboación de referencia do Complejo Hospitalario Universitario de Santiago significa que o número de pacientes anciáns sometidos a substitución de válvula aórtica por bioprótese en posición aórtica é elevado. Os estudos realizados ata a data sobre a incidencia da disfunción protésica no noso entorno son heteroxéneos e, ata certo punto, contraditorios e descoñécese ata que punto o deseño da prótese, o estrés hemodinámico e as comorbilidades asociadas dos pacientes afectan á deterioración da válvula.

Polo tanto, os obxectivos deste traballo son:

1. Coñecer a frecuencia de erro estrutural das biopróteses en posición aórtica no noso contorno.

2. Identificar os factores relacionados coa deterioración estrutural.

3. Estudar o impacto da falla estrutural das válvulas no noso contorno en termos de supervivencia e a necesidade de reintervención.

4. Realizar un estudo comparativo entre dous tipos de biopróteses empregadas no noso contorno para avaliar o papel do deseño de válvulas no fallo estrutural.

5. Definir accións en pacientes sometidos á substitución da válvula aórtica por bioprótese para evitar complicacións derivadas da falla estrutural.

Métodos

Levouse a cabo un estudo clínico observacional descritivo coa recollida de datos retrospectivos da serie histórica de pacientes aos que se lles realizou a substitución da válvula aórtica por prótese pericárdica biolóxica bovina no Complejo Hospitalario Universitario de Santiago de Compostela.

Recolléronse parámetros demográficos e clínicos preoperatorios, datos correspondentes ao protocolo cirúrxico, seguimento postoperatorio, evolución clínica e complicacións de cada paciente.

Estudáronse as características do paciente, o diagnóstico preoperatorio, as comorbilidades, o risco cirúrxico, a taxa de mortalidade e as complicacións postoperatorias. Analizouse a relación entre o tipo e o tamaño da prótese de válvula implantada, as características clínicas dos pacientes e a aparición de fallo protésico estrutural, así como o seu impacto en termos de supervivencia.

Todos os pacientes adultos de ambos sexos aos que se lles fixo unha substitución urxente ou electiva de válvula aórtica por bioprótese pericárdica bovina, illados ou combinados con outros procedementos, foron incluídos no estudo, en circulación extracorpórea no Complejo

Hospitalario Universitario de Santiago de Compostela entre 1 Xaneiro de 2008 e 31 de decembro de 2012.

Rexistráronse de cada paciente a idade, o sexo, o peso, a altura, a clase funcional, as intervencións cardíacas previas e as comorbilidades, incluíndo diabetes mellitus, enfermidade pulmonar obstructiva crónica, enfermidade arterial periférica, hipertensión arterial, fibrilación auricular e insuficiencia renal. O acceso á información do paciente realizouse a través do sistema electrónico de historia clínica na atención especializada actual no Servizo Galego de Saúde IANUS.

As válvulas implantadas foron a bioprótese Mitroflow 12A e Mitroflow LX e a bioprótese Carpentier-Edwards Perimount Magna.

A válvula Mitroflow 12A (Sorin Group Canada Inc., Mitroflow Division, Burnaby, Canadá) é unha bioprótese composta por un soporte de polipropileno flexible, cuberto de poliéster trenzado, un anel de sutura de silicona recuberto de poliéster e unha banda continua de pericardio bovino fixado externamente no soporte para maximizar o orificio da válvula. Estas características convérteno, a priori, nun substituto ideal para pequenos aneis aórticos. O modelo LX, introducido en 2010, incorpora pequenos cambios como a prefixación dos veos con glutaraldehído en lugar de post-fixación para facilitar a súa colocación no soporte. A nivel mundial, os modelos 12A e LX chamáronse "Mitroflow".

A prótese biolóxica Carpentier-Edwards Perimount Magna (Edwards Lifesciences, Irvine, CA, EUA), chamada "Carpentier", consiste nun soporte de aleación metálica Elgiloy® de cobalto-cromo recuberto de poliéster trenzado, un anel de sutura de silicona cuberto por unha capa de politetrafluoroetileno e tres cunchas semilunares individuais de pericardio bovino fixadas internamente no soporte.

Despois da intervención e unha vez dados de alta, os pacientes foron vistos na consulta ambulatoria de Cirurxía Cardíaca 1-3 meses despois da intervención. Posteriormente foron seguidos polo seu cardiólogo de

referencia.

O protocolo de seguimento da cardioloxía era moi heteroxéneo e dependía de cada cardiólogo. Algúns realizaban rutineiramente un estudo ecocardiográfico, electrocardiográfico e analítico anualmente ou cando a situación clínica ou o exame do paciente o xustificaban. Outros, tras unha primeira revisión, deron de alta ao paciente e derivárono ao médico de familia para o seu seguimento e non volveron estudialo, excepto por petición expresa do médico de atención primaria.

Nos casos en que se realizou, a avaliación da prótese aórtica mediante ecocardiografía Doppler incluíu o cálculo do gradiente máximo (mmHg) por Doppler continuo aplicando a ecuación simplificada de Bernoulli e o gradiente medio desde a integral ao longo do período expulsión. Considerouse unha estenose grave cando o gradiente medio transpróstico foi > 40 mmHg. Considerouse unha estenose bioprótesica moderada cando o gradiente medio era de 30- 40 mmHg. A avaliación da insuficiencia protésica fíxose a partir da relación do ancho do chorro regurgitante ao tracto de saída medida na proxección parasternal de eixe longo en modo M. Considerouse unha insuficiencia transprotética grave cando a relación foi > 0,65 e moderada para valores entre 0,25- 0,65. Nalgúns casos, a insuficiencia transprotésica calculouse a partir da gravación Doppler continua do chorro de insuficiencia e calculou o tempo de hemipresión, considerándose grave se foi < 200 cm/s e moderado para valores de 200- 500 cm/s.

A efectos prácticos, considerouse que a bioprótese aórtica presentaba un deterioro estrutural grave cando o gradiente sistólico medio era grave; cando a insuficiencia foi grave ou cando se combinaron estenose moderada con insuficiencia moderada.

Accedeuse á historia clínica electrónica para recompilar datos de seguimento do paciente, incluído o deterioro estrutural da bioprótese, as complicacións e a supervivencia.

O seguimento do paciente concluíu o 30 de marzo de 2020, o que

significa un seguimento mínimo de 99 meses e un máximo de 147 meses.

Os valores numéricos exprésanse como porcentaxe (%) ou como media ± desviación estándar. O estudo estatístico realizouse utilizando a versión 3.6 do programa R (fundación R, Viena, Austria).

Para a comparación de variables categóricas, utilizouse a proba Chi Square empregando a corrección de Yates. Para a comparación de variables continuas, utilizouse a proba de Wilcoxon. Todos os valores p foron penalizados co procedemento Benjamini-Hochberg de "False Discovery Ratio".

Para a comparación das curvas de supervivencia, utilizouse a proba Log-rank e a representación gráfica por curvas de Kaplan-Meier con intervalos de confianza do 95%.

Para a identificación de factores asociados á disfunción ou mortalidade protésica estrutural ou á necesidade de reoperación, empregáronse modelos de supervivencia que tiveron en conta os riscos competitivos.

O Comité de Ética para a Investigación Clínica da Área Sanitaria de Santiago-Lugo informou favorablemente do estudo (código de rexistro 2015/2009). Os anexos 1 e 2 inclúen o texto completo da resolución e a incorporación do autor da tese ao equipo de investigación.

Resultados

Neste estudo incluíronse un total de 409 pacientes aos que se lles realizou a substitución da válvula aórtica entre o 1 de xaneiro de 2008 e o 31 de decembro de 2012. O seguimento pechouse o 31 de marzo de 2020, o que significa un seguimento medio de 122 meses (rango 99-147) para un total de 2,162 pacientes-anos. O seguimento foi posible en todos os pacientes excepto en seis, o que representa unha porcentaxe de seguimento completo do 98,54%.

A idade media dos pacientes incluídos no estudo foi do 48,2% eran mulleres e do 51,8% eran homes. Cómpre ter en conta que o 59,4% tiña algún grao de obesidade. Outras comorbilidades na poboación estudada incluíron diabetes mellitus (27,4%), enfermidade pulmonar obstructiva crónica (22%), fibrilación auricular (17,4%), enfermidade arterial periférica (10%), hipertensión arterial (71,3%), hipercolesterolemia (40,5%). O 6,6% da poboación xa fora sometido a implantación de stent coronario e o 5,37% fora sometido a cirurxía de corazón aberto.

Analíticamente, a concentración media de hemoglobina foi de 12,7 ± 1,7 mg/dL e a creatinina sérica foi de 1,1 ± 0,4 mg/dL. Unha taxa media de filtración glomerular estimada de 57,6 ± 20 ml/kg/min e certo grao de insuficiencia renal crónica no 7,5% dos pacientes operados. O 18,4% tiña un marcapasos permanente.

Desde un punto de vista cínico antes da intervención, o 38,4% dos pacientes estaban na clase II da NYHA, o 46,7% na clase III e o 14,7% na clase IV.

A mortalidade hospitalaria estimada preoperatoriamente segundo o EuroSCORE II foi de 4,8 ± 4,5.

De todos os pacientes incluídos no estudo, un grupo de 235 recibiu unha prótese da válvula aórtica Mitroflow. A idade media deste grupo foi de 78,6 ± 4,8 anos e as mulleres representaron o 56,5%. O 58,2% tiña algún grao de obesidade. Outras comorbilidades no grupo de implantes de

prótese Mitroflow incluíron diabetes mellitus (27,6%), enfermidade pulmonar obstructiva crónica (17,4%), fibrilación auricular (21,7%), enfermidade arterial periférica (11,4%), hipertensión arterial (77,02%), hipercolesterolemia (45,5%). O 7,6% da poboación xa fora sometido a implantación de stent coronario e o 4,6% fora sometido a cirurxía de corazón aberto. O 19,1% tiña un marcapasos permanente.

Analíticamente, neste grupo, a concentración media de hemoglobina foi de 12,5 ± 1,6 mg/dL e a creatinina sérica foi de 1,1 ± 0,4 mg/dL. Unha taxa media de filtración glomerular estimada de 53,9 ± 17 ml/ kg/min e certo grao de insuficiencia renal crónica no 9,3% dos pacientes operados. Desde un punto de vista cínico, antes da intervención, o 36,5% dos pacientes estaban na clase II da NYHA, o 48,5% na clase III e o 14,8% na clase IV. A mortalidade hospitalaria estimada preoperatoriamente segundo o EuroSCORE II foi de 5,4 ± 4,6.

De todos os pacientes incluídos no estudo, un grupo de 174 recibiu unha prótese de válvula aórtica Carpentier. A idade media deste grupo foi de 74,9 ± 7,4 anos e as mulleres representaron o 37,7%. Cómpre ter en conta que o 60,9% tiña algún grao de obesidade. Outras comorbilidades do grupo de implantes de prótese Carpentier incluíron diabetes mellitus (27%), enfermidade pulmonar obstructiva crónica (28,1%), fibrilación auricular (11,4%), enfermidade das arterias periféricas (8%), hipertensión arterial (63,7 %), hipercolesterolemia (33,9%). O 5,1% da poboación sometérase previamente a implantación de stent coronario e o 6,3% fora sometido a cirurxía de corazón aberto. O 16% tiña un marcapasos permanente.

Analíticamente, no grupo Carpentier, a concentración media de hemoglobina foi de 12,9 ± 1,7 mg/dL e a creatinina sérica foi de 1,1 ± 0,6 mg/dL. A taxa media de filtración glomerular estimada de 62,5 ± 22,6 ml/kg/min e algún grao de insuficiencia renal crónica estiveron presentes no 5,1% dos pacientes operados. Desde o punto de vista cínico, antes da intervención, o 40,8% dos pacientes estaban na clase II da NYHA, o 44,2% na clase III e o 14,3% na clase IV. A mortalidade hospitalaria estimada preoperatoriamente segundo o EuroSCORE II foi

de 4,1 ± 4,2.

A decisión de implantar un tipo de prótese ou outro en cada paciente dependía exclusivamente da decisión do cirurxián responsable da intervención. Esta decisión influíu sen dúbida en aspectos como o tamaño do anel de tecido aórtico do paciente, a idade e a superficie corporal, a presenza de comorbilidades, a dificultade técnica do procedemento debido á anatomía cardíaca e ao deseño da prótese e a experiencia persoal. do cirurxián.

Os datos presentados amosan diferenzas entre a poboación de pacientes que recibiron unha bioprótese Mitroflow e unha Carpentier. O máis rechamante é que as persoas con próteses Mitroflow eran predominantemente mulleres, máis vellas e de menor tamaño que as que recibiron unha prótese Carpentier. Tamén se pode verificar que os pacientes coa bioprótese Mitroflow tiñan máis comorbilidades e, en consecuencia, un maior risco cirúrxico que a prótese de Carpentier.

A substitución da válvula aórtica illada realizouse no 74,81% dos pacientes. A reposición da válvula mitral asociouse no 3,66% dos casos e a revascularización miocárdica no 21,51%.

As 409 próteses implantadas distribuíronse segundo o tamaño do seguinte xeito: nº 19: 53 (13%); nº 21: 207 (50,6%); nº 23: 122 (29,8%); nº 25: 24 (5,9%) e nº 27: 3 (0,7%).

O orificio efectivo da válvula indexada das biopróteses implantadas para o grupo total foi de 1 ± 0,2 cm2/m2. A ausencia de desaxuste (EOAI > 0,85 cm2/m2) observouse no 73,3% dos casos; Desaxuste moderado (EOAI 0,65- 8,85 cm2/m2) no 25,7% e desaxuste grave (EOAI < 0,65 cm2/m2) no 1% dos pacientes operados.

No grupo de pacientes que recibiron unha bioprótese Mitroflow, realizouse un intercambio aórtico illado no 72,34% dos casos. A substitución da válvula mitral asociouse no 4,25% dos casos e a revascularización do miocardio no 23,40%.

A distribución dos pacientes segundo o tamaño da prótese foi a seguinte: nº 19: 43 (18,29%); nº 21: 123 (52,34%); nº 23: 60 (25,53); nº 25: 9 (3,82%).

O orificio efectivo da válvula indexado medio para as biopróteses Mitroflow foi de 0,9 ± 0,1 cm2/m2. A ausencia de discordancia observouse no 55,74%, discordancia moderada no 43,8% e discordancia grave no 0,42% dos pacientes.

A substitución da válvula aórtica illada realizouse no 78,16% dos pacientes. A reposición da válvula mitral asociouse no 2,87% dos casos e a revascularización miocárdica no 18,96%.

No grupo de 174 pacientes que recibiron unha bioprótese de Carpentier, a distribución segundo o tamaño da prótese foi a seguinte: nº 19: 10 (5,74%); nº 21: 84 (48,27%); nº 23: 62 (35,63%); nº 25: 15 (8,62); nº 27: 3 (1,72%).

O orificio de válvula efectivo indexado medio para as biopróteses de Carpentier foi de 1,1 ± 0,2 cm2/m2. A ausencia de discordancia observouse no 97,11%, discordancia moderada no 1,14% e discordancia grave no 1,72% dos pacientes.

As intervencións nas que se implantaron as biopróteses Mitroflow foron máis complexas na medida en que houbo procedementos asociados.

En canto ao tamaño, no grupo Carpentier, o tamaño da prótese foi maior e, ademais, a taxa de discrepancia entre o tamaño do burato protésico e o tamaño do paciente foi anecdótica, mentres que no grupo Mitroflow, máis da metade dos pacientes permaneceron con certo grao de estenose aórtica residual.

O 70% das próteses Mitroflow implantáronse en pacientes con tamaños pequenos (19 + 21), mentres que no caso de Carpentier os pequenos aneis aórticos representaron o 54%.

No grupo total de pacientes operados, houbo 33 mortes hospitalarias, o que representa o 8,06%. A mortalidade no grupo de pacientes que se someteron a bioprótese de Mitroflow foi de 16 persoas (6,8%), mentres que no grupo Carpentier morreron 17 (9,77%) (p = 0,3662).

A causa máis frecuente de morte hospitalaria foi a parada cardíaca (14) seguida de insuficiencia múltiple de órganos (11), endocardite protésica precoz (2), mediastinite (1), ictus (2), hemorraxia postoperatoria (1) e choque séptico (2).

No momento de pechar o seguimento, morreran un total de 263 pacientes (64,30%) e dos 147 superviventes (35,5%), 41 pacientes (10,02%) tiñan máis de 10 anos de evolución. Segundo os datos contidos na historia clínica, as causas da morte tardía foron cardíacas no 38,58% e non cardíacas no 61,4%. A principal causa de mortalidade foi a neoplasia (20,48%), seguida de procesos sépticos de orixe abdominal / urolóxica (9,03%), insuficiencia cardíaca non relacionada coa prótese (9,03%), demencia (8,43%), morte súbita inexplicable (8,43%) e endocardite infecciosa (7,22%).

A análise axustada dos riscos competitivos de morte, disfunción da válvula estrutural e reoperación usando o modelo de risco Cox para unha causa específica e a función de incidencia acumulada do evento segundo o modelo Fine Grey mostrou unha asociación significativa de mortalidade coa idade no tempo de intervención, presenza de fibrilación auricular, implantación dunha prótese Mitroflow e insuficiencia renal crónica. Non se demostrou ningunha asociación entre mortalidade e xénero, presenza de diabetes mellitus, hipertensión arterial, desaxuste e cirurxía combinadas coa reposición da válvula aórtica.

A análise de supervivencia comparativa entre os grupos con próteses de Mitroflow e Carpentier mostrou diferenzas significativas a favor da bioprótese de Carpentier aos 6 anos da intervención. Despois de 10 anos as diferenzas entre os dous grupos adoitan desaparecer.

A presenza de disfunción da válvula estrutural comprobouse

ecocardiográficamente en 35 pacientes (8,55%) dos cales 29 casos corresponderon a pr Prótese mitroflow (tamaño nº 19: 7; nº 21: 17 e nº 23: 5) e 6 casos na prótese de Carpentier (tamaño nº 19: 1 e nº 21: 5).

Dos 35 pacientes diagnosticados de disfunción da válvula estrutural, só 14 foron reoperados por esta causa, realizando cirurxía aberta en 8 casos e implantación dunha prótese transcatéter en 6 pacientes.

A ausencia de disfunción da válvula estrutural para o grupo global aos 5 e 10 anos foi do 95% e 77%, respectivamente.

A análise estatística permitiu demostrar unha relación estatisticamente significativa entre a disfunción da válvula estrutural e a idade no momento da cirurxía e da implantación da bioprótese Mitroflow. Non se observou ningunha relación entre a disfunción da válvula estrutural e o xénero, presenza de diabetes, hipertensión arterial, insuficiencia renal, tamaño da prótese e desaxuste.

A análise axustada para os riscos competitivos de morte, disfunción da válvula estrutural e reoperación usando o modelo de risco Cox para unha causa específica e a función de incidencia acumulada do evento segundo o modelo Fine Grey mostrou unha asociación significativa da disfunción da válvula estrutural coa idade. no momento da intervención, fibrilación auricular, implantación de prótese Mitroflow e insuficiencia renal crónica. Non se demostrou ningunha asociación entre a disfunción da válvula estrutural e o xénero, a presenza de diabetes mellitus, a hipertensión arterial, o desaxuste e a cirurxía combinados coa reposición da válvula aórtica.

A análise comparativa da disfunción da válvula estrutural entre os grupos de portadores de prótese Mitroflow e Carpentier demostrou unha maior taxa de disfunción da válvula estrutural en pacientes con prótese Mitroflow despois de 4 anos de evolución postoperatoria, cunha taxa de ausencia de deterioro de 94,2% e 67,2% aos 5 e 10 anos respectivamente. Un total de 17 pacientes foron diagnosticados de endocardite prostética (4,15%). En dous casos o diagnóstico realizouse

antes do alta hospitalaria e morreron sen ser reoperados. Despois do alta, diagnosticáronse endocardite a 15 pacientes (5 temperáns e 10 tardíos). Reoperáronse once pacientes (4 endocardite precoz e 7 tardías) e 4 pacientes só recibiron tratamento médico.

Ao realizar unha análise comparativa da aparición de endocardite entre pacientes con bioprótese de Mitroflow e Carpentier, non se mostraron diferenzas significativas.

Reoperáronse un total de 28 pacientes (6,84%). En tres pacientes, a reintervención non estivo relacionada coa bioprótese aórtica (2 substitutos da válvula mitral e 1 revascularización do miocardio). En 25 pacientes operouse a prótese aórtica. O motivo da reoperación aórtica foi a disfunción da válvula estrutural en 14 casos e a endocardite nunha prótese en 11 casos.

A análise axustada dos riscos competitivos de morte, disfunción estrutural da válvula e reoperación usando o modelo de risco Cox para unha causa específica e a función de incidencia acumulada do evento segundo o modelo Fine Grey mostrou unha asociación significativa de reoperación co implante da prótese. Mitroflow. Non se demostrou ningunha asociación entre a reoperación e o xénero, a presenza de diabetes mellitus, a hipertensión, o desaxuste e a cirurxía combinados coa reposición da válvula aórtica.

A análise comparativa entre pacientes con próteses Mitroflow e Carpentier en relación coa ausencia de reoperación mostrou unha maior taxa de reoperacións no grupo Mitroflow.

Conclusións

1. A frecuencia de deterioro estrutural das biopróteses en posición aórtica no noso entorno é do 4% e do 22% aos 5 e 10 anos respectivamente.

2. A bioprótese Mitroflow presenta un deterioro estrutural máis precoz e intenso que a bioprótese de Carpentier.

3. A bioprótese Mitroflow implántase en pacientes maiores, con máis comorbilidades, menor tamaño do anillo aórtico e maior risco cirúrxico que a bioprótese de Carpentier.

4. O deterioro estrutural das próteses é inversamente proporcional á idade dos pacientes.

5. Despois da substitución da válvula aórtica por bioprótese, os factores asociados a unha maior mortalidade a longo prazo inclúen a idade, a presenza de fibrilación auricular, a implantación dunha prótese Mitroflow e a insuficiencia renal crónica.

6. O tamaño da prótese implantada e a presenza dun desaxuste moderado entre o orificio efectivo da válvula protésica e o paciente non inflúen na evolución a longo prazo.

7. No noso entorno, hai unha grande heteroxeneidade nos protocolos de seguimento clínico e ecocardiográfico postoperatorio en pacientes con bioprótese, o que fai imposible coñecer a taxa de deterioro estrutural clínicamente relevante e asintomático.

8. A endocardite infecciosa segue a ser unha complicación relevante en pacientes con próteses valvulares, polo que é necesario tomar medidas extremas de profilaxe e considerala no diagnóstico diferencial de procesos febriles en persoas maiores.

9. É necesario un seguimento ecocardiográfico periódico de pacientes

con bioprótese, incluídos os asintomáticos, para facilitar un diagnóstico precoz de deterioro estrutural.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Castellano

Introducción y objetivos

El recambio valvular aórtico por bioprótesis ya sea mediante catéter o quirúrgico continúa siendo la única herramienta efectiva para el tratamiento de la estenosis aórtica degenerativa y que, debido al envejecimiento de la población, esta técnica se expandirá notablemente durante los próximos años.

Por otro lado, el deterioro estructural de las bioprótesis valvulares es un fenómeno constante a pesar de los continuos avances y mejoras en el diseño y en los materiales de fabricación y por ese motivo constituye el principal factor limitante para el uso de estos sustitutos valvulares en la población.

Se han identificado varios factores relacionados con el deterioro estructural como son el tipo de prótesis, la desproporción entre el tamaño valvular y corporal y otras características como son la edad y ciertos trastornos metabólicos de los pacientes, sin descartar una predisposición individual cuya etiopatogenia es desconocida.

El envejecimiento de la población de referencia del Complejo Hospitalario Universitario de Santiago hace que el número de ancianos intervenidos de recambio valvular aórtico por bioprótesis en posición aórtica sea elevado. Los estudios realizados hasta la fecha sobre incidencia de disfunción protésica en nuestro medio son heterogéneos y, en cierto modo, contradictorios, desconociéndose hasta qué punto el diseño de la prótesis, el estrés hemodinámico y las comorbilidades asociadas de los pacientes afectan al deterioro valvular.

Por lo tanto, los objetivos de este trabajo son:

1. Conocer la frecuencia de fallo estructural de las bioprótesis en posición aórtica en nuestro medio.

2. Identificar los factores relacionados al deterioro estructural.

3. Estudiar el impacto del fallo estructural valvular en nuestro medio en términos de supervivencia y necesidad de reintervención.

4. Realizar un estudio comparativo entre dos tipos de bioprótesis utilizadas en nuestro medio para valorar el papel del diseño valvular en el fallo estructural.

5. Definir actuaciones sobre los pacientes intervenidos de recambio valvular aórtico por bioprótesis con el fin de prevenir las complicaciones derivadas del fallo estructural.

Métodos

Se realizó un estudio clínico observacional descriptivo con toma de datos retrospectiva de la serie histórica de pacientes sometidos a recambio valvular aórtico por prótesis biológica de pericardio bovino en el Complejo Hospitalario Universitario de Santiago de Compostela.

De cada paciente se recogieron los parámetros clínicos y demográficos preoperatorios, los datos correspondientes al protocolo quirúrgico, seguimiento postoperatorio, evolución clínica y complicaciones.

Se estudiaron las características de los pacientes, diagnóstico preoperatorio, comorbilidades, riesgo quirúrgico, tasa de mortalidad y complicaciones postoperatorias. Se analizó la relación entre el tipo y tamaño de prótesis valvular implantada, las características clínicas de los pacientes y la aparición de fallo estructural protésico, así como su repercusión en términos de supervivencia.

Se incluyeron en el estudio todos los pacientes adultos de ambos sexos intervenidos de modo urgente o electivo de reemplazo valvular aórtico por bioprótesis de pericardio bovino, aislado o combinado con otros

procedimientos, bajo circulación extracorpórea en el Complejo Hospitalario Universitario de Santiago de Compostela entre el 1 de enero de 2008 y el 31 de diciembre de 2012.

De cada paciente se registró la edad, sexo, peso, talla, clase funcional, intervenciones cardiacas previas y comorbilidades incluyendo diabetes mellitus, enfermedad pulmonar obstructiva crónica, arteriopatía periférica, hipertensión arterial, fibrilación auricular, e insuficiencia renal. El acceso a la información de los pacientes se realizó a través del sistema de historia clínica electrónica en atención especializada vigente en el Servicio Gallego de Salud IANUS.

Las válvulas implantadas fueron la bioprótesis Mitroflow 12A y Mitroflow LX y la bioprótesis Carpentier-Edwards Perimount Magna.

La válvula Mitroflow 12A (Sorin Group Canada Inc., Mitroflow Division, Burnaby, Canada) es una bioprótesis compuesta de un soporte flexible de polipropileno, recubierto de poliéster trenzado, un anillo de sutura de silicona cubierta de poliéster y una banda continua de pericardio bovino fijada externamente sobre el soporte con el fin de maximizar el orificio valvular. Estas características la convierten, a priori, en un sustituto ideal para anillos aórticos pequeños. El modelo LX, introducido en el año 2010 incorpora pequeños cambios para como la prefijación de los velos con glutaraldehído en lugar de la post-fijación para facilitar su aposición sobre el soporte. Globalmente a los modelos 12A y LX fueron denominados "Mitroflow".

La prótesis biológica de Carpentier-Edwards Perimount Magna (Edwards Lifesciences, Irvine, CA, USA), denominada "Carpentier", consta de un soporte de aleación metálica de cobalto-cromo Elgiloy® recubierto de poliéster trenzado, un anillo de sutura de silicona cubierto por una capa de politetrafluoroetileno y tres valvas semilunares individuales de pericardio bovino fijadas internamente sobre el soporte.

Después de la intervención y una vez dados de alta, los pacientes fueron revisados en la consulta ambulatoria de Cirugía Cardiaca transcurridos

entre 1- 3 meses de la intervención. Posteriormente fueron seguidos por su Cardiólogo de referencia.

El protocolo de seguimiento cardiológico fue muy heterogéneo atendiendo y dependía de cada Cardiólogo. Algunos realizaban habitualmente un estudio ecocardiográfico, electrocardiográfico y analítico anual o cuando la situación clínica o la exploración del paciente lo aconsejara. Otros, después de una primera revisión daban de alta al paciente y lo remitían al Médico de Familia para seguimiento y no volvía a estudiar al paciente salvo por petición expresa del Facultativo de Atención Primaria.

En los casos donde se llevó a cabo, la valoración de la prótesis aórtica mediante ecocardiografía Doppler incluyó el cálculo del gradiente máximo (mmHg) mediante Doppler continúo aplicando la ecuación de Bernoulli simplificada y el gradiente medio a partir de la integral a lo largo del periodo eyectivo. Se consideró estenosis severa cuando el gradiente transprotésico medio era > 40 mmHg. Se consideró estenosis bioprotésica moderada cuando el gradiente medio era 30- 40 mmHg. La valoración de la insuficiencia protésica se realizó a partir de la relación de la anchura del jet regurgitante respecto al tracto de salida medido en proyección paraesternal eje largo en modo M. Se consideró regurgitación transprotésica severa cuando la relación era > 0,65 y moderada para valores entre 0,25- 0,65. En algunos casos la regurgitación transprotésica se calculó a partir del registro con Doppler continuo del jet regurgitante y calculando el tiempo de hemipresión, considerándose severa si era < 200 cm/s y moderada para valores de 200- 500 cm/s.

Se consideró a efectos prácticos que una bioprótesis aórtica presentaba deterioro estructural grave cuando el gradiente sistólico medio era severo; cuando la regurgitación era severa o bien cuando se combinaban una estenosis moderada con una insuficiencia moderada.

Se accedió a la historia clínica electrónica para recoger los datos de seguimiento de los pacientes, incluyendo deterioro estructural de la

bioprótesis, complicaciones y supervivencia.

El seguimiento de los pacientes fue concluido a fecha de 30 de marzo de 2020, lo que supone un seguimiento mínimo de 99 meses y máximo de 147 meses.

Los valores numéricos están expresados en forma de porcentaje (%) o bien como media ± desviación estándar. El estudio estadístico se realizó mediante el programa R versión 3,6 (R foundation, Vienna, Austria).

Para la comparación de variables categóricas se utilizó la prueba de Chi Cuadrado utilizando la corrección de Yates. Para la comparación de variables continuas se utilizó la prueba de Wilcoxon. Todos los p-valores fueron penalizados con el procedimiento de Benjamini-Hochberg de "False Discovery Ratio".

Para la comparación de curvas de supervivencia se utilizó el test Log-rank y la representación gráfica mediante curvas de Kaplan-Meier con intervalos de confianza al 95%.

Para la identificación de factores asociados a disfunción estructural protésica o mortalidad o necesidad de reoperación se utilizaron modelos de supervivencia que tuviesen en consideración los riesgos competitivos.

El Comité Ético de Investigación Cínica del Área Sanitaria de Santiago-Lugo informó favorablemente la realización del estudio (código de registro 2015/2009). En los anexos 1 y 2 se incorpora el texto íntegro de la resolución y la incorporación del autor de la Tesis al equipo investigador.

Resultados

Se incluyeron en este estudio un total de 409 pacientes intervenidos de recambio valvular aórtico entre el 1 de enero de 2008 y el 31 de diciembre de 2012. El seguimiento se cerró el 31 de marzo de 2020 lo que significa un seguimiento medio de 122 meses (rango 99- 147) para un total de 2,162 pacientes-año. El seguimiento fue posible en todos los pacientes excepto en seis lo que supone un porcentaje de seguimiento completo del 98.54%.

La edad media de los pacientes incluidos en el estudio fue El 48,2% eran mujeres y el 51,8% varones. Cabe destacar que el 59,4% presentaba algún grado de obesidad. Otras comorbilidades de la población estudiada incluyeron diabetes mellitus (27,4%), enfermedad pulmonar obstructiva crónica (22%), fibrilación auricular (17,4%), arteriopatía periférica (10%), hipertensión arterial (71,3%), hipercolesterolemia (40,5%). Había sido sometidos previamente a implante de stent coronario el 6,6% de la población y a una cirugía cardiaca abierta previa el 5,37%.

Analíticamente la concentración media de hemoglobina 12,7 ± 1,7 mg/dL y la creatinina sérica de 1,1 ± 0,4 mg/dL. Presentaban una tasa estimada de filtración glomerular promedio de 57,6 ± 20 ml/kg/min y algún grado de insuficiencia renal crónica el 7,5% de los pacientes intervenidos. El 18,4% era portador de marcapasos definitivo.

Desde un punto de vista cínico antes de la intervención se encontraba en clase II de la NYHA el 38,4% de los pacientes, en clase III 46,7% y en clase IV el 14,7%.

La mortalidad hospitalaria estimada preoperatoriamente de acuerdo con el EuroSCORE II resultó de 4,8 ± 4,5.

Del total de los pacientes incluidos en el estudio un grupo de 235 recibieron una prótesis valvular aórtica Mitroflow. La edad media de este grupo fue de 78,6 ± 4,8 años y las mujeres representaron el 56,5%.

El 58,2% presentaba algún grado de obesidad. Otras comorbilidades del grupo con implante de prótesis Mitroflow incluyeron diabetes mellitus (27,6%), enfermedad pulmonar obstructiva crónica (17,4%), fibrilación auricular (21,7%), arteriopatía periférica (11,4%), hipertensión arterial (77,02%), hipercolesterolemia (45,5%). Había sido sometidos previamente a implante de stent coronario el 7,6% de la población y a una cirugía cardiaca abierta previa el 4,6%. El 19,1% era portador de marcapasos definitivo.

Analíticamente, en este grupo, la concentración media de hemoglobina fue 12,5 ± 1,6 mg/dL y la creatinina sérica de 1.1 ± 0,4 mg/dL. Presentaban una tasa estimada de filtración glomerular promedio de 53,9 ± 17 ml/kg/min y algún grado de insuficiencia renal crónica el 9,3% de los pacientes intervenidos. Desde un punto de vista cínico antes de la intervención se encontraba en clase II de la NYHA el 36,5% de los pacientes, en clase III 48,5% y en clase IV el 14,8%. La mortalidad hospitalaria estimada preoperatoriamente de acuerdo con el EuroSCORE II resultó de 5,4 ± 4,6.

Del total de los pacientes incluidos en el estudio un grupo de 174 recibieron una prótesis valvular aórtica Carpentier. La edad media de este grupo fue de 74,9 ± 7,4 años y las mujeres representaron el 37,7%. Cabe destacar que el 60,9% presentaba algún grado de obesidad. Otras comorbilidades del grupo con implante de prótesis Carpentier incluyeron diabetes mellitus (27%), enfermedad pulmonar obstructiva crónica (28,1%), fibrilación auricular (11,4%), arteriopatía periférica (8%), hipertensión arterial (63,7%), hipercolesterolemia (33,9%). Había sido sometidos previamente a implante de stent coronario el 5,1% de la población y a una cirugía cardiaca abierta previa el 6,3%. El 16% era portador de marcapasos definitivo.

Analíticamente, en el grupo de Carpentier, la concentración media de hemoglobina fue 12,9 ± 1,7 mg/dL y la creatinina sérica de 1.1 ± 0,6 mg/dL. Presentaban una tasa estimada de filtración glomerular promedio de 62,5 ± 22,6 ml/kg/min y algún grado de insuficiencia renal crónica el 5,1% de los pacientes intervenidos. Desde un punto de vista

cínico antes de la intervención se encontraba en clase II de la NYHA el 40,8% de los pacientes, en clase III 44,2% y en clase IV el 14,3%. La mortalidad hospitalaria estimada preoperatoriamente de acuerdo con el EuroSCORE II fue de 4,1 ± 4,2.

La decisión de implantar un tipo de prótesis u otro a cada paciente dependió exclusivamente de la decisión del cirujano responsable de la intervención. En esa decisión influyeron, sin duda, aspectos como el tamaño del anillo tisular aórtico del paciente, la edad y superficie corporal, la presencia de comorbilidades, la dificultad técnica del procedimiento debida a la anatomía cardiaca y al diseño de la prótesis y la experiencia personal del cirujano.

Los datos expuestos demuestran diferencias entre la población de pacientes que recibió una bioprótesis Mitroflow y una Carpentier. La más llamativa es que las personas con prótesis Mitroflow eran predominantemente mujeres, de más edad y menor tamaño corporal que las que recibieron una prótesis Carpentier. Así mismo se puede constatar que los pacientes con bioprótesis Mitroflow presentaban más comorbilidades y, en consecuencia, un mayor riesgo quirúrgico que en la prótesis Carpentier.

Se realizó recambio valvular aórtico aislado en el 74,81% de los pacientes. Se asoció una sustitución valvular mitral en el 3,66% de los casos y una revascularización miocárdica en el 21,51%.

Las 409 prótesis implantadas se distribuyeron de acuerdo con el tamaño del siguiente modo: nº 19: 53 (13%); nº 21: 207 (50,6%); nº 23: 122 (29,8%); nº 25: 24 (5,9%) y nº 27: 3 (0,7%).

El orificio valvular efectivo indexado de las bioprótesis implantadas para el grupo total fue de 1 ± 0,2 cm^2/m^2. Se observó ausencia de mismatch (EOAI > 0,85 cm^2/m^2) en el 73,3% de los casos; mismatch moderado (EOAI 0,65- 8,85 cm^2/m^2) en el 25,7% y mismatch grave (EOAI < 0,65 cm^2/m^2) en el 1% de los pacientes intervenidos.

En el grupo de pacientes que recibió una bioprótesis Mitroflow se realizó recambio aórtico aislado en el 72,34% de los casos. Se asoció una sustitución valvular mitral en el 4,25% de los casos y una revascularización miocárdica en el 23,40%.

La distribución de los pacientes de acuerdo con el tamaño protésico fue la siguiente: nº 19: 43 (18,29%); nº 21: 123 (52,34%); nº 23: 60 (25,53); nº 25: 9 (3,82%).

El orificio valvular efectivo indexado medio para las bioprótesis Mitroflow fue de 0,9 ± 0,1 cm^2/m^2. Se observó ausencia de discordancia en el 55,74%, discordancia moderada en el 43,8% y discordancia grave en el 0,42% de los pacientes.

Se realizó recambio valvular aórtico aislado en el 78,16% de los pacientes. Se asoció una sustitución valvular mitral en el 2,87% de los casos y una revascularización miocárdica en el 18,96%.

En el grupo de 174 pacientes que recibieron una bioprótesis Carpentier la distribución de acuerdo con el tamaño protésico fue la siguiente: nº 19: 10 (5,74%); nº 21: 84 (48,27%); nº 23: 62 (35,63%); nº 25: 15 (8,62); nº 27: 3 (1,72%).

El orificio valvular efectivo indexado medio para las bioprótesis Carpentier fue de 1,1 ± 0,2 cm^2/m^2. Se observó ausencia de discordancia en el 97,11%, discordancia moderada en el 1,14% y discordancia grave en el 1,72% de los pacientes.

Las intervenciones en las que se implantaron bioprótesis de Mitroflow fueron más complejas en la medida que hubo procedimientos asociados.

En cuanto al tamaño, en el grupo Carpentier, el tamaño protésico fue mayor y además la tasa de discrepancia entre el tamaño del orificio protésico y el tamaño del paciente fue anecdótica, mientras que en el grupo Mitroflow, más de la mitad de los pacientes quedaron con un cierto grado de estenosis aórtica residual.

El 70% de las prótesis Mitroflow se implantaron en pacientes con pequeños tamaños (19 + 21) mientras que en el caso de las Carpentier los anillos aórticos pequeños representaron el 54%.

En el grupo total de pacientes intervenidos hubo 33 muertes hospitalarias lo que representa un 8,06%. La mortalidad en el grupo de pacientes intervenidos con bioprótesis Mitroflow fue de 16 personas (6,8%) mientras que en el grupo Carpentier fallecieron 17 (9,77%) (p = 0,3662).

La causa de muerte hospitalaria más frecuente fue fallo cardiaco (14) seguido por fallo multiorgánico (11), endocarditis protésica precoz (2), mediastinitis (1), ictus (2), hemorragia postoperatoria (1) y shock séptico (2).

En el momento de cerrar el seguimiento, un total de 263 pacientes (64.30%) habían fallecido y de los 147 supervivientes (35.5%), 41 pacientes (10,02%) presentaban más de 10 años de evolución. De acuerdo con los datos contenidos en la historia clínica las causas de muerte tardía fueron en el 38,58% de causa cardiaca y en 61.4% no cardiaca. La principal causa de mortalidad fue la neoplasia (20,48%), seguida de los procesos septicémicos de origen abdominal/urológico (9,03%), la insuficiencia cardiaca no relacionada con la prótesis (9,03%), la demencia (8,43%), la muerte súbita no explicada (8,43%) y la endocarditis infecciosa (7,22%).

El análisis ajustado para los riesgos competitivos de muerte, disfunción valvular estructural y reoperación utilizando el modelo de Cox de riesgo para una causa específica y la función de incidencia acumulada del evento según el modelo de Fine Gray demostró asociación significativa de mortalidad con la edad en el momento de la intervención, presencia de fibrilación auricular, implante de prótesis Mitroflow e insuficiencia renal crónica. No se demostró asociación entre mortalidad y género, presencia de diabetes mellitus, hipertensión arterial, mismatch y cirugía combinada con el recambio valvular aórtico.

El análisis comparativo de supervivencia entre los grupos con prótesis Mitroflow y Carpentier demostró diferencias significativas a favor de la bioprótesis de Carpentier a partir de los 6 años de la intervención. Transcurridos 10 años las diferencias entre ambos grupos tienden a desaparecer.

Se constató ecocardiográficamente la presencia de disfunción valvular estructural en 35 pacientes (8.55%) de los que 29 casos correspondieron a la prótesis Mitroflow (tamaño nº 19: 7; nº 21: 17 y nº 23: 5) y 6 casos en la prótesis Carpentier (tamaño nº 19:1 y nº 21: 5).

De los 35 pacientes diagnosticados de disfunción valvular estructural fueron reintervenidos solamente 14 por dicha causa, realizándose cirugía abierta en 8 casos e implante de prótesis transcatéter en 6 pacientes.

La ausencia de disfunción valvular estructural para el grupo global a los 5 y a los 10 años fue respectivamente 95% y 77%.

El análisis estadístico permitió demostrar relación estadísticamente significativa entre disfunción valvular estructural y edad en el momento de la cirugía e implante de bioprótesis Mitroflow. No se observó relación entre disfunción valvular estructural y género, presencia de diabetes, hipertensión arterial, insuficiencia renal, tamaño de prótesis y mismatch.

El análisis ajustado para los riesgos competitivos de muerte, disfunción valvular estructural y reoperación utilizando el modelo de Cox de riesgo para una causa específica y la función de incidencia acumulada del evento según el modelo de Fine Gray demostró asociación significativa de disfunción valvular estructural con la edad en el momento de la intervención, fibrilación auricular, implante de prótesis Mitroflow e insuficiencia renal crónica. No se demostró asociación entre disfunción valvular estructural y género, presencia de diabetes mellitus, hipertensión arterial, mismatch y cirugía combinada con el recambio valvular aórtico.

El análisis comparativo de disfunción valvular estructural entre los grupos portadores de prótesis Mitroflow y Carpentier demostró a partir de los 4 años de evolución postoperatoria una mayor tasa de disfunción valvular estructural en los pacientes para la prótesis Mitroflow con una tasa de ausencia de deterioro de 94,2% y 67,2% a los 5 y 10 años respectivamente. Un total de 17 pacientes fueron diagnosticados de endocarditis protésica (4.15%). En dos casos el diagnóstico se realizó antes del alta hospitalaria y fallecieron sin ser reintervenidos. Después del alta 15 pacientes fueron diagnosticados endocarditis (5 precoces y 10 tardías). Se reintervinieron 11 pacientes (4 endocarditis precoces y 7 tardías) y 4 pacientes recibieron solamente tratamiento médico.

Al realizar un análisis comparativo en la aparición de endocarditis entre los pacientes portadores de bioprótesis Mitroflow y Carpentier no se demostraron diferencias significativas.

Fueron reintervenidos un total 28 pacientes (6,84%). En tres pacientes la reintervención no tuvo relación con la bioprótesis aórtica (2 recambio valvular mitral y 1 revascularización miocárdica). En 25 pacientes se actuó sobre la prótesis aórtica. El motivo de reintervención aórtica fue disfunción valvular estructural en 14 casos y endocarditis sobre prótesis en 11 casos.

El análisis ajustado para los riesgos competitivos de muerte, disfunción valvular estructural y reoperación utilizando el modelo de Cox de riesgo para una causa específica y la función de incidencia acumulada del evento según el modelo de Fine Gray demostró asociación significativa de reoperación con el implante de prótesis Mitroflow. No se demostró asociación entre reoperación y género, presencia de diabetes mellitus, hipertensión arterial, mismatch y cirugía combinada con el recambio valvular aórtico.

El análisis comparativo entre los pacientes portadores de prótesis Mitroflow y Carpentier en relación con la ausencia de reintervención demostró una mayor tasa de reintervenciones en el grupo Mitroflow.

Conclusiones

1. La frecuencia de deterioro estructural de las bioprótesis en posición aórtica en nuestro medio se sitúa en el 4% y el 22% a los 5 y 10 años respectivamente.

2. La bioprótesis Mitroflow presenta un deterioro estructural más precoz e intenso que la bioprótesis Carpentier.

3. La bioprótesis Mitroflow se implanta en pacientes más ancianos, con más comorbilidades, menor tamaño del anillo aórtico y mayor riesgo quirúrgico que la bioprótesis Carpentier.

4. El deterioro estructural de las prótesis es inversamente proporcional a la edad de los pacientes.

5. Después del recambio valvular aórtico por bioprótesis los factores relacionados con una mayor mortalidad a largo plazo incluyen la edad, la presencia de fibrilación auricular, el implante de una prótesis Mitroflow y el fallo renal crónico.

6. El tamaño de la prótesis implantada y la presencia de desajuste moderado entre el orificio valvular efectivo protésico y el paciente no influyen en la evolución a largo plazo.

7. En nuestro medio existe una gran heterogeneidad en los protocolos de seguimiento postoperatorio clínico y ecocardiográfico en los pacientes portadores de bioprótesis que impide conocer la tasa de deterioro estructural tanto clínicamente relevante como asintomático.

8. La endocarditis infecciosa continúa siendo una complicación relevante en los pacientes portadores de prótesis valvulares por lo que es preciso extremar las medidas de profilaxis y considerarla en el diagnóstico diferencial de los procesos febriles en el anciano.

9. Es preciso realizar un seguimiento periódico ecocardiográfico de los pacientes portadores de bioprótesis, incluidos los asintomáticos, para facilitar un diagnóstico precoz del deterioro estructural.

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1. INTRODUCTION

1.1. EPIDEMIOLOGY AND NATURAL HISTORY OF AORTIC STENOSIS

Aortic valve stenosis (AS) is the most common cause of left ventricle outflow tract (LVOT) obstruction. The etiology of AS varies markedly among countries. Whereas the most common cause of AS in Europe and the USA is sclerosis and calcification of a tricuspid aortic valve (senile degenerative AS) or a congenitally bicuspid valve, in the rest of the world the most common cause is rheumatic heart disease (rheumatic AS).

The prevalence of calcific AS increases with age, reaching around 0.2% in patients aged 50 to 59 years, 1.3% in those 60 to 69 years, and 9.8% in those aged 80 to 89 years. The mortality of patients with asymptomatic AS and patients who undergo aortic valve replacement (AVR) does not differ from that of the general population (Eveborn et al., 2013) (figure 1.1).

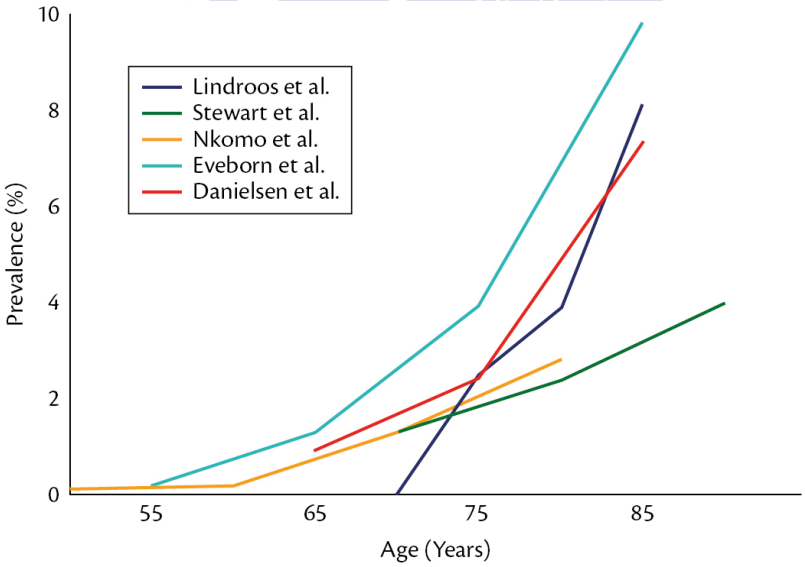


Figure 1.1. Prevalence of calcific degenerative aortic stenosis according to age, with permission from (Baumgartner et al., 2018).

The rate of AS related to tricuspid aortic valve degeneration verses that are related to bicuspid aortic valve degeneration depends on age. In patients younger than 60 years old, bicuspid degeneration is the more common cause of AS; bicuspid and tricuspid degeneration are an equally common cause of AS in patients between 60 and 70 years old, whereas senile calcific AS is the most common cause of AS in patients older than 70 years old (Roberts & Ko, 2005).

Longitudinal follow-up studies have shown that AS is an initially silent and progressive disease in nearly all patients. Progression manifests as a decrease in the valve area and an increase in transvalvular pressure gradients (ΔP).

In adults with degenerative or congenital AS, progression is faster in cases caused by a bicuspid valve than in those caused by a tricuspid valve (Roberts & Ko, 2005).

In patients with a normal aortic valve (AV), the valve effective orifice area (EOA) is similar to the sectional-cross area of the left ventricular outflow tract (LVOT), around 3 cm^2 to 4 cm^2 in the adult. As the valve leaflets thicken and calcify, the transvalvular velocity measured by Doppler remains normal without creating a gradient until the valve orifice area is reduced to half of its normal value.

When AS becomes hemodynamically significant, it causes an increase in the resistance to the ejection of the left ventricle (LV). AS is a gradual process that involves an adaptive process of the LV. The increase in the intraventricular pressure causes concentric hypertrophy as a compensatory mechanism that ensures normal parietal stress. Ventricular hypertrophy maintains the left ventricular ejection fraction (LVEF), end-diastolic volume, and cardiac output in the normal ranges for a long time despite the pressure gradient between the LV and the aorta.

However, if the AS persists and the hypertrophy continues, the LV becomes less distensible, and the end-diastolic pressure increases, despite the ventricle being standard size. This alteration of diastolic function contributes to the onset of symptoms. Often, persistent interstitial fibrosis after valve replacement for AS results in a degree of diastolic dysfunction that remains after the procedure. Another factor that may contribute to diastolic and systolic ventricular dysfunction is segmental contraction abnormalities, fibrosis, or subendocardial ischemia (Jin et al., 1996).

In general, when ventricular function is normal, symptoms very rarely appear until AS is severe (aortic valve area < 1 cm^2, jet velocity > 4 m/s, and/or mean transvalvular gradient (ΔP) > 40 mmHg). Many patients do not develop symptoms until AS is critical. In contrast, others become symptomatic when the stenosis is less severe, particularly if aortic regurgitation coexists. This means that the gradient "per se" is not always related to the onset of symptoms.

Most patients with AS develop symptoms before the onset of systolic dysfunction. In some cases, systolic dysfunction precedes symptoms. However, this situation does not usually last long as it ends up producing a reduction in the systolic volume and cardiac output, eventually causing signs and symptoms of heart failure.

In longitudinal studies of patients with AS followed by hemodynamic evaluation (Cheitlin et al., 1979) (Wagner & Selzer, 1982) (Cha et al., 1982) (Jonasson et al., 1983) (Nestico et al., 1983) (Turina et al., 1987) (Davies et al., 1991) or echocardiographic evaluation (Eveborn et al., 2013) (Otto et al., 1997) (Brener et al., 1995), the speed of progression of AS is similar in different studies. However, it varies widely among patients within each study. The mean increase in the transvalvular gradient ranges from 3 to 7 mmHg/year. However, in some patients, this increase may reach 15- 19 mmHg/year. Similarly, it occurs with a reduction in aortic valve area. The mean reduction is 0.1 cm^2/year, some patients progress faster than the mean, and others do not progress at all. The mean aortic jet velocity measured by Doppler in patients with AS

is 0.2 m/s/year. However, this parameter also varies widely among individuals (Rosenhek et al., 2000).

Patients with mild AS (transvalvular velocity < 3 m/s) are unlikely to develop symptoms during the next five-year period (Otto et al., 1997). Conversely, although a significant number of patients with severe AS are asymptomatic, approximately 75% will have some type of event over the next 4 to 5 years (Rosenhek et al., 2000) (Pellikka et al., 2005).

Different observational studies in patients with asymptomatic AS suggest that the peak of maximum jet velocity measured with Doppler or the rate of progression of jet velocity is associated with the risk of death or aortic valve replacement (AVR). One study found that the probability of remaining alive or free of surgery is estimated at around 84% when the jet velocity is < 3 m/s, 66% when the jet velocity is between 3 and 5 m/s, and 21% when it is > 4 m/s (Otto et al., 1997). In other studies, the probability of patients with asymptomatic severe AS and jet velocity > 4 m/s remaining alive without requiring surgery ranged from 33% at four years (Rosenhek et al., 2000) to 35% at five years (Pellikka et al., 2005).

The AS progression rate and the time to the onset of symptoms varies markedly among patients and is difficult to predict (Faggiano et al., 2000). Several risk factors that accelerate the progression of the disease in asymptomatic patients have been identified: jet velocity, valve area, valve calcification, age, male sex, hypercholesterolemia, kidney failure, hypercalcemia, smoking, metabolic syndrome, and diabetes mellitus (Palta, 2000) (Otto et al., 1997) (Rosenhek et al., 2000) (Freeman & Otto, 2005) (Briand, Lemieux et al., 2006) (Bahler et al., 1999) (Pohle et al., 2001) (Kamalesh et al., 2009).

The value of the stress test and plasma levels of natriuretic peptides to stratify the risk of asymptomatic patients with AS have also been studied. The stress test is recommended to confirm the absence of symptoms, assess exertion tolerance, and assess hemodynamic changes during stress (Otto, 2006) (Das et al., 2005). However, the stress test is

contraindicated in patients with symptomatic AS (Nishimura et al., 2014).

Patients with symptomatic severe AS usually have higher plasma concentrations of natriuretic peptides than asymptomatic ones (Gerber et al., 2003); concentrations usually decrease after AVR (Weber et al., 2005). On the other hand, an increase in natriuretic peptides is associated with the appearance of symptoms and mortality in AS (Bergler-Klein et al., 2004) (Clavel, Malouf et al., 2014).

The prognosis of symptomatic patients with severe AS who do not undergo AVR is poor as mortality increases rapidly once symptoms appear. This observation, together with improved survival rates after AVR constitutes the basis for recommending prompt valve replacement in these patients. The grim prognosis of patients with symptomatic AS without AVR has been documented in historical studies (Turina et al., 1987) (Chizner et al., 1980) (Ross & Braunwald, 1968) (Schwarz et al., 1982) and revalidated in recent series of medically treated patients (Kitai et al., 2011) (Leon et al., 2010) (Ben-Dor et al., 2010). However, the high mortality rate in symptomatic patients who do not undergo AVR might also be partially due to comorbidities that contraindicate surgery (figure 1.2).

The rate of sudden death in asymptomatic patients with non-intervened AS is less than 1%/year (Pellikka et al., 2005) while in symptomatic patients it is between 8% to 34%/year (Sorgato et al., 1998). The risk of sudden death is reduced by AVR.

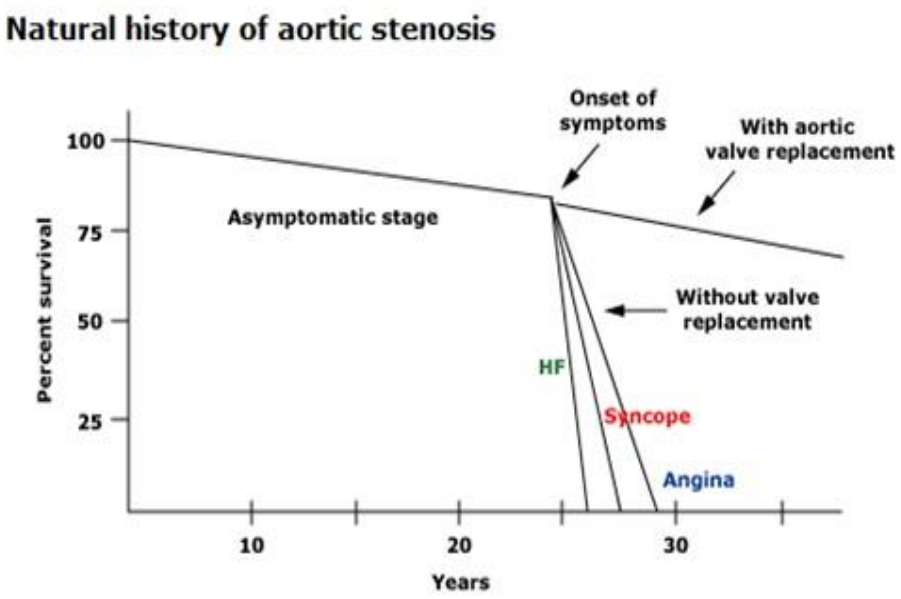


Figure 1.2. The natural history of aortic stenosis in relation to symptoms and effect of valve replacement, modified from (Lester et al., 1998).

Pulmonary arterial hypertension (systolic pressure > 30 mmHg) is common in patients with symptomatic AS and is associated with a more severe clinical picture as well as a worse prognosis after AVR. About 50% of patients develop light to moderate systolic pulmonary hypertension (30- 50 mmHg), and 15% develop severe hypertension (> 50 mmHg). The factors associated with severe pulmonary hypertension are heart failure and elevated LV end-diastolic pressure. In contrast, aortic valve area and LVEF are unrelated to pulmonary pressure (Faggiano et al., 2000).

1.2. DIAGNOSIS OF AORTIC STENOSIS

Aortic valve sclerosis is defined as thickening and calcification without a significant transvalvular pressure gradient (Doppler velocity < 2 m/s). Aortic valve stenosis (AS) is defined as transvalvular flow > 2 m/s. AS is considered severe when the maximum transvalvular velocity is > 4 m/s, a finding that is generally accompanied by an aortic valve area < 1 cm^2. AS is considered very severe when the jet velocity is > 5 m/s.

When AS provoke symptoms, it is considered then symptomatic. The most frequent early symptoms in patients followed prospectively are dyspnea on exertion, reduced exercise tolerance, dizziness during exertion-presyncope, syncope, and exertional angina. In advanced cases of AS, the classic symptomatic triad includes heart failure, angina, and syncope.

The diagnostic test of choice in AS is transthoracic Doppler echocardiography, which allows the assessment of the anatomy and structure of the valve, its hemodynamic performance, its consequences (ventricular size and function, and presence of pulmonary hypertension), and concomitant aortic valve insufficiency or other associated valve diseases.

As mentioned above, AS is a progressive disease. Various stages of the disease have been defined based on the anatomy, hemodynamics, and consequences of valve disease.

Stage A: Asymptomatic patients -without AS- with maximum transvalvular jet velocity < 2 m/s who have a bicuspid valve or aortic sclerosis on a tricuspid valve.

Stage B: Patients with moderately calcified valve leaflets with reduced mobility and light AS (maximum jet velocity 2- 2.9 m/s or mean ΔP < 20 mmHg) or moderate AS (maximum jet velocity 3- 3.9 m/s or mean ΔP of 20- 39 mmHg).

Stage C: Asymptomatic patients with severe AS (calcified/thickened leaflets with maximum jet velocity > 4 m/s). The aortic valve area in severe AS is often < 1 cm^2 (indexed to the body surface area BSA < 0.6 cm^2/ m^2).

Stage D: Asymptomatic patients with severe AS. Several substages are distinguished:

D1: Severe AS with peak gradient ΔP, with jet velocity > 4 m/s or mean ΔP > 40 mmHg, generally with aortic valve area < 1 cm^2 (indexed < 0.6 cm^2/m^2), but the aortic valve area may be larger when aortic insufficiency is also present due to the failure of the stiff and calcified leaflets to coapt.

D2: Severe AS with low flow and low ΔP with LVEF < 50%, maximum jet velocity < 4 m/s, mean ΔP < 40 mmHg, and aortic valve area < 1 cm^2. The dobutamine stress echocardiogram can show an aortic valve area of < 1 cm^2 and a maximum jet velocity of > 4 m/s.

D3: Severe AS with low gradient, with normal LVEF and aortic valve area < 1 cm^2, maximum jet velocity < 4 m/s, also known as paradoxical severe AS. The LV is small, with systolic volume index SVI < 35 mL/m^2.

The body surface should be considered for the calculation of the valve area, especially in small size patients. However, indexing for body surface is not recommended in obese or overweight subjects.

The most methodologically correct way to determine the severity of AS is to calculate the maximum jet velocity or the mean gradient ΔP when the LV is normal. However, it is only essential to calculate the aortic valve area when the ventricle is small, or its systolic function has deteriorated.

Computerized axial tomography (CT-SCAN) may contribute to characterize the severity of aortic stenosis, especially in patients with paradoxical AS in whom stress echocardiography is inconclusive as well as in symptomatic patients with normal flow and low gradient. Computerized tomography allows calculating the degree of calcification of the AV, which is correlated with the prognosis and the degree of valvular stenosis (Baumgartner et al., 2018) (Clavel, Pibarot et al., 2014).

1.3. TREATMENT OF AORTIC STENOSIS

1.3.1. Medical Treatment

An association between the progression of AS and the presence of hypercholesterolemia has been observed (Pohle et al., 2001). According to the clinical practice guidelines, even though many asymptomatic patients with AS meet criteria to receive statin treatment based on control factors, this group of drugs has not been shown to affect the process of sclerosis and the progressive calcification of the valve leaflets (Thiago et al., 2016). On the other hand, numerous patients with AS present other concomitant pathologies such as arterial hypertension, coronary heart disease and ventricular dysfunction that may require the administration of different drugs (antiplatelet agents, anticoagulants, calcium antagonists, vasodilators, etc.), although none of them is capable of slowing down the progression of AS.

The only effective treatment for symptomatic severe AS is surgical valve replacement SVR or transcatheter aortic valve implantation TAVI. Valve replacement improves symptoms and life expectancy, while the medical treatment does not extend the life of patients with severe symptomatic AS and is of limited use in treating symptoms (Carabello, 2012) (figure 1.3).

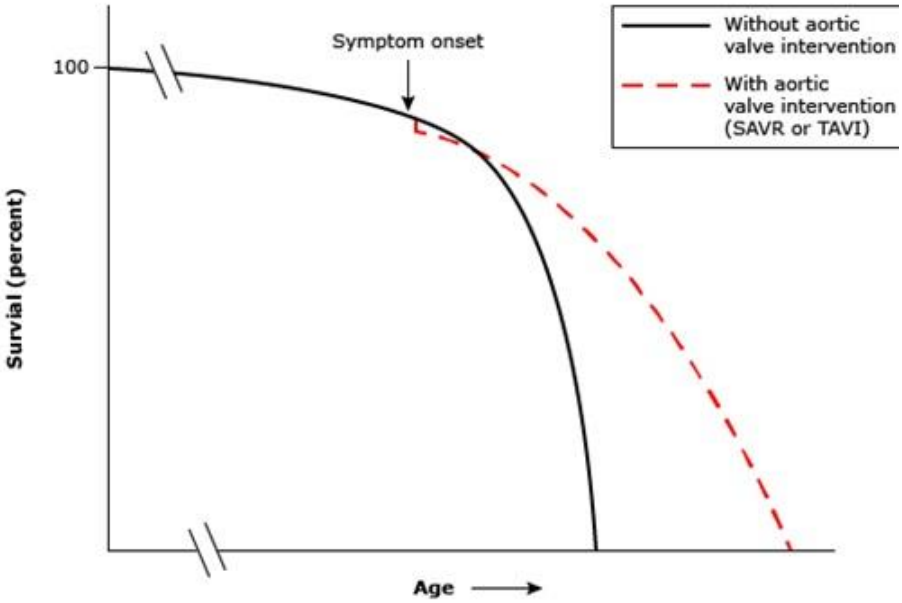


Figure 1.3. Survival of patients with symptomatic severe aortic stenosis with and without valve replacement treatment, modified from (Carabello, 2012).

Although valve replacement is the only treatment capable of improving the prognosis in patients with symptomatic severe AS, it does not restore normal life expectancy to the operated patients, but rather incurs a shorter life expectancy compared to the general population (figure 1.4) (Glaser et al., 2019).

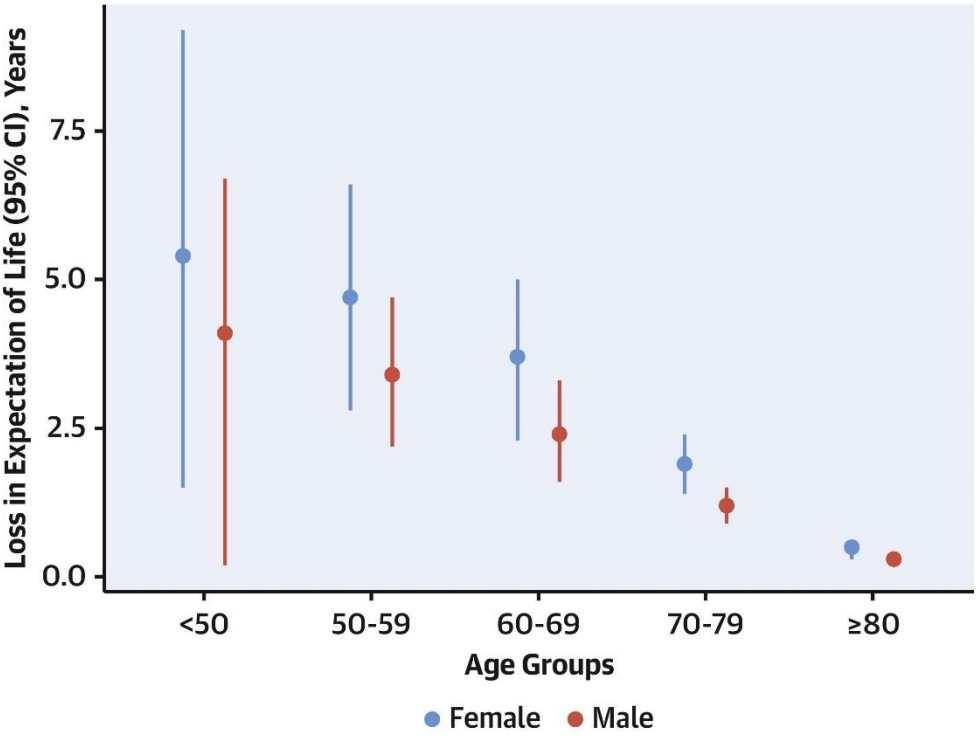


Figure 1.4. Loss of life expectancy in patients undergoing AVR compared to the general population, modified from (Glaser et al., 2019).

In patients with symptomatic severe AS pending surgical or percutaneous valve replacement, it is generally recommended to minimize drug administration due to the risk of clinical destabilization. In these patients, the safest therapeutic measure is to proceed with a valve replacement.

In patients with symptomatic severe AS who for various reasons cannot be subjected to SAVR or TAVI (high risk for comorbidities, refusal of treatment, etc.), the goals of medical treatment should be to improve

other associated disorders that often exacerbate the effects of valve stenosis, maintain optimal hemodynamic conditions, and alleviate symptoms. It is recommended to properly treat hypertension and maintain optimal blood volume. In this sense, prudent use of diuretics is recommended to avoid excessive reduction of preload, the same as for beta-blockers, especially in patients with heart failure. In these patients, angiotensin-converting enzyme inhibitors may be a good alternative (Carabello & Paulus, 2009).

1.3.2. Surgical Treatment

The current guidelines of the European Society of Cardiology (ESC) / European Society of Cardiothoracic Surgery (EACTS) (Baumgartner et al., 2018) recommend the surgical valve replacement as a class I (should be performed) in the following situations of severe AS (aortic valve area less than 1 cm^2):

a) Patients with symptomatic severe AS and a mean transvalvular gradient > 40 mmHg or maximum jet velocity > 4 m/s.

b) Patients with symptomatic severe AS with low-flow and low-gradient, reduced LVEF, and evidence of contractile reserve.

c) Asymptomatic patients with severe AS and left ventricular systolic dysfunction (LVEF < 50%) not due to other causes.

d) Asymptomatic patients with severe AS and abnormal stress test presenting symptoms during exercise that clearly related to aortic stenosis.

e) Patients with severe AS undergoing coronary artery bypass surgery or ascending aorta or other valve surgery.

There are other situations where AVR can be performed if the criterion is class IIa (could be performed):

a) Symptomatic severe AS with low flow/low gradient (< 40 mmHg) and normal LVEF.

b) Symptomatic severe AS with low flow/low gradient (< 40 mmHg) and reduced LVEF without contractile reserve.

c) Asymptomatic severe AS with hypotensive response during the stress test.

d) Asymptomatic severe AS with any of the following characteristics:

i. maximum jet velocity > 5.5 m/s.
ii. severe calcification and jet velocity progression rate > 0.3 m/s/year.
iii. elevation of the plasma concentration of natriuretic peptides three times above the normal value without any other explanation.
iv. Systolic pulmonary arterial hypertension > 60 mmHg without other explanation.

e) Patients with moderate AS undergoing coronary artery bypass surgery or ascending aorta or other valve surgery.

1.3.3. Transcatheter Aortic Valve Replacement

The first transcatheter replacement/implantation of an aortic valve prosthesis (Transcatheter aortic valve replacement/implantation), hereinafter TAVR/TAVI, was performed in 2002 (Cribier et al., 2002). Since then, this technique has experienced continuous advances in the design of prostheses, preoperative evaluation, intraoperative imaging, and technology for femoral, subclavian, aortic, carotid, and transapical

access (Figulla et al., 2016).

The main advantage of TAVR over surgery is that it is a less invasive procedure that prevents extracorporeal circulation. In most cases, it can be performed without general anesthesia. TAVR is an appropriate technique, especially for patients at high surgical risk, frail, elderly, or who have some form of contraindication for conventional surgery. Several studies have shown that TAVR is superior to surgery not only in high-risk patients (Reardon et al., 2015) (Kapadia et al., 2015) but also in low-risk patients (Mack et al., 2019).

Despite being a less invasive procedure, TAVR is not exempted from complications, highlighting a significantly higher rate of pacemaker and periprosthetic leaks comparing to conventional surgery (Figulla et al., 2016).

Currently, in some countries such as Germany, the number of valve prostheses implanted by catheter exceeds those implanted by surgery, and it is expected that, as the price of the prostheses decreases, a similar situation will occur in our environment in the coming years (Beckmann et al., 2019).

There is an aspect related to prostheses implanted by TAVR that is not entirely known and is directly related to the subject of this Thesis. All prostheses implanted by TAVR are biological - most of them manufactured with bovine and porcine pericardium - and as we will see in section 1.7 of this Introduction, therefore, these prostheses are subject to the possibility of structural deterioration over time.

To date, the rate of structural valve deterioration of TAVR at five years of follow-up is very low (Barbanti et al., 2015) (Toggweiler et al., 2013), with some cases of calcification and stenosis that have been described (Mylotte et al., 2015). However, it is worth to keep in mind that there is hardly any long-term follow-up in this type of patients since these are ancient populations with a reduced life expectancy despite TAVR (Webb & Dvir, 2015). It is not known how TAVRs will be

performed in the long term in non-aging, low-risk populations that may have a life expectancy long enough for structural valve deterioration to appear.

Few topics have sparked so much debate in recent years regarding the choice of the type of surgical or transcatheter valve replacement. The current guidelines of the European Society of Cardiology (ESC) / European Society of Cardiothoracic Surgery (EACTS) establish a series of clinical and anatomical aspects that must be considered to make a joint decision by surgeons and cardiologists on the choice of the most appropriate technique for each patient as reflected in (table 1.1) (Baumgartner et al., 2018).

1.4. PROSTHETIC SUBSTITUTES IN AORTIC VALVE SURGERY

1.4.1. Characterization of Aortic Valve Prostheses

In both biological and mechanical prostheses, except for stentless prostheses and some types of suture-less rapid deployment prostheses, we can identify and signalize a rigid structure (housing, support), the cusps (leaflets or hemi-disks) and the sewing ring.

The housing is the external, non-compressible rigid part of the prosthesis. It is usually made of metal, pyrolytic carbon, or polymer material.

The hemi-disks are placed inside the housing of mechanical prostheses, and the cusps of the biological prostheses are mounted on the metal or polymer and covered with textile material.

Table 1.1. Selection of the prosthetic valve implantation procedure in aortic stenosis, with permission from (Baumgartner et al., 2018).

	Favors TAVI	Favors SAVR
Clinical characteristics		
TS/EuroSCORE II <4% (logistic Euro SCORE I <10%)		+
STS/EuroSCORE II ≥4% (logistic Euro SCORE I ≥10%)	+	
Presence of severe co-morbidity (not adequately reflected by scores)	+	
Age <75 years		+
Age ≥75 years	+	
Previous cardiac surgery	+	
Frailty	+	
Restricted mobility and conditions that may impact the rehabilitation process after the procedure	+	
Suspicion of endocarditis		+
Anatomical and technical aspects		
Favorable access for transfemoral TAVI	+	
Unfavorable access (any) for TAVI		+
Sequelae of chest radiation	+	
Porcelain aorta	+	
Presence of intact coronary bypass grafts at risk when sternotomy is performed	+	
Expected patient–prosthesis mismatch	+	
Severe chest deformation or scoliosis	+	
Short distance between coronary Ostia and aortic valve annulus		+
Size of aortic valve annulus out of range for TAVI		+
Aortic root morphology unfavorable for TAVI		+
Valve morphology (bicuspid, degree of calcification, calcification pattern) unfavorable for TAVI		+
Presence of thrombi in the aorta or left ventricle		+
Cardiac conditions in addition to AS that require consideration for concomitant intervention		
Severe coronary artery disease requiring revascularization by coronary artery bypass grafting		+
Severe primary mitral valve disease		+
Severe tricuspid valve disease		+
Aneurysm of the ascending aorta		+
Septal hypertrophy suggesting myectomy		+

The sewing ring is the sleeve made from textile material (polyester, PTFE) that allows the prosthesis to be sutured to the patient's tissues. In general, the less voluminous and more foldable the sewing ring, the greater the diameter of the internal orifice for the same total size of the prosthesis (figure 1.5). The design and situation of the sewing ring concerning the housing can facilitate the implantation of the prosthesis in the supra-annular position.

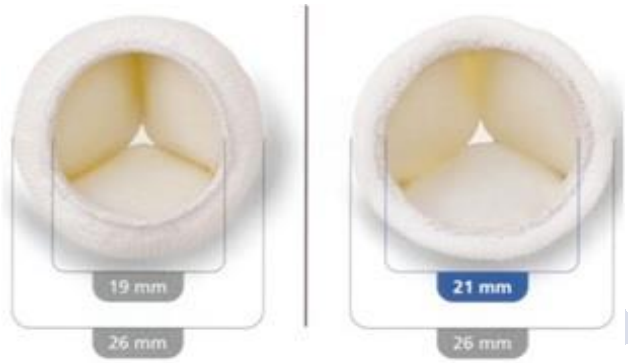


Figure 1.5. Two prostheses of the same total size with different diameters of the valvular orifice.

1.4.2. Geometric Characteristics

There is great variability between the different manufacturers in the terminology used to define the dimensions of the prostheses. From a geometric point of view, the main descriptors related to the dimensions of the prostheses are height, the diameter of the internal orifice, geometric valve area, external prosthetic diameter, the external diameter of the sewing ring, nominal size and tissue annulus size and orifice/ annulus ratio. We will briefly analyze each of these descriptors:

a) Height: the height of the prosthesis profile is defined as the maximum distance (mm) between the lower edge of the prosthesis and the highest point of the hemi-disks, in the position of the maximum opening in the mechanical prostheses, or of the posts in the case of biological prostheses (figure 1.6).

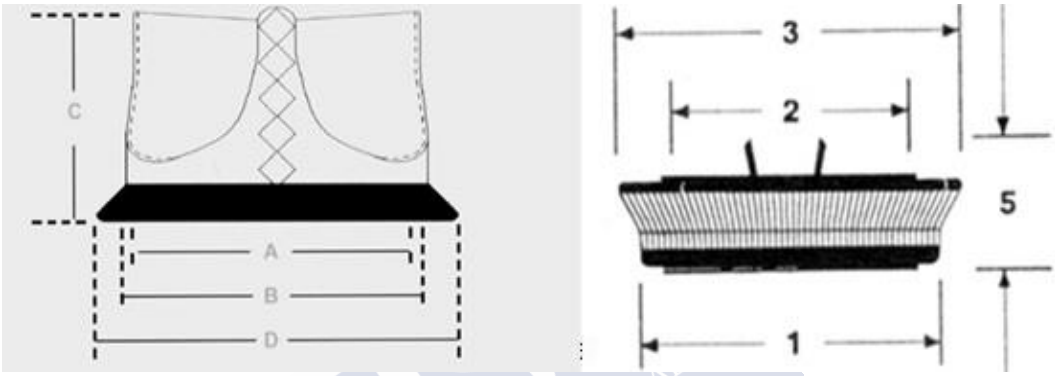


Figure 1.6. On the left: A bovine pericardium bioprosthesis. A: internal diameter; B: external diameter; C: height; D: total size or diameter of the sewing ring. On the right: A mechanical prosthesis. 1: external diameter; 2: internal diameter; 3: sewing ring diameter or overall size; 5: height.

b) Diameter of the internal orifice: it is the distance between the edges of the internal orifice or between the cusps of the prosthesis at its maximum opening (mm). It is a value provided by the manufacturers (figure 1.7).

c) Geometric valve area: also called the geometric orifice area or the internal orifice area (cm^2). It is defined as the maximum cross-sectional area between the internal edges of the open prosthesis. The geometric area is identical for all

prostheses of the same size and of the same model. It does not depend on flow or implant technique. It is a preoperatively known value, provided by the manufacturer and calculated from the internal diameter by subtracting the area occupied by the hinges and cusps at their maximum opening. In mechanical prostheses, the geometric area is constant over time. While, in biological prostheses, the geometric valve area can be reduced by time as the cusps become rigid and calcified. The geometric area is always more significant than the effective area.

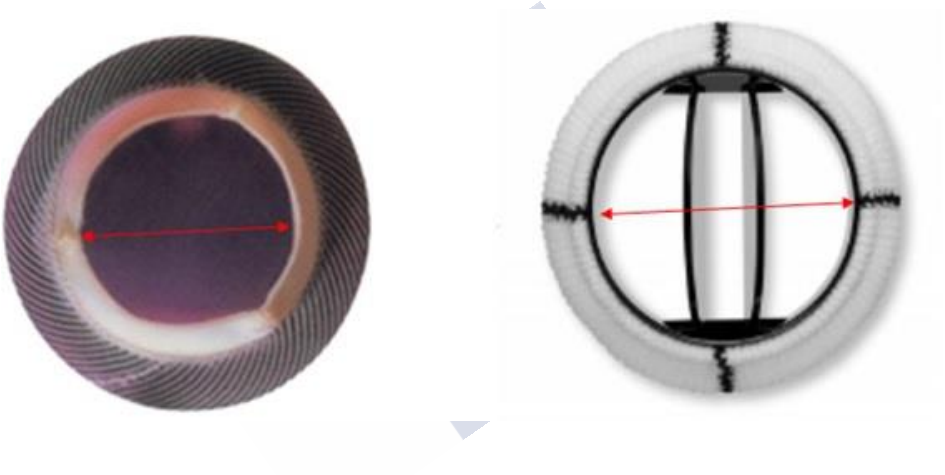


Figure 1.7. The red arrow indicates the diameter of the internal orifice at its maximum opening.

d) External prosthetic diameter (mm): is the diameter of the prosthesis without including the sewing ring and represents the non-compressible part of a prosthesis (figure 1.8). The external diameter of the prosthesis (outside diameter) generally coincides with the nominal size of the prosthesis, and many manufacturers use both terms interchangeably. It is a static parameter provided by the manufacturer.

e) The diameter of the sewing ring (mm): also called the total diameter, the external diameter of the suture sleeve, or the total size of the prosthesis. It refers to the maximum incorporated distance between the outer edges of the sewing ring (figure 1.8). It is a static concept that sometimes appears in the information provided by the manufacturers. Some manufacturers distinguish between external diameter with compressed and uncompressed sewing ring. The volume of the sewing ring determines that the same nominal size and model of the prosthesis has a different total size depending on whether it is considered a reduced, standard, or expanded sewing ring. Reducing the volume of the sewing ring may allow a larger size of the internal valve orifice for the same total size of the prosthesis.

f) Nominal size and tissue annulus size (mm): all prostheses are labeled with a numerical value called nominal size. In general, this size corresponds to the external diameter of the prosthesis, that is, of the non-compressible part of the prosthesis. The nominal size also corresponds to the diameter of the patient's aortic annulus in which it is intended to be implanted, so these terms have been used mutually, although there may be differences of up to ± 3mm between the nominal size and size of the patient's annulus. The nominal size of the prosthesis does not include the sewing ring, so the total size, that is, with the sewing ring, is usually several mm greater than the nominal size.

The nominal size has received multiple denominations depending on the manufacturers. Most call it tissue annulus diameter, and others call it outer diameter, label size, mounting diameter, and implant diameter.

Faced with this classic concept where the manufacturers use the nominal size of the prosthesis, the external diameter, and the tissue annulus diameter mutually, the norm of the International Standards Organization (ISO 5840: 2005) establishes differences between both concepts (ISO, 2005) (Eichinger et al., 2007).

This standard defines the tissue annulus diameter as the smallest measured diameter of the patient's aortic valve annulus (mm) after resection of the diseased valve and the calcium. The diameter of the patient's aortic annulus is calculated by inserting a gauge, for example, a Hegar dilator, into the patient's aortic annulus, assuming it is circular in shape. According to this standard, the nominal size of a concrete prosthesis is a term that the manufacturer uses to refer to the diameter of the patient's tissue annulus for which that prosthesis is suitable. Consequently, the nominal size of a prosthesis for the same patient, whether of intra-annular or supra-annular design, must be the same since the diameter of the aortic tissue annulus is the same although the total size of the prosthesis and the internal prosthetic orifice may be different (figure 1.8).

Both the tissue annulus diameter and the nominal size of the prosthesis are static concepts. They do not depend on the flow or the implant technique.

g) Orifice/Annular Ratio: it is the ratio between the internal diameter of a prosthesis and the tissue annulus diameter. The higher this ratio, the more efficient the design of the prosthesis.

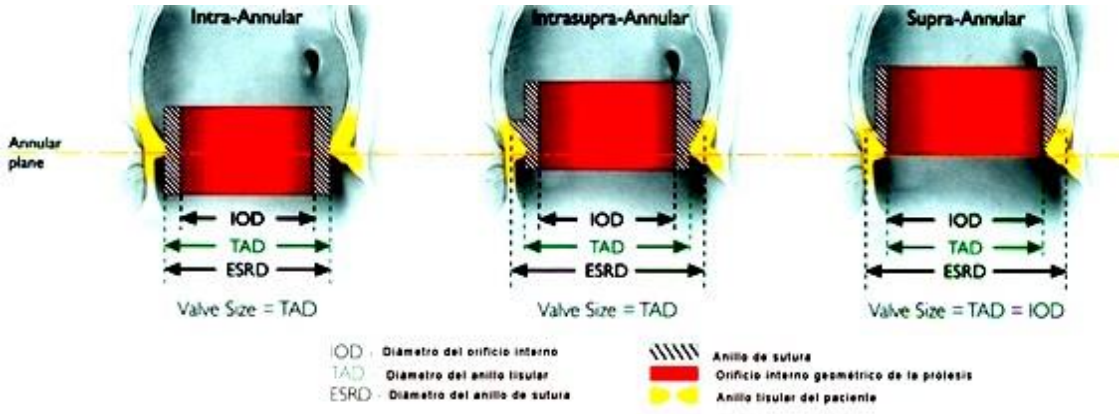


Figure 1.8. The diameter of the internal orifice, the sewing ring, and the tissue annulus in intra-annular, intra-supra-annular, and supra-annular implant prostheses.

1.4.3. Hemodynamic Characteristics

The functional characterization of valve prostheses is carried out considering their hemodynamic performance both *in vitro* and *in vivo*, independently of the design or the material in which they are manufactured.

From the functional point of view, the most important parameters to characterize a prosthesis are: Effective valve area (orifice), peak and mean transprosthetic pressure gradient, regurgitant volume, energy loss per beat, and the performance index. We will briefly analyze these parameters hereunder:

a) Effective valve area (effective valve orifice, effective orifice area EOA): is a measurement obtained under dynamic conditions that indicates the minimum cross-sectional area of the distal transprosthetic flow jet to the orifice of the prosthesis (cm^2) and, therefore, distal to the point where there is a change

in diameter (figure 1.9). The point where this minimum cross-sectional area of the flow jet is located is called the Vena Contracta and indicates the place where the flow velocity is maximum and where the direction is almost horizontal.

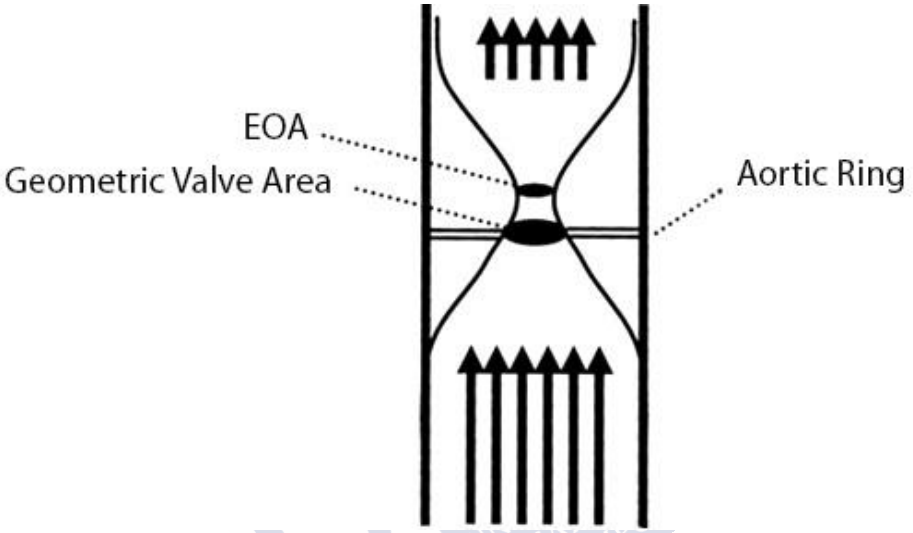


Figure 1.9. Relationship between the geometric valve orifice and the effective valve orifice (EOA).

The EOA is always less than the geometric area. The EOA is a dynamic concept and depends on several factors such as the geometric area, prosthetic design, shape, and size of the left ventricular outflow tract LVOT and the ascending aorta. For the same prosthesis, the EOA can vary depending on the flow, stroke volume, heart rate, blood pressure, patient's body surface area BSA, implant technique, and postoperative evolution time.

In clinical evaluation, the calculation of the EOA (cm^2) is performed by Doppler echocardiography using the formula:

$EOA = TSVI \times (TVI_{LVOT}/TVI_{AO})$

TSVI: Diameter of the left ventricular outflow tract LVOT (mm).

TVI_{LVOT}: Velocity time integral calculated using pulsed Doppler in the left ventricular outflow tract.

TVI_{AO}: Velocity time integral calculated through the prosthesis using continuous Doppler.

The indexed effective valve area or the effective orifice area indexed (EOAI cm^2/m^2) is calculated by dividing the effective valve area by the body surface.

b) Peak and mean transprosthetic pressure gradient (mmHg): the transprosthetic pressure gradient, also called pressure drop, indicates the limitation or resistance that the prosthetic valve opposes to the passage of blood. The concept of peak and mean gradient and the way it is calculated is similar in prosthetics and native valves.

In clinical evaluations, the peak gradient through the prosthesis is determined using a continuous Doppler probe and applying the simplified Bernoulli equation:

$$\text{Peak Gradient} = 4 \times V_{max}^2$$

V_{max}: maximum transprosthetic velocity (m/s).

The mean gradient (mmHg) through the prosthesis is determined by using a continuous Doppler probe and calculating the velocity/time integral (TVI_{AO}).

Both EOA and gradients are data that manufacturers typically provide and are calculated from *in vitro* and *in vivo* studies.

The *in vitro* tests are carried out in a pulse duplicator that allows the study of the prosthesis hemodynamic performance by monitoring heart rate, blood pressure, and cardiac output. These tests provide directly and easily reproducible values of the transprosthetic pressure gradients, the effective valve area (Gorlin formula), and the regurgitation volume (ml) under different conditions.

The *in vivo* studies are carried out in a series of intervened patients that allow estimating both the average EOA and the transprosthetic gradients in real conditions, where the parameters of frequency, afterload, and cardiac output show inter-individual variations.

The EOA and the gradients of a prosthesis in a specific patient are unique and specific for that case and may vary over time, although there are tables drawn from clinical studies that allow approximate preoperative estimation of the EOA for each prosthesis and BSA. The transprosthetic gradient and the EOA are correlated. Generally, a small EAO is accompanied by high transprosthetic gradients.

Regulatory agencies have established minimum EOA limits for each of the prosthetic nominal sizes (ISO, 2005) (Eichinger et al., 2007). The minimum accepted EOA is 0.7 cm^2 in prostheses of size 19, 0.85 cm^2 for size 21, and 1 cm^2 for size 23.

c) Regurgitant volume (ml): the total regurgitant volume is defined as the sum of the closing volume and the leakage volume.

The closing volume (dynamic regurgitation) is the return required in each heartbeat to close the prosthesis, which depends on the prosthesis model and the time required for closure.

The leakage volume (physiological regurgitation or lavage volume) is the central transvalvular leak per heartbeat that exists in all mechanical prostheses and some biological prostheses after closure. The volume of leakage is intrinsic to the design of the prosthesis and depends on the time that the prosthesis remains closed.

The percentage of regurgitation is calculated by dividing the total regurgitation by the systolic volume. Most often, the larger the size of the prosthesis, the greater the regurgitation. The maximum percentage of regurgitation accepted by regulatory agencies ranges from 10% for small prostheses to 20% for larger prostheses (ISO, 2005) (Eichinger et al., 2007).

d) Loss of energy per heartbeat: it is defined as the relationship between the mean transprosthetic gradient and peak intraventricular systolic pressure. The loss of energy per heartbeat is expressed as a percentage. It indicates the loss of energy due to the resistance generated by the prosthesis.

e) Performance index: is defined as the ratio between the effective valve area and the total area of the prosthesis calculated from the diameter of the sewing ring provided by the manufacturer. This index reports on the efficiency of a prosthesis to allow the passage flow concerning the prosthesis size.

1.4.4. Prosthesis Position, Design, and Implant Technique

The position of the implanted prosthesis in relation to the patient's aortic annulus as well as the prosthetic design and the implant technique are aspects that have a decisive influence on the implanted prosthetic size and, logically, the effective valve orifice.

Depending on the position of the prosthesis in relation to the patient's aortic annulus, it is considered that the implants can be in the supra-annular, supra-intraannular or intraannular position (Eichinger et al., 2007) (Botzenhardt et al., 2005) (Ruzicka et al., 2009) (figure 1.10) and (figure 1.11).

A prosthesis is considered to be implanted in a completely supra-annular position when none of its components lie below the plane of the aortic annulus. In the implant in the supra-intraannular position, a part of the prosthesis is located above and another part within the aortic annulus and sometimes below it. When most of the prosthesis remains within the aortic annulus, it is considered in an intraannular position (Eichinger et al., 2007) (Botzenhardt et al., 2005).

The prosthesis housing and sewing ring occupy a space that could be used for the flow. To increase the area available for the flow, some manufacturers reduce the size of the sewing ring. Another solution is to raise the entire prosthesis to a supra-annular position. Based on this idea, prostheses have been designed for the implant in the supra-annular position. In these prostheses, the sewing ring is located at the base of the housing so that once all the components of the prosthesis (including the sewing ring) are implanted, they would be located above the plane of the aortic annulus (Botzenhardt et al., 2005) (Ruzicka et al., 2009) (figure 1.10).



Figure 1.10. From left to right, a bovine pericardium prosthesis of supra-intraannular design, the same prosthesis of purely supra-annular design, a mechanical prosthesis of supra-intraannular design and the same prosthesis of supra-annular design.

In prostheses designed for supra-intraannular implantation, the sewing ring is often eyelash-shaped and is located above the aortic annulus. However, part of the prosthetic housing remains within the annulus (figure 1.11).

Both stentless and stented bioprostheses, and mechanical prostheses that are designed for a fully supra-annular implant allow the sewing ring and the housing to be placed above the aortic annulus ring, reducing greatly the resistance to blood flow and thus achieving excellent hemodynamic performance with respect to the other prostheses. Besides, the supra-annular design allows the diameter of the prosthetic internal orifice to be equal to the tissue annulus diameter, and a prosthetic internal orifice/tissue annulus ratio of 100% can be obtained; which gives it a clear hemodynamic advantage over other designs (Eichinger et al., 2007) (Botzenhardt et al., 2005) (Ruzicka et al., 2009)

(figure 1.11).

Under (ISO 5840: 2005) standards, the nominal size of the supra-annular prostheses is equal to the size of the tissue annulus and corresponds to the internal prosthetic diameter (ISO, 2005). This is not possible in prostheses of non- supra-annular design since, for the same nominal size, logically, the diameter of the internal orifice is smaller as part of the housing remains inside the ring.

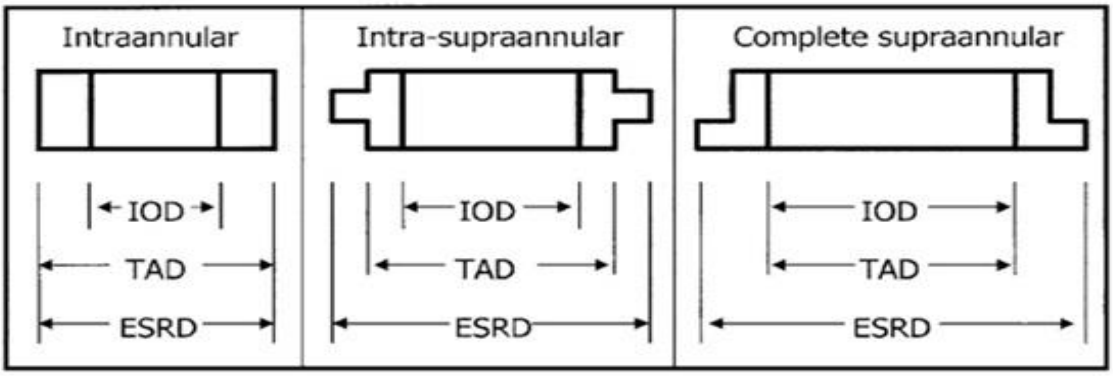


Figure 1.11. Relationship between internal valve (orifice) diameter (IOD), tissue annulus diameter (TAD), and sewing ring diameter (ESRD).

However, not all supra-annular prostheses have advantages since some are relatively voluminous and can cause problems depending on the shape and size of the aortic root and height of the coronary ostia (Eichinger et al., 2007). A supra-annular prosthesis may be appropriate in one patient. In contrast, the same prosthesis in another patient with the same tissue annulus diameter may interfere with the coronary Ostia or the aortic wall and may require implantation of a smaller prosthetic size (Eichinger et al., 2007).

In addition to the design of the sewing ring, another factor that determines the position of the prosthesis in relation to the plane of the patient's aortic ring is the suture technique. The same prosthesis model can be implanted at the supra-annular, intra- supra-annular, or intraannular levels depending on the suture technique.

The suture of the prosthesis using non-everting mattress sutures (with or without pledgets of textile material) facilitates the implant in the supra-annular or supra-intraannular position depending on the design of the prosthesis (Doenst et al., 2011) (Ruzicka et al., 2009). The suture using single loose stitches in a figure of 8 and continuous suture also allows a supra-annular implant. In contrast, the use of everting mattress sutures (with or without pledgets of textile material) provides a predominantly intraannular implant (figure 1.12).

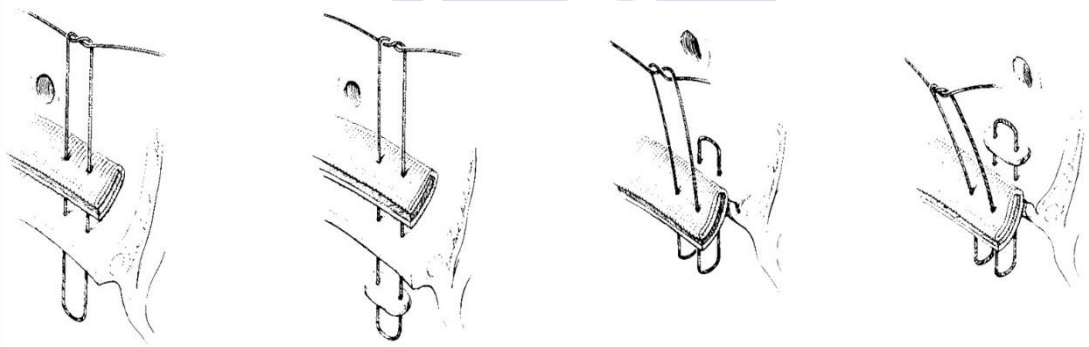


Figure 1.12. The first two figures on the left represent a non-everting mattress suture. The two figures on the right represent the everted mattress suture.

The implant technique conditions the size of the prosthesis, since the everting mattress sutures carry the presence of suture threads to be within the aortic orifice and forces the prosthesis to be within the limits of the annulus (Doenst et al., 2011), which mean in general the use of a smaller prosthesis (figure 1.13).

The good postoperative gradients and effective orifice areas observed in transcatheter aortic prostheses and rapidly deployable "sutureless" prostheses are to a large extent due to the absence of sutures, so this aspect must be taken into account in the designs of future prosthetic substitutes.

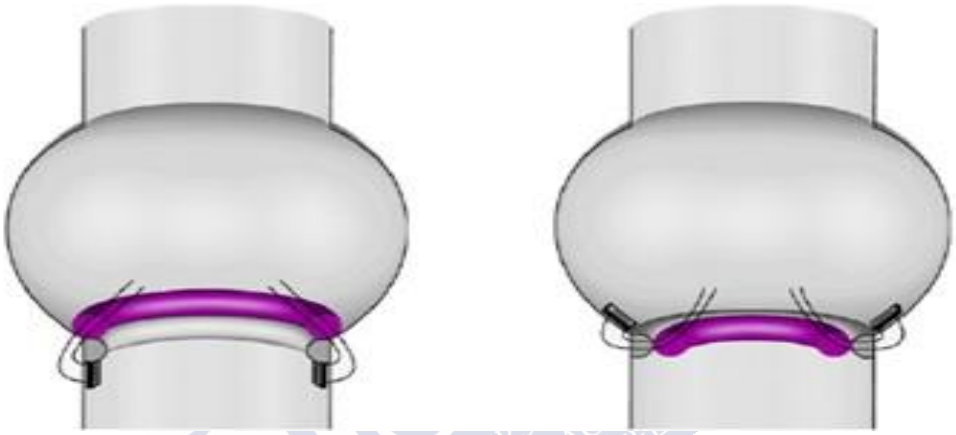


Figure 1.13. Effect of the everting / non-everting sutures on the size of the prosthetic substitute.

1.4.5. Mechanical Prostheses Vs. Biological Prostheses

The prostheses used as substitutes for heart valves are classified into two main groups: Mechanical prostheses and Biological or Bioprosthesis.

The old mechanical prostheses – of a box, a ball, and a single disc - have fallen out of use. Currently, the prostheses in use are formed of a pyrolytic carbon bidisc and polyester ring. The main characteristics of mechanical prostheses are their long duration -theoretically, unlimited duration- and the need for whole life anticoagulant treatment e.g. with

vitamin K antagonists.

Bioprostheses can be made from porcine valve xenografts or equine, porcine, or bovine pericardium. According to the design, the bioprostheses are classified as supported (stented) or not supported (stentless). In some studies, the latter has shown a better hemodynamic profile, even though it has not been accompanied by longer durability (van der Straaten, Ellen P. J. et al., 2016).

The main advantage of bioprostheses is that they do not require anticoagulant treatment. Their most significant disadvantage is that they have a limited duration since they can present structural valve deterioration (SVD) after a variable period after implantation.

Recently, a new type of bioprosthesis called "rapid deployment" or "sutureless" bioprostheses has seen a huge spike in usage, which shortens the aortic clamping time and facilitates implantation through minimally invasive approaches (Phan et al., 2015). Furthermore, "sutureless" bioprostheses compared to conventional ones provide a greater effective valve orifice area, a lower transprosthetic gradient, and a lower rate of mismatch between the size of the prosthesis and the size of the patient (Haverich et al., 2014). The absence of prosthetic material used to suture the valve to the aortic annulus explains the optimal hemodynamic performance of "sutureless" bioprostheses. The main short-term disadvantage of "sutureless" bioprostheses is that a higher rate of patients requires a definitive pacemaker in the postoperative period compared to conventional prostheses (Dalén et al., 2016).

Several randomized studies compare mechanical and biological prostheses (Rodríguez-Caulo et al., 2018) (Oxenham et al., 2003) (Stassano et al., 2009), as well as numerous retrospectives analysis (Chiang et al., 2014) (Glaser et al., 2016). Survival is similar among patients with mechanical and biological prostheses, as well as the rate of valve thrombosis and thromboembolism. However, the hemorrhage rate is higher in patients with mechanical prostheses, and the rate of reoperation is higher in patients with bioprosthesis.

The choice between a mechanical or a biological prosthesis in adults is mainly based on the risk of hemorrhage and thromboembolism associated with anticoagulation in mechanical prostheses versus the risk of structural valve deterioration and the need for reoperation on bioprostheses. Patient preferences and lifestyle should also be considered.

In turn, the risk of hemorrhage in patients with mechanical prosthesis depends on the therapeutic objective -expressed as the International Normalized Ratio (INR)-, the quality of anticoagulation control, the concomitant use of antiplatelet agents and the risk of patient`s hemorrhage.

In the case of bioprostheses, the risk of SVD is greater in mitral than in aortic valves and inversely proportional to age. On the other hand, the risk of reoperation is only slightly higher than the mechanical (Butchart et al., 2005). Besides, it is possible to implant a transcatheter prosthesis inside a dysfunctional one "valve-in-valve" which can be an incentive for the use of bioprosthesis. However, it should be recalled that in bioprostheses of size 21 or smaller the "valve-in-valve" technique can lead to high transprosthetic gradients.

The current guidelines of the ESC/EACTS (Baumgartner et al., 2018) recommend the use of mechanical prostheses (table 1.2) in the following situations:

- Class I (should be done):

a) The patient, properly informed, desires it, and there are no contraindications to long-term anticoagulation.

b) Patients at risk of accelerated bioprosthetic structural deterioration.

- Class IIa (can be done):

a) The patient already has a mechanical prosthesis in another valve

position.

b) Patients < 60 years of age for prostheses in the aortic position and < 65 years of age for prostheses in the mitral position.

c) Patients with a reasonable life expectancy for whom a future valve reoperation would be at high risk.

The same guidelines recommend the use of bioprosthesis (table 1.2) in the following situations:

- Class I (should be done):

a) The desire of the properly informed patient.

b) Adequate anticoagulation is unlikely, or there is a contraindication for anticoagulation.

c) Reoperation for mechanical prosthesis thrombosis despite good anticoagulant control.

- Class IIa (can be done):

a) Patients with little chance of requiring future valve surgery or with low operative risk in case needed.

b) Young women with a desire for pregnancy.

c) Patients > 65 years old for the aortic position or > 70 years old for mitral or those with a life expectancy less than the expected durability for the bioprosthesis.

1.5. SURGICAL RISK IN AORTIC REPLACEMENT

The morbidity and mortality associated with valve surgery depend on numerous factors. The best method to estimate the preoperative risk of an intervention is to use one of the existing models for risk stratification. These models are useful because they allow us to estimate the hospital morbidity and mortality associated with a procedure and thus evaluate and advise individual patients as well as to plan the postoperative care. However, risk stratification models have limitations that reduce their prognostic value. This is due to the fact that these are models generated from specific populations and their generalization for patients who do not belong to those population can generate errors. Furthermore, some important variables associated with mortality are not included in these models, such as the presence of a severely calcified ascending aorta, fragility, nutritional status, and hemodynamic factors such as right ventricular function.

The most commonly used models are the EuroSCORE scales and the Society of Thoracic Surgeons score (STS).

The first EuroSCORE model was developed from data extracted in 1995 to stratify the risk of hospital death (Nashef et al., 1999). This model was replaced by the EuroSCORE II developed from data on 22,381 patients from 43 countries operated between May and July 2010 (Nashef et al., 2012).

Table 1.2. Recommended situations in favor of choosing an aortic mechanical prosthesis or bioprosthesis, with permission from (Baumgartner et al., 2018).

Choice of the aortic/mitral prosthesis in favour of a mechanical prosthesis; the decision is based on the integration of several of the following factors

Recommendations	Class[a]	Level[b]
A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contraindications to long-term anticoagulation.[c]	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated structural valve deterioration.[d]	I	C
A mechanical prosthesis should be considered in patients already on anticoagulation because of a mechanical prosthesis in another valve position.	IIa	C
A mechanical prosthesis should be considered in patients <60 years of age for prostheses in the aortic position and <65 years of age for prostheses in the mitral position.[e]	IIa	C
A mechanical prosthesis should be considered in patients with a reasonable life expectancy[f] for whom future redo valve surgery would be at high risk.	IIa	C
A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to the high risk for thromboembolism.[g]	IIb	C

LV: left ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]Increased bleeding risk because of comorbidities, compliance concerns or geographic, lifestyle or occupational conditions.
[d]Young age (<40 years), hyperparathyroidism.
[e]In patients 60–65 years of age who should receive an aortic prosthesis and those between 65 and 70 years of age in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of factors other than age.
[f]Life expectancy should be estimated at >10 years according to age, sex, comorbidities and country-specific life expectancy.
[g]Risk factors for thromboembolism are atrial fibrillation, previous thromboembolism, hypercoagulable state and severe LV systolic dysfunction.

Choice of the aortic/mitral prosthesis in favour of a bioprosthesis; the decision is based on the integration of several of the following factors

Recommendations	Class[a]	Level[b]
A bioprosthesis is recommended according to the desire of the informed patient.	I	C
A bioprosthesis is recommended when good-quality anticoagulation is unlikely (compliance problems, not readily available) or contraindicated because of high bleeding risk (previous major bleed, comorbidities, unwillingness, compliance problems, lifestyle, occupation).	I	C
A bioprosthesis is recommended for reoperation for mechanical valve thrombosis despite good long-term anticoagulant control.	I	C
A bioprosthesis should be considered in patients for whom there is a low likelihood and/or a low operative risk of future redo valve surgery.	IIa	C
A bioprosthesis should be considered in young women contemplating pregnancy.	IIa	C
A bioprosthesis should be considered in patients >65 years of age for a prosthesis in the aortic position or >70 years of age in a mitral position or those with a life expectancy[c] lower than the presumed durability of the bioprosthesis.[d]	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
[c]Life expectancy should be estimated according to age, sex, comorbidities and country-specific life expectancy.
[d]In patients 60–65 years of age who should receive an aortic prosthesis and those between 65 and 70 years of age in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of factors other than age.

The STS model was developed and validated from the data of 774,881 patients operated between 2002 and 2006 (O'Brien et al., 2009) (Shahian et al., 2009). In addition to the risk of hospital death, this model also allows estimating the risk of serious complications.

The prognostic value of the risk stratification models depends on the population in which they are applied. Some studies showed that the first version of the EuroSCORE overestimated mortality in some subpopulations, including high-risk patients undergoing AVR (Grossi et al., 2008) (Kalavrouziotis et al., 2009). On the other hand, both the EuroSCORE II and STS models have a similar and appropriate discriminatory power for patients undergoing surgery for isolated valve replacement (Vahanian & Otto, 2010) (Vahanian et al., 2012).

1.6. DISCORDANCE BETWEEN PROSTHETIC SIZE AND PATIENT SIZE

The ideal valve prosthesis should perform minimal resistance to flow and allow only trivial regurgitation during the closure, with minimal turbulence and stasis areas. No prosthetic valvular substitute is hemodynamically as efficient as a healthy native valve.

The goal of aortic valve replacement in patients with aortic stenosis is to correct the valvular obstruction and to ensure a postoperative EOAI greater than 0.85 cm^2/m^2. However, a certain residual gradient often persists after valve replacement, especially in small-size prostheses and in patients with a large body surface area. This is because despite being normal-functioning prostheses, both the sewing ring and the housing and the way the leaflets or hemi-disks open can cause a certain degree of obstruction to the passage of blood.

When the implanted prosthesis is too small for the size of the patient, a phenomenon occurs called "disproportion between the size of the patient and the size of the prosthesis" also called discordance,

mismatch, or prosthesis-patient mismatch PPM, hereinafter (mismatch).

The mismatch concept was introduced by Rahimtoola in the 1970s to refer to a clinical situation that occurred when the area of the aortic prosthesis was smaller than the patient's normal valve area where the postoperative residual stenosis prevented the regression of the ventricular mass, maintaining high transprosthetic gradients especially during exercise and limiting the clinical improvement in the postoperative period (Rahimtoola, 1978a).

Currently, the mismatch is defined as the presence of an effective valvular orifice indexed for the body surface area smaller than that of a normal human valve (Pibarot, P. & Dumesnil, 2006). The mismatch is considered to be: not clinically significant when the postoperative indexed EOA determined by Doppler Echocardiography is greater than 0.85 cm^2/m^2, moderate between 0.65 and 0.85 cm^2/m^2 and severe when it is less than or equal to 0.65 cm^2/m^2. The pathophysiological consequence of the mismatch is the presence of high transprosthetic gradients and, consequently, a functional stenosis through a prosthesis that opens in a normal way (Blais et al., 2003).

Some papers have suggested that moderate or severe prosthetic mismatch is associated with an absence of improvement in the functional class after the surgery (Ruel, Kulik et al., 2004) (Ruel, Rubens et al., 2004), reduced functional capacity (Bleiziffer et al., 2008), absence of left ventricular remodeling (Tasca et al., 2005), lower coronary flow reserve (Bakhtiary et al., 2007) and increased frequency of adverse events (Ruel et al., 2004) (Ruel et al., 2004) (Bleiziffer et al., 2008) (Tasca et al., 2005) (Ruel et al., 2006). Furthermore, several authors have observed a significant increase in early mortality (Blais et al., 2003) (Walther, 2006) (Adams et al., 1999) and late mortality (Ruel et al., 2006) (Walther, 2006) (Mohty et al., 2006) (Blackstone et al., 2003) (Tasca et al., 2006), although some papers only show an increase in mortality in patients with preoperative ventricular dysfunction (Mohty et al., 2009) (Ruel et al., 2006) (Blais et al., 2003). On the other

hand, it has been possible to verify that the negative effect of mismatch is more evident in young patients than in the elderly (Moon et al., 2006), which would reflect the fact that physical activity and increased cardiac output, maintained together, could make the deleterious effect of mismatch more evident (Mohty et al., 2009).

Paradoxically, there are papers in which the multivariate study has not been able to demonstrate that the mismatch is an independent predictive factor associated with late mortality or regression of the left ventricular mass (Jamieson et al., 2010) (LaPar et al., 2011) (Medalion et al., 2000) (Taggart, 2006). Regarding the regression of the left ventricular mass after aortic valve replacement and its relationship with the postoperative residual gradient, the published studies are also inconclusive (Akins et al., 2008). In our experience, light or moderate degrees of mismatch in biological prostheses of 21 mm do not seem to negatively influence the regression of ventricular mass, especially in elderly and sedentary patients, so other factors such as high blood pressure and the degree of physical activity can condition the ventricular remodeling (García-Bengochea et al., 2006).

Several aspects add confusion about the clinical consequences of mismatch and may explain the disparate results of published studies.

First, the concept of mismatch was emerged in the 1970s (Rahimtoola, 1978b). Since then, the design of mechanical and biological prostheses has improved in a way that the magnitude of the mismatch problem has been significantly reduced.

Second, studies on mismatch analyze groups of patients that are heterogeneous in age, comorbidities, physical activity, and preoperative ventricular function (Adams et al., 1999) (Pibarot, Philippe & Dumesnil, 2009) (LaPar et al., 2011) (Medalion et al., 2000).

Third, although the postoperative regression of the left ventricular mass and the presence of residual gradients may be affected by the mismatch, the type of prosthesis can also have an impact since the bidiscs

mechanical prostheses are less obstructive than the biological ones of the same size and are associated with a greater reduction in ventricular mass (Bech-Hanssen et al., 1999) (Moon et al., 2006). This fact may be due to both the obstruction generated by the posts and the sewing ring of the bioprostheses and to the progressive rigidity and calcification of the cusps, which further reduce the EOA (Botzenhardt et al., 2005).

The clinical practice guidelines consider severe residual stenosis due to mismatch as an iatrogenic problem resulting in a non-structural dysfunction of the aortic prosthesis (Akins et al., 2008). The guidelines of the ESC / EACTS published in 2012 recommend preventing the mismatch by implanting the prosthesis with the largest possible EOA (Vahanian et al., 2012) (Svensson et al., 2013) or considering the enlargement of the aortic annulus when a severe mismatch is anticipated (EOA < 0.65 cm^2/m^2). These Guidelines warn that the values of the geometric valve area or the EOA obtained *in vitro* in the pulse duplicator are not reliable to preoperatively estimate the EOA of a prosthesis implanted in a patient. Consequently, it is necessary to know the EOA data obtained in historical clinical series to be able to make a closer estimation to reality (Pibarot & Dumesnil, 2009).

1.7. STRUCTURAL VALVE DETERIORATION OF THE BIOPROSTHESES IN AORTIC POSITION

The mechanical prostheses have excellent durability, nowadays, it is very rare to present a structural deterioration, although some mechanical failure (fracture of the pivot or the cusps, the release of the cusps) has been described in the past. In contrast, the Achilles heel of bioprostheses continues to be postoperative structural valve deterioration (SVD).

Once a bioprosthesis is implanted, it begins to be subject to hemodynamic overload; and a slow process of structural deterioration begins and increases over time, especially after 7- 8 years of

intervention. The average SVD rate is estimated between 10- 30% after 10 years of intervention and 20- 50% after 15 years of intervention (Schoen & Levy, 2005) (Ruel et al., 2004) (Vesey & Otto, 2004). The etiopathogenic mechanism of SVD is not entirely known, although several interrelated factors have been suggested.

First, there are factors related to the manufacturing of the bioprosthesis. To reduce immunogenicity in both porcine xenografts and prostheses made from bovine pericardium, animal tissues are fixed in glutaraldehyde. This fixation favors the interbreeding of collagen fibers allowing the masking of antigens. However, it also causes alterations in the membrane that favor the entry and accumulation of calcium that in turn, in combination with the membrane phospholipids subjected to mechanical stress, favor the formation of calcium phosphate crystals responsible for valve tears and stenosis (Cunanan et al., 2001) (Schoen & Levy, 2005). On the other hand, fixation at high pressure (80 mmHg) distorts the collagen conformation and can cause fragmentation of the extracellular matrix, making the cusps more rigid during the opening and favoring early degeneration. Currently, most prostheses are fixed at low pressure (less than 4 mmHg) to minimize the deterioration of collagen proteins. Likewise, the anti-mineralizing treatment of third generation bioprostheses with alpha oleic acid, ethanol, and surfactant intends to prevent calcium accumulation.

Second, valvular bioprostheses are not completely inert from an immunological point of view. The residual antigens can provoke a humoral and cellular response. This reaction -ultimately expressed by SVD and calcification- is more intense when the recipient of the prosthesis is younger which is a consequence of the most immunocompetent state typical of young organisms (Schoen & Levy, 2005) (Wheatley et al., 1987) (Manji et al., 2006). In children, IgG and IgM immunoglobulins can penetrate the extracellular matrix of the bioprosthesis and this process is accompanied by macrophage apposition on the surface, collagen fibers rupture, and calcification (Konakci et al., 2005).

Third, it has been observed that some of the risk factors for atherosclerosis (including diabetes, hypercholesterolemia, smoking, and metabolic syndrome) may favor the infiltration of low-density lipoproteins into the bioprosthesis tissue (Farivar & Cohn, 2003) (Briand, Pibarot et al., 2006) resulting in subsequent oxidation that could initiate an inflammatory process unmediated by the immune mechanism (Shetty et al., 2009).

Fourth, the surgical trauma to the patient's aortic ring during the implantation provokes a formation of platelet aggregates, accumulation of inflammatory cells, and release of cytokines. Initially, fibroblasts composed by the cell population end up forming a collagen layer coated with endothelial cells. The formation of this scar tissue -pannus- begins at the point of surgical trauma but gradually extends to the prosthesis ring, encompassing the sutures and creating a surface resistant to the formation of thrombus. There is a possibility that the pannus grows excessively and affects the areas of bioprosthesis near the cusps and commissures causing thickening, stiffness, stenosis, and calcification (Butany & Leask, 2001).

Fifth, in patients with bioprosthesis in aortic position, the rate of early subclinical thrombosis over the valvular leaflets can affect up to 14% (Puri et al., 2017). The formation of thrombus on the surface of the leaflets may stimulate an inflammatory response followed by secondary remodeling, fibrosis, stiffness, and calcification (Rodriguez-Gabella et al., 2017).

Finally, the hemodynamic stress during the opening, ejection period and closure of the prosthesis may also modulate the appearance of SVD, proving why bioprostheses in mitral position and bioprostheses in aortic position in hypertensive patients have a higher SVD rate than bioprostheses in aortic position in normotensive patients or those implanted in the right heart (Ruel et al., 2004).

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2. OBJECTIVES AND JUSTIFICATIONS

From all that is mentioned throughout the Introduction, we can conclude that aortic valve replacement by bioprosthesis, either through transcatheter or surgical, continues to be the only effective method for the treatment of degenerative aortic stenosis. Additionally, due to the increasing collective aging of the population, this technique will remarkably expand in the next years.

On the other hand, the structural valve deterioration of bioprostheses SVD is a constant phenomenon, despite the continuous advances and improvements in the design and the manufacturing materials. For this reason, it constitutes the main limiting factor for the use of these types of valve substitutes in the population.

Several factors related to structural deterioration have been identified, such as the type of prosthesis, the disproportion between valve size and the patient and other characteristics such as age and certain metabolic disorders; without ruling out the unknown etiopathogenesis for individual predisposition.

The aging of the reference population of the University Hospital Complex of Santiago makes the number of elderly patients undergoing aortic valve replacement by bioprosthesis in aortic position high.

Therefore, the objectives of this thesis are to:

1. Know the frequency of structural deterioration of bioprostheses in aortic position in our environment.

2. Identify the factors related to structural deterioration.

3. Study the impact of the structural deterioration of bioprostheses in our environment in terms of survival and the need for reoperation.

4. Carry out a comparative study between two types of bioprosthesis

used in our environment, in order to assess the role of the valve design in the structural deterioration.

5. Define practice actions on patients intervened with aortic valve replacement in order to prevent complications derived from structural deterioration.

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3. MATERIALS AND METHODS

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3.1. STUDY DESIGN AND PROTOCOL

We carried out a descriptive observational clinical study with retrospective data collection from the historical series of patients undergone aortic valve replacement with a biological bovine pericardium prosthesis at the University Hospital Complex of Santiago de Compostela.

We collected, from each patient, preoperative clinical and demographic parameters, surgical protocol data, postoperative follow-up, clinical evolution, and complications.

Patient characteristics, preoperative diagnosis, comorbidities, surgical risk, mortality rate, and postoperative complications were studied. Furthermore, we analyzed the relationship between the type and size of the implanted valve prosthesis, the clinical characteristics of the patients, and the onset of prosthetic structural deterioration such as its impact in terms of survival.

3.2. SUBJECTS

3.2.1. Inclusion Criteria

We included in the study, all adult patients of both sexes who underwent emergency or elective surgery for aortic valve replacement by bovine pericardial bioprosthesis, isolated or combined with other procedures, under extracorporeal circulation in the University Hospital Complex of Santiago de Compostela between January 1st, 2008 and December 31st, 2012.

3.2.2. Demographic Parameters, History, and Risk Factors

We recorded age, sex, weight, height, functional class, previous cardiac interventions, and comorbidities for each patient, including diabetes mellitus, chronic obstructive pulmonary disease, peripheral arteriopathy, arterial hypertension, atrial fibrillation, and renal failure. Access to patient's information was made through the electronic medical record system in active specialized care at the Galician Health Service IANUS (XUNTA DE GALICIA, 2008).

(https://www.sergas.es/cas/Publicaciones/Docs/AtEspecializada/PDF-2141-es.pdf).

3.2.3. Preoperative Studies

All patients were preoperatively studied, performing complete analyses with CBC and ESR (ADVIA120® Hematology System, Siemens Healthcare Diagnostics, Deerfield, IL, USA), determination of blood electrolytes, liver function tests, urea, creatinine, and blood glucose (ADVIA 1650® Chemistry System, Siemens Healthcare Diagnostics, Deerfield, IL, USA).

Creatinine clearance was calculated according to the Cockroft-Gault formula, and following the recommendations of the EuroSCORE II database, severe renal failure was labeled when the preoperative creatinine clearance was less than 50 ml/h (The EuroSCORE Study Group, 2011).

(http://www.euroscore.org/calc.html)

A complete 12-lead electrocardiogram was performed. The characterization and quantification of aortic valve disease as well as abnormalities in other valves, systolic pulmonary artery pressure, and left ventricular function were performed using transthoracic Doppler

echocardiography. Continuous Doppler was used to calculate aortic transvalvular velocity. The maximum pressure gradient (mmHg) was calculated by applying the simplified Bernoulli equation, and the mean pressure gradient from the Integral throughout the ejection period. The effective valve area EOA was quantified using the continuity equation. To determine systolic ventricular function, the left ventricular ejection fraction was estimated using the Teichholz method. Selective coronary angiography was performed in all patients except those with endocarditis on the aortic valve.

The surgical risk stratification system was applied for each patient using the EuroSCORE II model (The EuroSCORE Study Group, 2011).

(http://www.euroscore.org/calc.html)

3.3. SURGICAL INTERVENTION

3.3.1. Anesthetic Technique

The patients were premedicated with 1 mg of morphine/10 Kg (Morphine 1% ® Serra Palies S.A., Spain); 5 mg of diazepam, (Valium®, Almirall, Spain) and 1 mg of scopolamine (Escopo-lamina Braun®, Spain) administered intramuscularly.

All patients were monitored in the operating room by 5-lead electrocardiography, pulse oximetry, and non-invasive blood pressure measurement by sphygmomanometry. A peripheral vein was cannulated with a catheter No. 14 Abocath-T venisystems® (Abbott, Ireland) and the radial artery with a catheter No. 18 Arrow International Radial Artery Catheterization Set ® (Arrow, USA).

Subsequently, anesthetic induction was performed with 0.2 mg/kg midazolam (Dormicum®, Roche Farma, Spain); and with 0.7 µg/kg/min remifentanil (Ultiva ®, Glaxo-Smithkline, Spain); a 0.1

mg/kg bolus of vecuronium bromide (Norcuron®, Organon, Spain) and inhaled sevoflurane at 2% with oxygen (Sevorane®, Abbot, Spain).

Then endotracheal intubation was carried out, maintaining standard ventilation parameters with a tidal volume of 8- 10 ml/kg, inspiratory time of 33%, frequency of 10- 12 cycles/minute for an expiratory CO_2 of 32- 38 mmHg. Anesthesia was maintained with sevoflurane at a FiO_2 of 40- 60% and an intermittent infusion of remifentanil of 0.2- 0.6 µg/kg/min.

After anesthetic induction, a Swan-Ganz catheter coated with Opti-Q Heparin, Abbott-Critical Care System (Abbott Laboratories, IL, USA) was inserted through the right internal jugular vein equipped with a device for pressure measurement, continuous cardiac output using thermodilution and mixed venous saturation using spectrophotometry. The catheter was connected to a continuous cardiac output monitor and mixed venous saturation Q2 CCO/SvO_2 Computer (Abbott Laboratories, IL, USA).

During the intervention, we monitored systemic, pulmonary. Central venous blood pressure, pulse oximetry, 5-lead electrocardiogram, pharyngeal, and bladder temperature and ventilatory parameters were monitored, all through a standard anesthesia device (Datex-Ohmeda Aestiva 3000; AS/3 monitor, Datex-Ohmeda Intrumentarium Corp., Helsinki, Finland).

Antibiotic prophylaxis consisted of administration of 1.5 grams of cefuroxime intravenously one hour before the skin incision. The cefuroxime dose was repeated every 8 hours during the first 24 hours of postoperative.

3.3.2. Extracorporeal Circulation and Myocardial Protection

The ascending aorta and right atrium were cannulated habitually. A single Cavo-atrial cannula was used in patients with isolated aortic valve surgery or mixed coronary and aortic valve surgery. In the mitral-aortic patients, both venae cavae were cannulated separately.

Patients were intervened using extracorporeal circulation with cardiopulmonary bypass, mild hypothermia between 32- 33ºC, and electromechanical cardiac arrest by aortic clamping, and administration of a cardioplegic solution.

An extracorporeal circulation machine was used (Stöckert SIII®, Germany) equipped with four modules with rollers and a centrifugal pump (Stöckert SCP Revolution®, Germany). It was attached to a heat exchanger (Stöckert SIII®). Before connecting to the extracorporeal circulation, patients were heparinized with 3 mg/kg of sodium heparin (Rovi, SA, Spain), maintaining an activated clotting time of over 300 seconds during the entire procedure (Hemotec ACT III®, Inc Medtronic, USA), adding where necessary, complementary doses of heparin. A dose of 16 mg of epsilon aminocaproic acid was administered intravenously (Caproamín® Fides®, Spain). When the extracorporeal circulation finished, the circulating heparin was wholly reversed with protamine (Rovi S.A., Spain).

A membrane oxygenator (Dideco Avant 903 D®, Italy) was used in all patients, priming the circuit with 1000 ml of Ringer lactate crystalloid solution (Ringer Lactate Braun®, Braun, Spain), 0.5 mg/Kg of mannitol, (Mannitol Braun 20% ®, Braun, Spain), 100 ml of sodium bicarbonate 1 molar (Venofusin®, Fresenius Kabi, Spain) and 0.5 mg/kg of sodium heparin (Rovi, SA, Spain). During the procedure, the partial pressure of oxygen in arterial blood was maintained between 200 and 300 mmHg, with a FiO_2 of 100% that was decreased as the patient cooled.

The heart was electromechanically stopped by aortic clamping and administration of 400- 600 ml of hyperkalemic cardioplegic solution at 3ºC prepared by the perfusionist and composed of: 47 mEq of KCl, 25 mg of $NaHCO_3$, 18.5 ml of 2% lidocaine and 5 mg of nitroglycerin (Solinitrina®, Berenguer Infale, Germany) diluted in the patient's blood at 33ºC in a 4/1 ratio.

Successive doses of cardioplegic solution were administered every 20 minutes at diluted 3ºC and consisted of: 37 mEq of KCl, 18.5 ml of 2% lidocaine, 5 mg of nitroglycerin (Solinitrina®, Berenguer Infale, Germany). A single dose of warm cardioplegic solution (Cardioplegia Braun) was administered at 37ºC, immediately before reperfusion, and consisting of:

Tromethamine: 856.2 mg/100ml; $2H_2O$ citrate: 619.63 mg/100ml; citric acid: 77.3 mg/100ml; $2H_2O$ monosodium phosphate: 59.13 mg/100ml; anhydrous glucose: 3687 mg/100ml; KCl: 234 mg/100ml; monosodium aspartate: 1027 mg/100ml; monosodium glutamate: 1119 mg/100ml; Na: 62 mmol/100ml; chlorides: 3.4 mmol/100ml; K: 3.14 mmol/100ml; phosphates: 0.37 mmol/100ml; osmolarity: 672 mOsmol/liter; pH approximates: 8.3.

3.3.3. Implanted Aortic Valve Prostheses

The implanted valves were the Mitroflow 12A bioprosthesis and the Carpentier-Edwards Perimount Magna bioprosthesis.

The Mitroflow 12A valve (Sorin Group Canada Inc., Mitroflow Division, Burnaby, Canada), which we will call "Mitroflow", is a bioprosthesis composed of a flexible plastic polymer housing, coated with braided polyester, a silicone sewing ring covered by polyester, and a continuous band of bovine pericardium fixed externally on the housing to maximize the valve orifice. These characteristics make it, a priori, an ideal substitute for small aortic rings (figure 3.1). The LX

model, introduced in 2010, incorporates small changes, such as the veils pre-fixation with glutaraldehyde instead of post-fixation to facilitate their apposition on the housing. Globally, throughout this work we will call the 12A and LX models "Mitroflow".



Figure 3.1. Components of the Mitroflow 12A aortic bioprosthesis.

The Carpentier-Edwards Perimount Magna biological prosthesis (Edwards Lifesciences, Irvine, CA, USA), which we will call "Carpentier", consists of a braided polyester cobalt-chrome metal alloy Elgiloy® housing, a sewing ring of silicone covered by a layer of polytetrafluoroethylene and three individual semilunar valves of bovine pericardium internally fixed on the housing (figure 3.2).



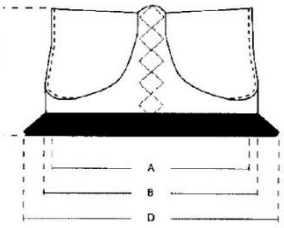
Figure 3.2. Components of the Carpentier bioprosthesis.

As for the size of the Mitroflow and Carpentier bioprostheses as well as their hemodynamic characteristics *in vivo*, they are reflected in (tables 3.1. and 3.2, respectively). It is noteworthy that the Mitroflow bioprosthesis is smaller than the Carpentier for the same nominal size. For example, the Mitroflow prosthesis No. 19 has a total external size of 21 mm, while the size of the Carpentier No. 19 is 24 mm. Conversely, the effective orifice valve area EOA of the Mitroflow prosthesis - except in No. 19 - is smaller than that of the Carpentier of the same nominal size.

Table 3.1. Size in mm, hemodynamic parameters, and EOA in cm² of the Mitroflow bioprosthesis for Nos. 19- 27 according to data provided by the manufacturer (https://www.accessdata.fda.gov/cdrh_docs/pdf6/p060038c.pdf) (CarboMedics Inc., 2007).

	A*	B*	C*	D*	
Model	Inside Diameter (mm)	Outside Diameter (mm)	Overall Height (mm)	Sewing Ring Width (Relaxed) (mm)	** Effective Orifice Area (cm^2)
12A19	15.4	18.5	11	21	1.6
12A21	17.3	20.6	13	24	2.0
12A23	19.0	22.6	14	26	2.4
12A25	21.0	25.0	15	28	3.0
12A27	22.9	27.2	16	32	3.5

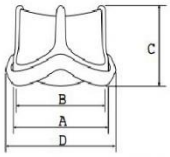
** In vitro data on file



Hemodynamic Data	Valve Size[2]				
	19 (N^3=34)	21 (N=143)	23 (N=193)	25 (N=128)	27 (N=42)
Mean gradient (mmHg)	n^4=33	n=136	n=189	n=122	n=39
Mean ± SD	13.4 ± 5.0	11.4 ± 4.4	10.5 ± 4.2	8.7 ± 3.3	7.4 ± 2.7
Effective orifice area (cm^2)	n=30	n=131	n=185	n=121	n=37
Mean ± SD	1.1 ± 0.2	1.2 ± 0.3	1.4 ± 0.3	1.6 ± 0.3	1.8 ± 0.3
Regurgitation	n=34	n=143	n=193	n=128	n=42

Table 3.2. Size in mm, hemodynamic parameters, and EOA in cm² of the Carpentier bioprosthesis for Nos. 19- 29, according to the data provided by the manufacturer (https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150048C.pdf) (Edwards Lifesciences, 2007).

Carpentier-Edwards PERIMOUNT Magna Pericardial Bioprosthesis, Model 3000TFX



Size	19 mm	21 mm	23 mm	25 mm	27 mm	29 mm
A. Stent Diameter (Wire Form)	19	21	23	25	27	29
B. Internal Diameter (Stent I.D.)	18	20	22	24	26	28
C. Profile Height	14	15	16	17	18	19
D. External Sewing Ring Diameter	24	26	28	30	32	34

Parameter	19 mm Mean±SD (n[1])	21 mm Mean±SD (n[1])	23 mm Mean±SD (n[1])	25 mm Mean±SD (n[1])	27 mm Mean±SD (n[1])
Mean Gradient (mmHg)	17.6 ±7.8 (16)	12.6 ±4.7 (97)	10.1 ±3.8 (158)	9.6 ± 5.2 (132)	8.2 ± 3.5 (69)
EOA (cm²)	1.1 ± 0.2 (16)	1.3 ± 0.3 (97)	1.6 ± 0.4 (155)	1.8 ± 0.5 (131)	2.2 ± 0.6 (68)

[1]n represents the number of subjects with evaluable data.

3.3.4. Prostheses Implant Technique

In all the patients included in this study, the aortic prosthesis was implanted in the supra-annular position using loose, non-everting mattress stitches reinforced with an expanded polytetrafluoroethylene pledget (PremiCron®, B. Braun Medical S.A, Barcelona, Spain) (figure 3.3).

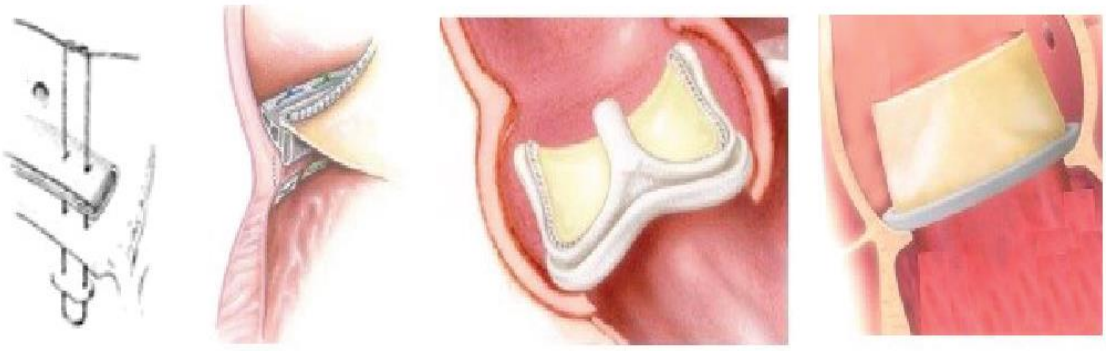


Figure 3.3. supra-annular implant technique used in both types of prostheses.

3.4. EARLY POSTOPERATIVE CARE

After the intervention, the patients were transferred to the post-anesthesia care unit where they remained sedated with propofol 5 ml/h (Lipuro®, Braun, Spain), morphine, (morphine 1% ®, Serra Palies SA) and midazolam (Dormicum®, Roche-Farma, Spain) administered as required. Patients remained intubated and connected to a mechanical ventilator (Servo Screen 390® Siemens, Germany) in synchronized SIMV mode between 6- 10 ml/kg at a respiratory rate of 12 R/M, PEEP between 5- 7 cm H_2O with a trigger between -1 and 1 and with an FIO_2 adjusted according to arterial gasometry. The minimum mechanical ventilation time was 6 hours, after that, all patients were extubated when the conditions of hemodynamic stability, ventilation, oxygenation, and temperature allowed.

Hemodynamic monitoring was maintained for the first 12 hours postoperative at least. Immediately after admission to the post-anesthesia care unit, complete laboratory tests were performed, including markers for myocardial damage, full blood count, 12-lead

superficial electrocardiogram, chest x-ray, and arterial gasometry. Patients with favorable evolution were transferred to the hospitalization plant where they completed the convalescence before discharge.

In-hospital mortality was defined as the mortality that took place during the thirty days directly following the procedure.

3.5. LONG-TERM POSTOPERATIVE FOLLOW-UP

Patients were reviewed at the Cardiac Surgery outpatient clinic 1- 3 months following the intervention. Subsequently, they were followed up by their reference cardiologist, usually performing an annual echocardiographic, electrocardiographic, and analytical study, or when the clinical situation or examination of the patient required it.

The evaluation of the aortic prosthesis by Doppler echocardiography included the calculation of the peak gradient (mmHg) by continuous Doppler applying the simplified Bernoulli equation, and the mean gradient from the Integral throughout the ejection period. Severe dysfunction was considered when the mean transprosthetic gradient was > 40 mmHg. The assessment of prosthetic insufficiency was made based on the ratio of the regurgitant jet width concerning the output tract measured in the long axis parasternal view in M mode. Severe transprosthetic regurgitation was considered when the ratio was > 0.65 and moderate for values between 0.25- 0.65. In some cases, transprosthetic regurgitation was calculated by continuous Doppler records of the regurgitating jet and calculating the pressure half-time, considering it to be severe if it was < 200 cm/s and moderate for values between 200- 500 cm/s.

For practical purposes, an aortic bioprosthesis was considered to present structural deterioration when the systolic gradient was severe, when regurgitation was severe or when moderate stenosis was combined with moderate insufficiency.

The electronic medical record was accessed to collect patient follow-up data, including structural deterioration of the bioprosthesis, complications, and survival.

The follow-up of the patients was completed on 30th of March 2020, which means a minimum follow-up of 99 months, and a maximum of 147 months.

3.6. STATISTICAL ANALYSIS AND PRESENTATION OF RESULTS

Numerical values are expressed as a percentage (%) or as mean ± standard deviation. The statistical analysis was carried out using the R program version 3.6 (R foundation, Vienna, Austria).

For the comparison of categorical variables, the Chi-Square test was utilized using the Yates correction. To compare continuous variables against a binary category, the Wilcoxon test was used. All p-values were penalized with the Benjamini-Hochberg procedure of "False Discovery Ratio" (FDR).

For the comparison of survival curves, the Log-rank test and the graphic representation by Kaplan-Meier curves with 95% confidence intervals were used.

Survival models that considered competitive risks were used to identify factors associated with structural prosthetic dysfunction or mortality or need for reoperation.

3.7. COMPETING RISKS MODELS

A competing risk (CR) is an event whose occurrence either precludes the occurrence of another event under examination or fundamentally alters the probability of occurrence of this other event (Teixeira et al., 2013).

The cause-specific hazard at time (Cox competing-risks model) is defined by the instantaneous risk of failure per time unit due to one risk, as if there were no competing events. However, the hazard ratios obtained are not directly related to the prediction of the cumulative incidence, thus they are not suitable to predict a given patient's global risk.

On the other hand, the hazard ratio of the subdistribution (Fine & Gray CR model) (Fine & Gray, 1999) is interpreted as the probability of observing an event of interest in the next time interval, while knowing that either the event of interest did not happen until then or that a competing event was observed.

Unfortunately, the absolute values of the regression coefficients in the Fine-Gray model have no direct interpretation. Subdistribution hazard ratio denotes the direction but does not directly provide the magnitude of the effect of the covariate on the cumulative incidence (CIF).

Cause-specific hazard models (Cox-CR) are better suited for studying the etiology of diseases (the risk independently posed by every covariate), whereas the Fine & Gray model has use in predicting an individual's risk (incidence) of an event.

Both models were implemented and compared with the GRACE score.

3.8. AUTHORIZATION OF THE CLINICAL RESEARCH ETHICS COMMITTEE

The Clinical Research Ethics Committee of the Sanitary Area of Santiago-Lugo reported favorably the completion of the study (registration code 2015/2009). Annexes 1, 2 incorporate the full texts of the resolution and the incorporation of the author of the thesis into the research team.

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4. RESULTS

4.1. PREOPERATIVE, DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

4.1.1 Global Population of Patients Included in The Study

A total of 409 patients who underwent aortic valve replacement between January 1, 2008, and December 31, 2012, were included in this study. Follow-up was closed on March 31, 2020, which means an average follow-up of 122 months (range 99- 147) for a total of 2.162 patient-years. Follow-up was possible in all patients except six, which represents a complete follow-up rate of 98.54%.

The mean age of the patients was 77 years old. The frequency distribution for sex of all patients included was 48.2% females and 51.8% males. It should be noted that 59.4% had some degree of obesity. Other comorbidities in the study population included Diabetes Mellitus 27.4%, Chronic Obstructive Pulmonary Disease (COPD) 22%, Atrial Fibrillation 17.4%, Peripheral Arterial Disease 10%, Arterial Hypertension 71.3%, and Hypercholesterolemia 40.5%. 6.6% of the population had previously undergone coronary stent implantation, and 5.37% had previously undergone open-heart surgery. 18.4% had a permanent pacemaker.

Analytically, the mean hemoglobin concentration was 12.7 ± 1.7 mg/dL, and the serum creatinine was 1.1 ± 0.4 mg/dL. They presented an estimated average Glomerular Filtration Rate of 57.6 ± 20 ml/kg/min, and 7.5% of the operated patients had some degree of Chronic Renal Failure.

From a cynical point of view before the intervention, 38.4% of the patients were in NYHA class II, 46.7% in class III, and 14.7% in class IV.

The preoperative estimated in-hospital mortality, according to the EuroSCORE II, resulted in 4.8 ± 4.5.

Table 4.1 summarizes the preoperative characteristics of the patients.

4.1.2. Patients with Mitroflow Prosthesis Implantation

Of the total patients included in the study, a group of 235 received a Mitroflow aortic valve prosthesis. The mean age of this group was 78.6 ± 4.8 years. Females represented 56.5%. Of the total patients, 58.2% had some degree of obesity. Other comorbidities in the group of Mitroflow prosthesis implantation included diabetes mellitus 27.6%, COPD 17.4%, atrial fibrillation 21.7%, peripheral arterial disease 11.4%, arterial hypertension 77.02%, and hypercholesterolemia 45.5%. 7.6% of the population had previously undergone coronary stent implantation, and 4.6% had previously undergone open-heart surgery. 19.1% had a permanent pacemaker.

Analytically, the mean hemoglobin concentration was 12.5 ± 1.6 mg/dL, and the serum creatinine was 1.1 ± 0.4 mg / dL. They presented an estimated average glomerular filtration rate of 53.9 ± 17 ml/kg/min, and 9.3% of the operated patients had some degree of chronic renal failure.

From a cynical point of view before the intervention, 36.5% of the patients were in NYHA class II, 48.5% in class III, and 14.8% in class IV.

The preoperative estimated in-hospital mortality, according to the EuroSCORE II, resulted in 5.4 ± 4.6.

Table 4.1 summarizes the preoperative characteristics of the patients.

4.1.3. Patients with Carpentier Prosthesis Implantation

Of the total patients included in the study, a group of 174 received a Carpentier aortic valve prosthesis. The mean age of this group was 74.9 ± 7.4 years. Females represented 37.7%. Of the total patients, 60.9% had some degree of obesity. Other comorbidities in the group of Carpentier prosthesis implantation included diabetes mellitus 27%, COPD 28.1%, atrial fibrillation 11.4%, peripheral arterial disease 8%, arterial hypertension 63.7%, and hypercholesterolemia 33.9%. 5.1% of the population had previously undergone coronary stent implantation, and 6.3% had previously undergone open-heart surgery. 16% had a permanent pacemaker.

Analytically, the mean hemoglobin concentration was 12.9 ± 1.7 mg/dL, and the serum creatinine was 1.1 ± 0.6 mg / dL. They presented an estimated average glomerular filtration rate of 62.5 ± 22.6 ml/kg/min, and 5.1% of the operated patients had some degree of chronic renal failure.

From a cynical point of view before the intervention, 40.8% of the patients were in NYHA class II, 44.2% in class III, and 14.3% in class IV.

The preoperative estimated in-hospital mortality, according to the EuroSCORE II, resulted in 4.1 ± 4.2.

Table 4.1 summarizes the preoperative characteristics of the patients.

4.1.4. Comparative Preoperative Analysis in The Mitroflow and Carpentier Groups

The decision to implant one type of prosthesis or another in each patient depended exclusively on the decision of the surgeon responsible for the intervention. This decision was undoubtedly influenced by aspects such as the size of the patient's aortic annulus tissue, age and body surface area, the presence of comorbidities, the technical difficulty of the procedure due to cardiac anatomy, and the design of the prosthesis, and the personal experience of the surgeon.

The data presented shows differences between the population of patients receiving a Mitroflow bioprosthesis and a Carpentier. The most notable is that patients with Mitroflow prostheses were predominantly females, older in age, and smaller in size than those who received Carpentier prostheses. Likewise, it can be noted that patients with Mitroflow bioprostheses had more comorbidities and, consequently, a higher surgical risk than patients with the Carpentier prostheses.

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Table 4.1 Demographic characteristics of patients and preoperative variables.

	Total Group (409)	Mitroflow (235)	Carpentier (174)	p
Males (%)	51.8	43.5	62.3	0.0005
Females (%)	48.2	56.5	37.7	0.0005
Age (years)	77 ± 6.3	78.6 ± 4.8	74.9 ± 7.4	< 0.0001
Weight (kg)	72.78 ± 12.51	71.73 ± 12.39	74.20 ± 12.56	0.08
Height (m)	1.58 ± 0.09	1.57 ± 0.08	1.60 ± 0.09	0.0006
BMI (kg/m^2)	29.04 ± 4.36	29.15 ± 4.49	28.89 ± 4.18	0.69
BSA (m^2)	1.78 ± 0.19	1.76 ± 0.18	1.81 ± 0.19	0.01
Hemoglobin (g/dL)	12.7 ± 1.7	12.5 ± 1.6	12.9 ± 1.7	0.03
Creatinine s (mg/dL)	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.6	0.69
Creatinine cl (mg/min)	57.7 ± 20	53.9 ± 17	62.5 ± 22.6	0.0005
AH (%)	71.3	77.02	63.7	0.005
Hypercholesterolemia (%)	40.5	45.5	33.9	0.69
Diabetes (%)	27.4	27.6	27	1
COPD (%)	22	17.4	28.1	0.03
AF (%)	17.4	21.7	11.4	0.02
PAD (%)	10	11.4	8	0.5
Pacemaker (%)	18.4	19.1	16	0.69
Coronary stent (%)	6.6	7.6	5.1	0.62
Previous Cardiac Surgery (%)	5.37	4.6	6.3	0.61
Functional Class III-IV (%)	53.1	63.3	59.7	0.03
Active Endocarditis (%)	3.91	3.82	4.02	1
Emergency (%)	14.9	14.36	15.31	0.98
EuroSCORE II	4.8 ± 4.5	5.4 ± 4 .6	4.1±4.2	0.0001
Follow-up time (days) (mean ±SD)	2042.5 ± 1088	2277 ± 1170.8	1868.4 ± 989.4	< 0.0001

BMI: body mass index; BSA: body surface area; AH: arterial hypertension; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; Creatinine s: serum creatinine concentration; creatinine cl: creatinine clearance.

4.2. SIZE OF IMPLANTED PROSTHESIS, ASSOCIATED PROCEDURES, AND DISCORDANCE BETWEEN PROSTHESIS SIZE AND PATIENT SIZE

4.2.1. Global Population of Patients Included in The Study

In 74.81% of the patients, an isolated aortic valve replacement was performed. Mitral valve replacement was associated with 3.66% of cases and myocardial revascularization in 21.51%.

The 409 implanted prostheses were distributed according to size as follows: No. 19: 53 (13%); No. 21: 207 (50.6%); No. 23: 122 (29.8%); No. 25: 24 (5.9%) and No. 27: 3 (0.7%).

The effective orifice area indexed for the implanted bioprostheses for the entire group was 1 ± 0.2 cm^2/m^2. The absence of mismatch (EOAI > 0.85 cm^2/m^2) was observed in 73.3% of the cases; moderate mismatch (EOAI 0.65- 0.85 cm^2/m^2) in 25.7%, and severe mismatch (EOAI $<$ 0.65 cm^2/m^2) in 1% of the operated patients.

Table 4.2 summarizes the number and size of the implanted prostheses and the degree of mismatch between the size of the prosthesis and the patient according to the data provided by the manufacturer.

4.2.2. Patients with Mitroflow Prosthesis Implantation

In the group of patients who received a Mitroflow bioprosthesis, isolated aortic valve replacement was performed in 72.34% of the cases. Mitral valve replacement was associated with 4.25% of cases and myocardial revascularization in 23.40%.

The distribution of patients according to prosthetic size was as follows: No. 19: 43 (18.29%); No. 21: 123 (52.34%); No. 23: 60 (25.53%); and No. 25: 9 (3.82%).

The effective orifice area indexed for the Mitroflow bioprostheses was 0.9 ± 0.1 cm^2/m^2. The absence of mismatch was observed in 55.74%, moderate mismatch in 43.8%, and severe mismatch in 0.42% of the patients.

Table 4.2 summarizes the number and size of the implanted Mitroflow prostheses and the degree of mismatch between the size of the prosthesis and the patient according to the data provided by the manufacturer.

4.2.3. Patients with Carpentier Prosthesis Implantation

Isolated aortic valve replacement was performed in 78.16% of the patients. Mitral valve replacement was associated with 2.87% of cases and myocardial revascularization in 18.96%.

In the group of 174 patients who received a Carpentier bioprosthesis, the distribution according to prosthetic size was as follows: No. 19: 10 (5.74%); No. 21: 84 (48.27%); No. 23: 62 (35.63%); No. 25: 15 (8.62) and No. 27: 3 (1.72%).

The effective orifice area indexed for the Carpentier bioprostheses was 1.1 ± 0.2 cm^2/m^2. The absence of mismatch was observed in 97.11%, moderate mismatch in 1.14%, and severe mismatch in 1.72% of patients.

Table 4.2 summarizes the number and size of the implanted Carpentier prostheses and the degree of mismatch between the size of the prosthesis and the patient according to the data provided by the manufacturer.

Table 4.2. Surgical procedures combined with aortic valve replacement. Distribution of the number and size of implanted prostheses and degree of mismatch between the size of the prosthesis orifice and the patient`s size.

	Total Group (409)	Mitroflow (235)	Carpentier (174)	p
AVR Isolated (%)	74.81	72.32	78.6	0.0009
AVR combined with other (%)	25.19	27.68	21.4	0.0009
Size 19 (%)	12.95	18.29	5.74	0.0004
Size 21 (%)	50.85	52.34	48.27	
Size 23 (%)	29.82	25.53	35.63	
Size 25 (%)	5.86	3.82	8.62	
Size 27 (%)	0.73	—	1.72	
Absence of Mismatch (%)	73.3	55.74	97.11	< 0.0001
Moderate Mismatch (%)	25.7	43.8	1.14	< 0.0001
Severe Mismatch (%)	1	0.42	1.72	

AVR: aortic valve replacement; EOAI: effective orifice area indexed.

4.2.4. Comparative Analysis of The Implanted Prosthesis Size and Other Associated Procedures in The Mitroflow and Carpentier Groups

The interventions in which Mitroflow bioprostheses were implanted were more complicated as there were associated procedures.

In terms of size, in the Carpentier group, the prosthetic size was greater and, furthermore, the rate of discrepancy between the size of the prosthetic orifice and the size of the patient was anecdotal, while in the Mitroflow group, more than half of the patients remained with a certain degree of residual aortic stenosis.

70% of the Mitroflow prostheses were implanted in patients with small size (19 + 21), while in the case of the Carpentier, small aortic annulus represented 54%.

4.3. IN-HOSPITAL MORTALITY

In the total group of operated patients, there were 33 in-hospital deaths, which represents 8.06%. Mortality in the group of patients who underwent Mitroflow bioprosthesis was 16 patients (6.8%). In comparison, in the Carpentier group, it was 17 patients (9.77%) ($p = 0.3662$).

The most common cause of in-hospital mortality was heart failure (14) followed by multiorgan failure (11), early prosthetic endocarditis (2), mediastinitis (1), stroke (2), postoperative hemorrhage (1) and septic shock (2).

4.4. LONG TERM RESULTS

4.4.1. Survival

At the time of closing the follow-up, a total of 263 patients (64.30%) had died, and of the 147 survivors (35.5%), 41 patients (10.02%) had presented more than 10 years of evolution. According to the data obtained from the electronic clinical history, the causes of late death were cardiac in 38.58% and non-cardiac in 61.4%. Table 4.3 shows the causes of late death. The main cause of mortality was neoplasia (20.48%), followed by sepsis of abdominal/urological origin (9.03%), heart failure not related to the prosthesis (9.03%), dementia (8.43%), unexplained sudden death (8.43%) and infectious endocarditis (7.22%). Table 4.4 shows the mortality prediction model coefficient in the cohort.

Table 4.3. Causes of late mortality

Cardiac deceased (38.58%)	
Deceased related to the valve	
	Prosthetic disfunction (5.6%)
	Unexplained sudden death (8.43%)
	Endocarditis (4.21%)
	Ictus (7.62%)
Deceased not related to the valve	
	Acute coronary syndrome (1.2%)
	AV block (0.8%)
	Cardiac insufficiency (10.42%)
Non cardiac deceased (61.42%)	
	Neoplasia (21.18%)
	Dementia (8.4%)
	Sepsis of abdominal/urinary origin (9.02%)
	Respiratory infection (8.4%)
	Renal insufficiency (6.02%)
	Other causes (8.4%)

The actuarial survival curve at 5 and 10 years for the total group was 65% and 20%, respectively (figure 4.1).

The comparative survival analysis between the groups of Mitroflow and Carpentier prostheses showed significant differences in favor of the Carpentier bioprosthesis after 6 years of the intervention. After 10 years the differences between the two groups tend to disappear. Figure 4.2 represents the Actuarial survival curve for the Mitroflow and Carpentier groups.

Table 4.4. Mortality prediction model coefficient in the cohort.

Mortality	CSH Mortality	CIF Mortality
Age	0.97(1.00- 1.06) **	1.07 (1.04- 1.11) ***
AF	0.99 (0.65- 1.51)	1.63 (1.14- 2.31) *
CRF	1.06 (0.55- 2.06)	1.8 (1.17- 2.70) *
Mitroflow	2.09 (1.53- 2.87) ***	0.99 (0.71- 1.38)

CSH: Cause-specific Cox regression model. CIF: the cumulative incidence function of the event according to the Fine-Gray regression model. In brackets: 95% confidence interval. AF: atrial fibrillation. CRF: chronic renal failure. Mitroflow: Mitroflow prosthesis carrier.

p 0,001 at < 0.05; ** p 0.0001- 0.001; *** p < 0.0001

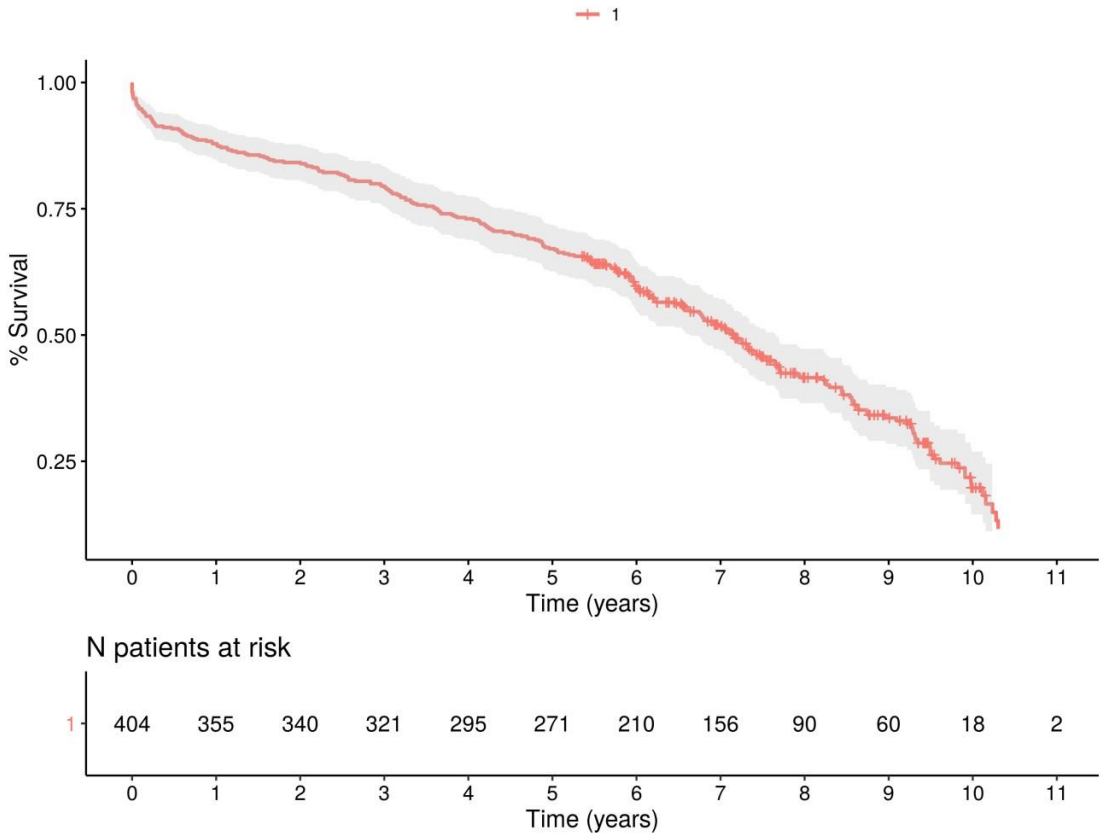


Figure 4.1. Actuarial survival curve in the total group of intervened patients.

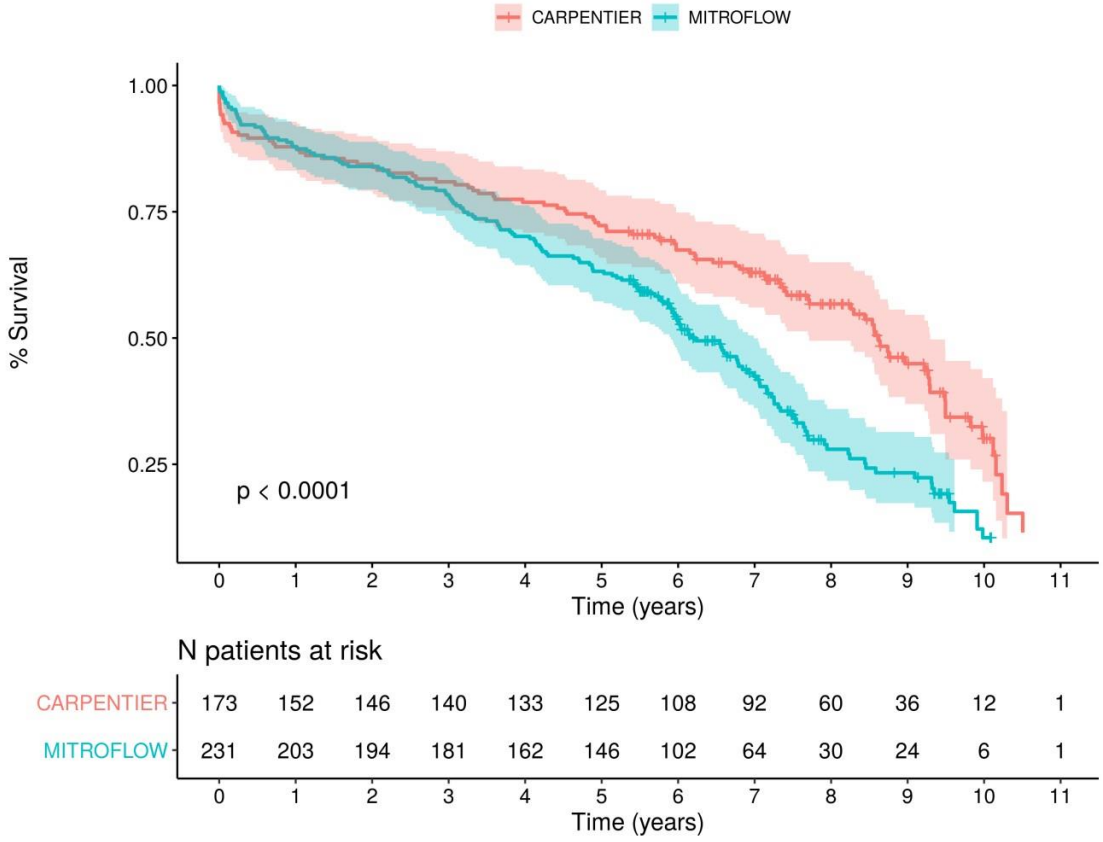


Figure 4.2. Actuarial survival curve of the Mitroflow and Carpentier groups.

4.4.2. Structural Valve Deterioration

The presence of structural valve deterioration, from now on SVD, was verified by echocardiography, according to the criteria defined in the materials and methods of this Thesis in 35 patients (8.55%) of which 29 cases corresponded to the Mitroflow prosthesis (size No.19: 7; No. 21: 17 and No. 23: 5) and 6 cases to the Carpentier prosthesis (size No. 19: 1 and No. 21: 5).

Of the 35 patients diagnosed with SVD, only 14 were re-operated for this cause, performing open-heart surgery in 8 cases and implantation of a transcatheter prosthesis in 6 patients.

The absence of SVD for the global group at 5 and 10 years was respectively 95% and 77%. Figure 4.3 represents the absence of SVD curve.

The statistical analysis showed a statistically significant relationship between SVD and age at the time of surgery and implantation of the Mitroflow bioprosthesis. No relationship was observed between SVD and gender, presence of diabetes, arterial hypertension, renal failure, prosthesis size, and mismatch.

The adjusted analysis for the competing risks of deaths, SVD and reoperation using the cause-specific Cox regression model and the cumulative incidence function of the event according to the Fine-Gray regression model showed a significant association of SVD with age at the time of intervention, atrial fibrillation, implantation of a Mitroflow prosthesis, and chronic renal failure (table 4.5). No association was demonstrated between SVD and gender, presence of diabetes mellitus, arterial hypertension, mismatch, and combined surgery with aortic valve replacement.

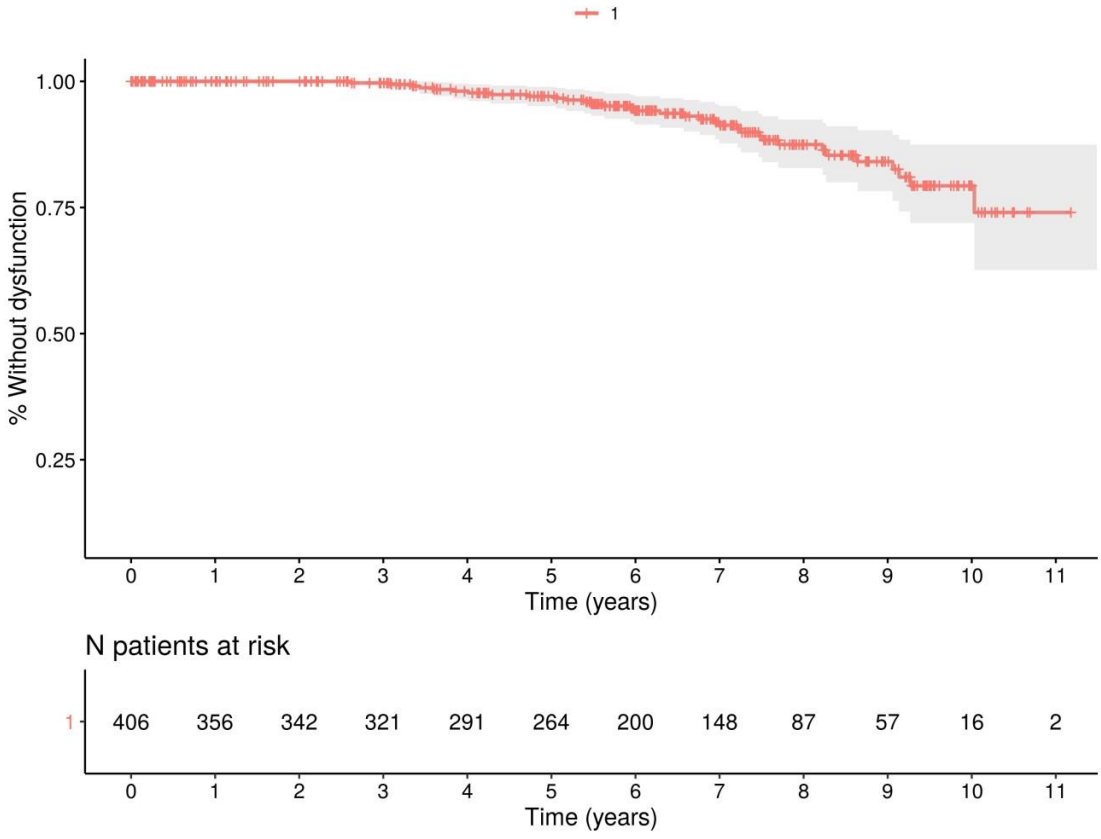


Figure 4.3. Actuarial curve representing the absence of SVD in the total group.

The comparative analysis of SVD between the groups with Mitroflow and Carpentier prostheses showed a higher rate of SVD in patients with the Mitroflow prosthesis after 4 years of postoperative evolution, with a deterioration absence rate of 94.2% and 67.2% at 5 and 10 years respectively. Figure 4.4 represents the SVD absence curve in the Mitroflow and Carpentier groups.

Table 4.5. Structural valve deterioration prediction model coefficient in the cohort.

	CSH Structural	CIF Structural
Age	1.01 (0.99- 1.03)	0.92 (0.88- 0.96) ***
AF	1.35 (1.02- 1.78) *	0.83 (0.30- 0.25)
CRF	1.57 (1.05- 2.34) *	0.55 (0.15- 1.98) *
Mitroflow	2.09 (1.53- 2.87) *	5.11 (1.64- 16) *

CSH: cause-specific Cox regression model. CIF: the cumulative incidence function of the event according to the Fine-Gray model. In brackets: 95% confidence interval. AF: atrial fibrillation. CRF: presence of chronic renal failure. Mitroflow: Mitroflow prosthesis carrier.

*** p 0.001 at < 0.05; ** p 0.0001- 0.001; *** p < 0.0001**

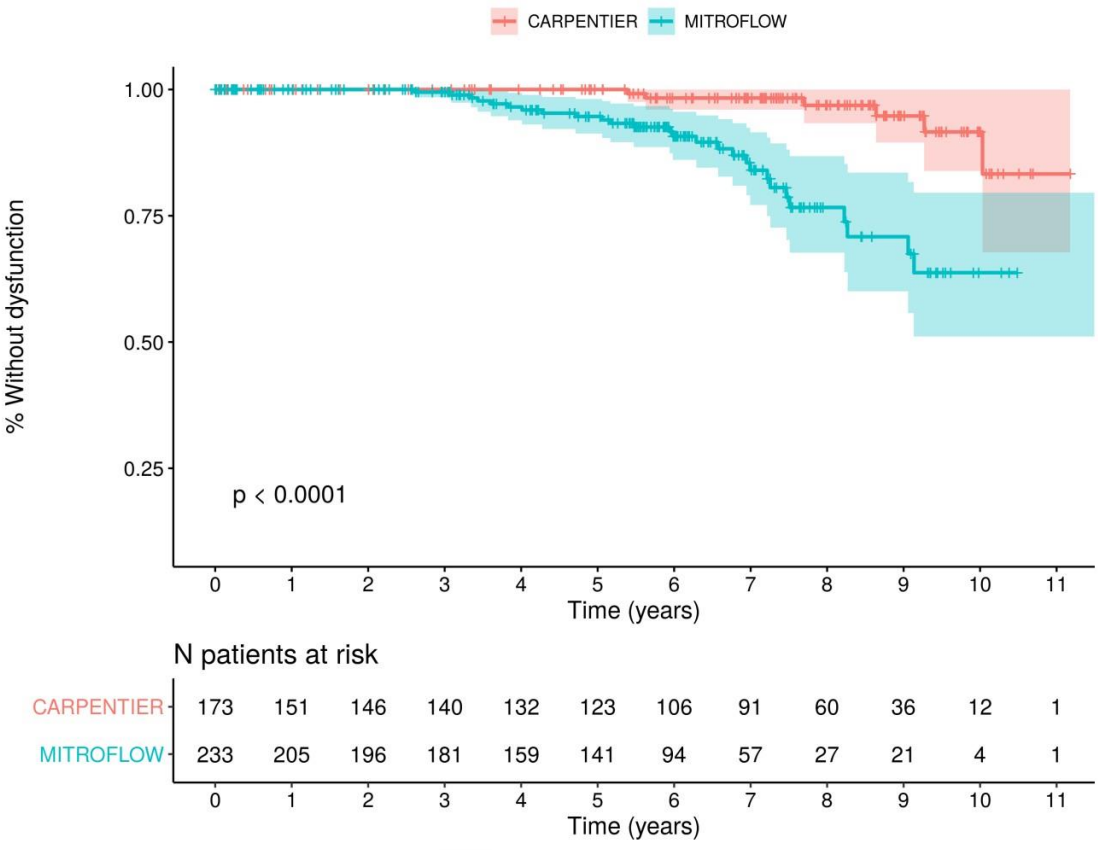


Figure 4.4. Actuarial curve representing the absence of SVD in the groups that received a Mitroflow and Carpentier bioprosthesis.

4.4.3. Endocarditis

A total of 17 patients were diagnosed with prosthetic endocarditis (4.15%). In two cases, the diagnosis was made before hospital discharge, and they died without being re-operated. After discharge, 15 patients were diagnosed with endocarditis (5 early and 10 late endocarditis). Eleven patients were re-operated (4 early and 7 late endocarditis), and 4 patients received only medical treatment. Figure 4.5 represents the curve of absence of endocarditis in the total group.

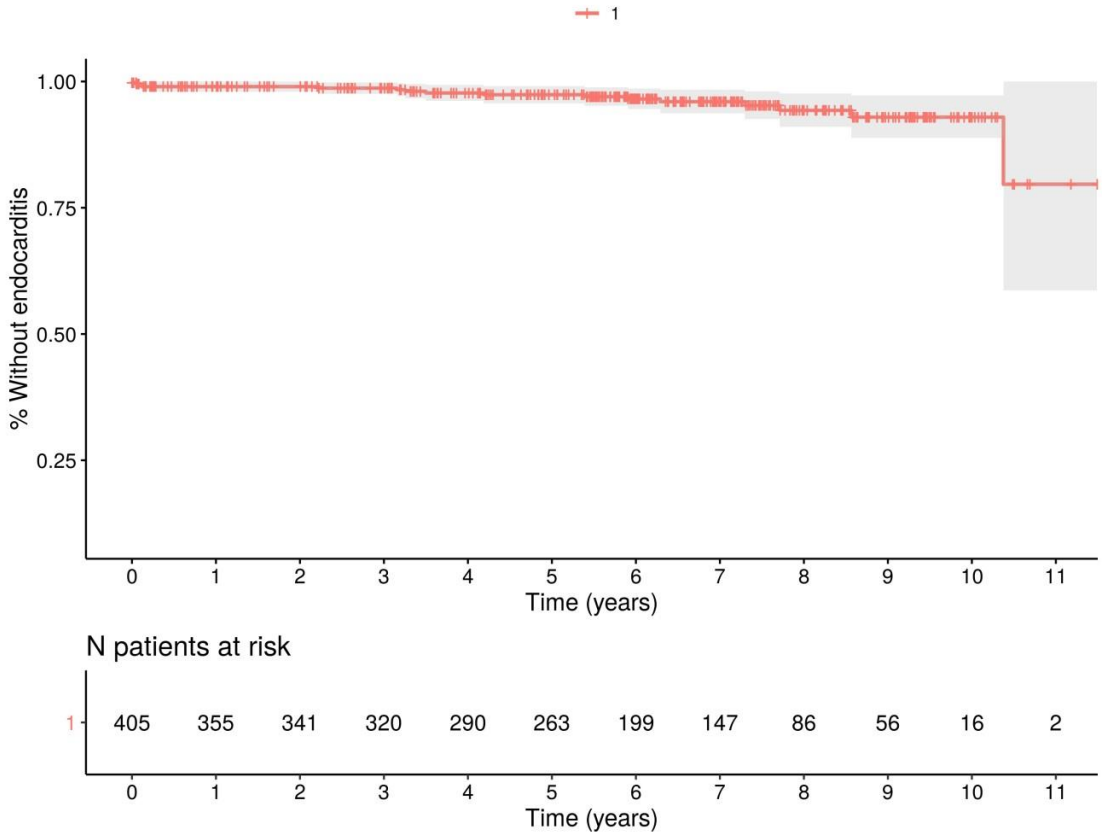


Figure 4.5. Actuarial curve for the absence of prosthetic endocarditis.

When performing a comparative analysis of the appearance of endocarditis between patients with Mitroflow and Carpentier bioprostheses, no significant differences were demonstrated. Figure 4.6 represents the actuarial curve for the absence of endocarditis in both groups of patients.

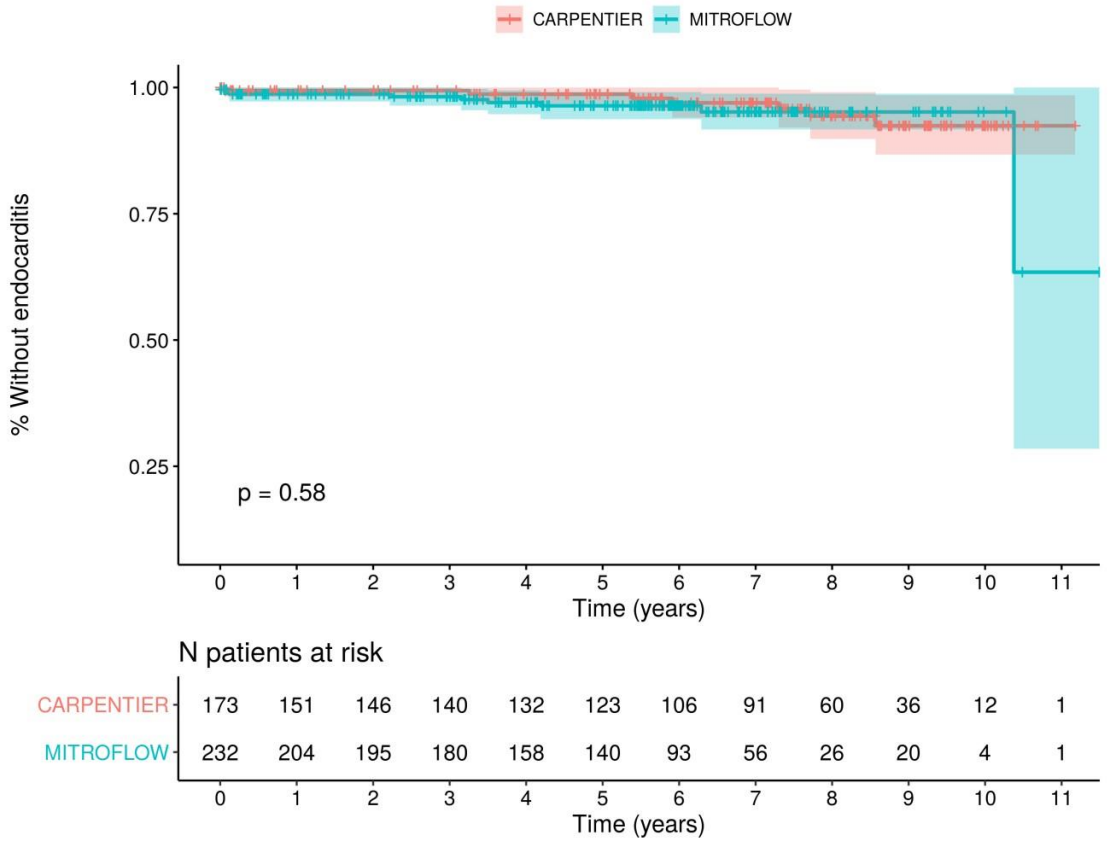


Figure 4.6. Actuarial curve for the absence of comparative endocarditis between the groups of patients with Mitroflow and Carpentier prostheses.

4.4.4. Reoperation

A total of 28 patients (6.84%) were re-operated. In three patients, reoperation was not related to the aortic bioprosthesis (2 mitral valve replacement and 1 myocardial revascularization). In 25 patients, the aortic prosthesis was operated. The reason for aortic reoperation was SVD in 14 cases and endocarditis on a prosthesis in 11 cases. Figure 4.7 represents the actuarial curve for the absence of reoperation for any cause.

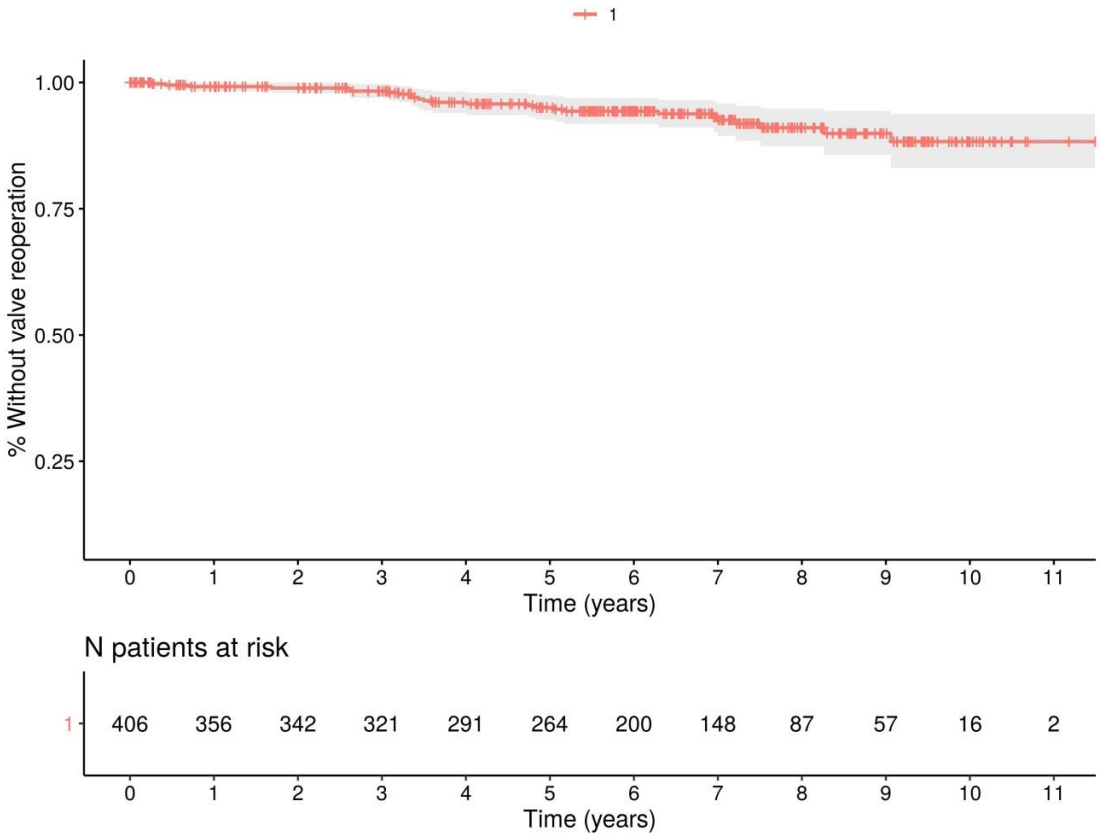


Figure 4.7. Actuarial curve for the absence of reoperation for any cause in the total group.

The adjusted analysis for the competing risks of deaths, SVD, and reoperation using the cause-specific Cox regression model and the cumulative incidence function of the event, according to the Fine-Gray regression model, demonstrated a significant association of reoperation with the Mitroflow prosthesis implantation. No association was shown between reoperation and gender, presence of diabetes mellitus, arterial hypertension, mismatch, and combined surgery with aortic valve replacement.

The comparative analysis between patients with Mitroflow and Carpentier prostheses about the absence of reintervention showed a higher rate of reoperations in the Mitroflow group. Figure 4.8 represents the curve of absence of comparative reintervention between the Mitroflow and Carpentier groups.

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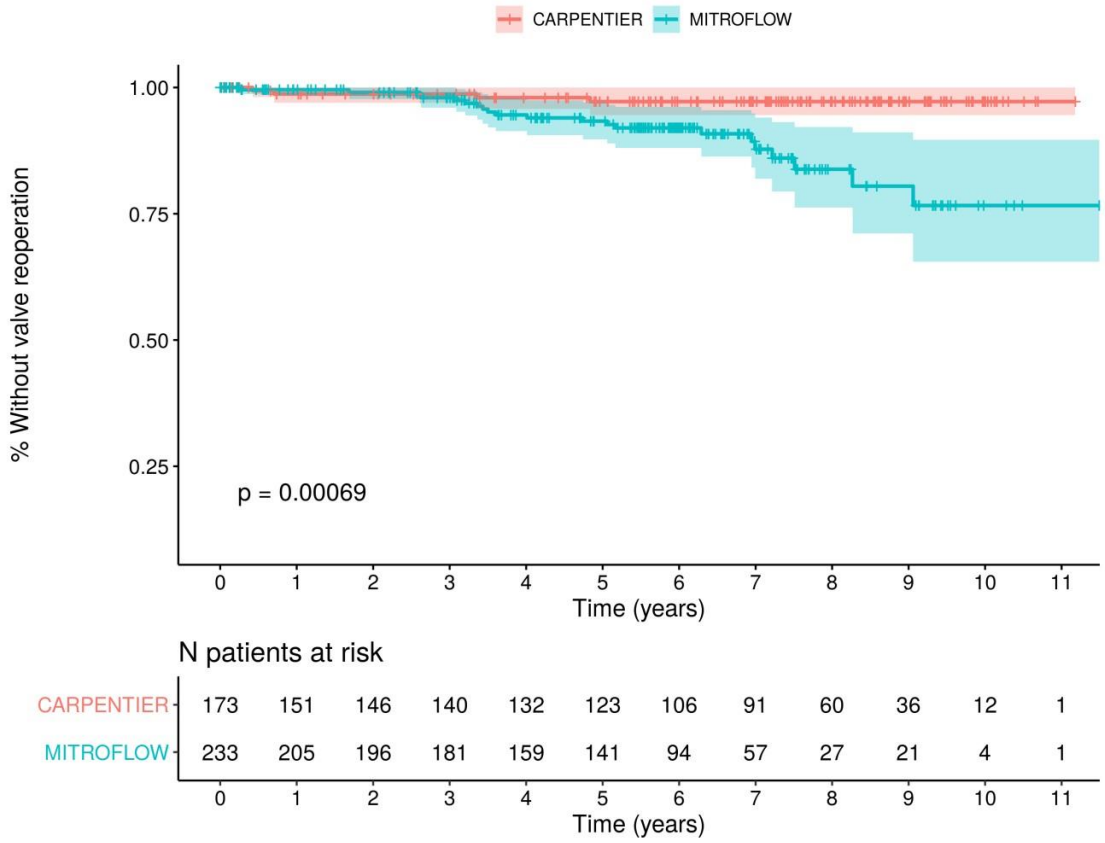


Figure 4.8. Actuarial curve that represents the absence of reoperation for any cause in the groups with Mitroflow and Carpentier prostheses.

4.4.5. Survival in Patients with Small Prostheses

The analysis of survival and absence of reoperation in patients with small prostheses (Nos. 19 and 21) did not reveal significant differences concerning the total group. The comparative results between the groups of patients with Carpentier and Mitroflow bioprostheses of sizes No. 19 and No. 21 were superimposed on the total group and are reflected in figures 4.9 and 4.10.

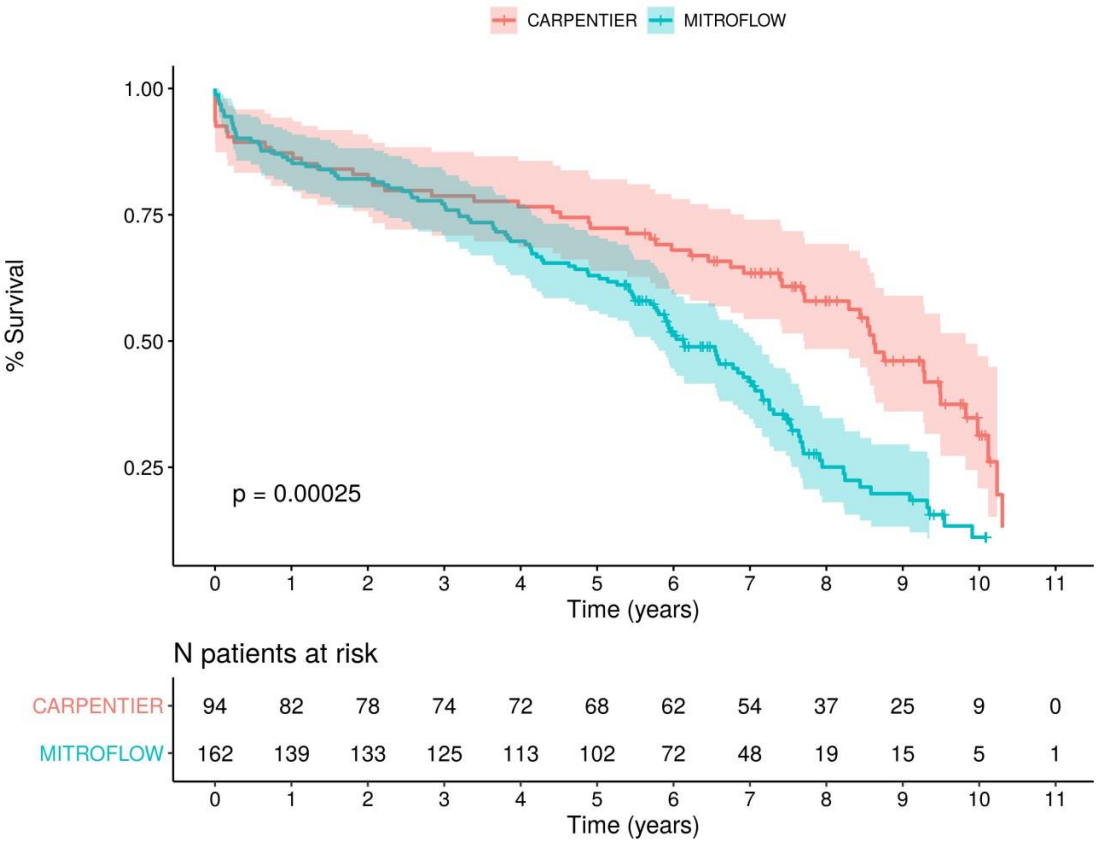


Figure 4.9. Actuarial survival curve of patients with Mitroflow and Carpentier bioprostheses of sizes Nos. 19 and 21.

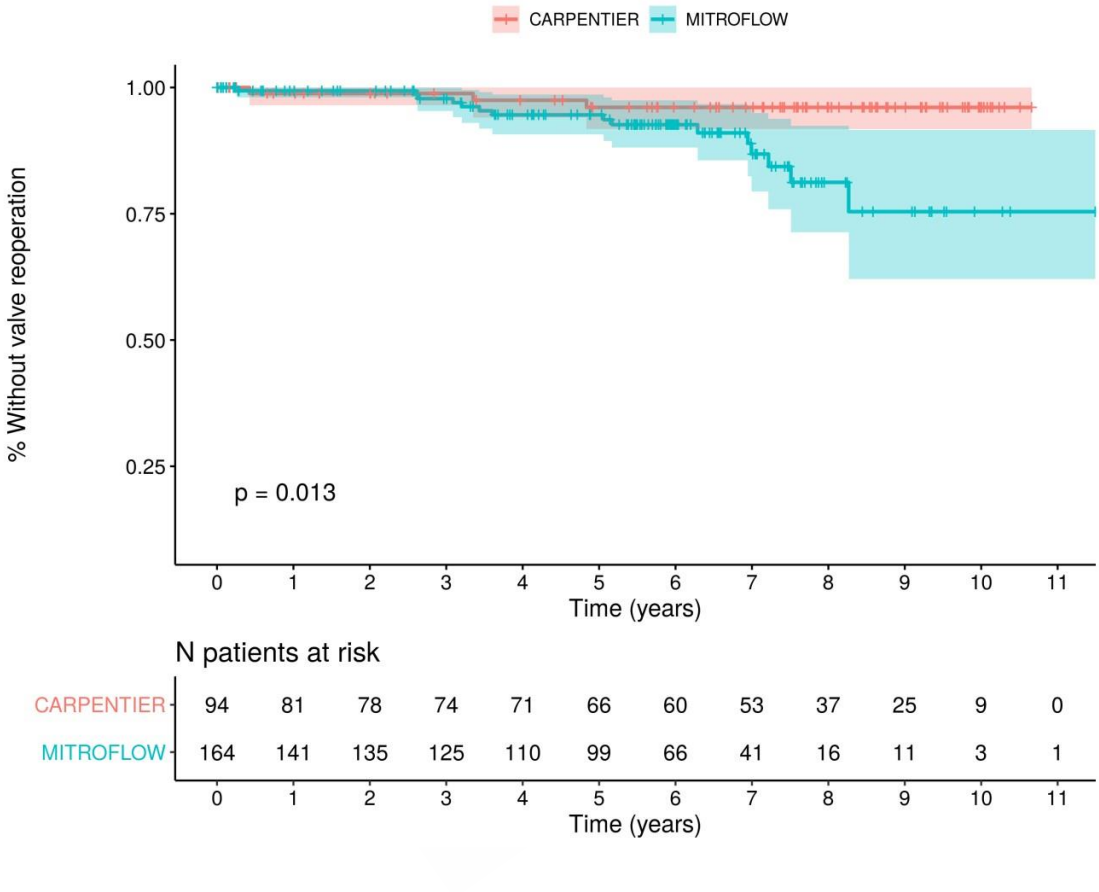


Figure 4.10. Actuarial curve for the absence of reoperation in patients with Mitroflow and Carpentier bioprosthesis sizes No. 19 and No. 21.

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5. DISCUSSION

5. 1. LIMITATIONS OF THE STUDY

5.1.1. Methodological Limitations

In this thesis, a descriptive observational study has been carried out with retrospective data collection on a cohort of patients undergoing aortic valve replacement. It presents all the limitations inherent in a retrospective study.

On the other hand, access to clinical data of patients, both in primary and specialized care, has been carried out through the electronic medical record system currently used in the Galician Health Service IANUS (XUNTA DE GALICIA, 2008). It is possible that some data on the clinical evolution of the patients, many of whom were institutionalized elderly, may not have been reflected in the clinical history.

Despite these limitations, follow-up through electronic history has been possible in all patients except six, which represents a percentage of complete follow-up of 98.54%.

Moreover, the diversity of surgeons and other physicians who provided care to the patients has been added to the heterogeneity of the patients studied. Different protocols have been used both at the hospital level and in long-term follow-up, including hospital treatment and controls before discharge, control of cardiovascular risk factors, prophylaxis of infectious endocarditis, echocardiographic study protocol, etc.

The sample studied of 409 patients includes all the bioprostheses implanted in the aortic position in our center between 2008- 2012. However, some of the trends observed in the results could not be confirmed from a statistical point of view, probably due to the small number of patients in some subgroups, such as the Carpentier prosthesis size No. 19.

5.1.2. Other Considerations

The main objective of this thesis is to know the frequency, related factors, and consequences of structural valve deterioration in bovine pericardial aortic bioprostheses. Between 2008 and 2012, the period in which the cohort of studied patients was operated on, there was no consensual definition of structural valve deterioration, hereinafter referred to as SVD.

As will be seen in section 5.2. from the discussion, until 2008 the term SVD was practically synonymous with reoperation, i.e., it was considered that SVD existed only and when it was necessary to re-operate the patient due to dysfunction of the bioprosthesis. The systematic performance of regulated and serial echocardiographic studies in asymptomatic patients, starting in the immediate postoperative period, was not contemplated. For this reason, in the cohort studied, the number and cadence of echocardiographic studies are highly variable and depend to a large extent on the referring cardiologist. Moreover, a considerable percentage of patients had advanced age, with limitations in mobility and other comorbidities, and did not undergo cardiological reviews after the intervention, either by their own decision, by the family, or by their referring cardiologist. This determines, on the one hand, that the SVD rate observed in this study probably underestimates the real rate and, on the other hand, the moment when the SVD appears cannot be set in time. In any case, it is accepted that in clinical studies, such limitations are foreseeable but unavoidable.

5.2. DIAGNOSIS AND QUANTIFICATION OF STRUCTURAL DETERIORATION

As discussed in the introduction of this Thesis, the Achilles heel of bioprostheses continues to be the SVD. Once a bioprosthesis is implanted, a slow deterioration process begins over time, which becomes more evident at 8 years after the intervention with an increasing rate after 10 years. For this reason, some authors consider that studies with a follow-up of fewer than 10 years have limited value for estimating SVD unless the degeneration rate is high and early between 5 and 10 years (Dvir et al., 2018). However, the mean age at which a bioprosthesis is implanted in our environment is around 77 years, so the number of patients with follow-up to 10 years is minimal (Puvimanasinghe et al., 2001). Studies with a follow-up to 15 or 20 years become important when the mean age of the patients is low (Bourguignon et al., 2016).

The first question to be considered is to define the diagnostic and staging criteria of the SVD.

Guidelines on how to report complications related to valve surgery were published for the first time in 1988 (Clark et al., 1988). Structural valve deterioration of a bioprosthesis (SVD) was defined as the worsening of the NYHA functional class of at least one point as a consequence of an intrinsic lesion of the prosthesis (fracture, sclerosis, calcification, tear) causing stenosis or insufficiency demonstrable during a reoperation, autopsy or in the course of a clinical examination.

Eight years later, the next edition of the guidelines (Edmunds et al., 1996) repeated the same definition of SVD without specifying clinical parameters that would allow unequivocally the diagnosis of SVD, avoiding the need to link it with reoperation.

In 2008, new guidelines were published to report morbidity and mortality in patients undergoing valve surgery (Akins et al., 2008). The definition of SVD included not only the need for reoperation due to dysfunction, post-mortem studies, and findings in clinical examinations, but also suggested for the first time a periodic echocardiographic follow-up of patients. Furthermore, it determined that the increase over time in the degree of stenosis or insufficiency of the bioprosthesis identified by echocardiography should be reported in a quantitative or semi-quantitative way. However, these guidelines did not agree on cut-off points for the echocardiographic parameters to stage the grade of SVD.

Due to the lack of specificity in the guidelines, numerous studies carried out on the duration and hemodynamic performance of bioprostheses. They followed very heterogeneous criteria to identify the presence of SVD, having identified more than 10 different definitions of SVD (Fatima et al., 2019) (Rodriguez-Gabella et al., 2017).

In some studies, the diagnosis of SVD was dependent on the need for reoperation (Nielsen et al., 2016). In other studies, SVD was identified with mixed echocardiographic or surgical criteria (deterioration demonstrated by echocardiography without specifying numerically the degree of effect or the need for reoperation) (Mosquera et al., 2016). Some authors defined the presence of SVD based on static echocardiographic findings considering severity criteria the presence of a mean transprosthetic gradient > 40 mmHg or a severe insufficiency (Bourguignon et al., 2016) (Lootens et al., 2017) (Piccardo et al., 2016) (Blasco-Lucas et al., 2017) (Ius et al., 2017). Faced with static echocardiographic findings, some studies defined the existence of SVD when an increase over time of the mean transprosthetic gradient between 30- 35 mmHg was observed (De Paulis et al., 2017) (Sénage et al., 2014) (Díaz et al., 2017). In other studies, static echocardiographic criteria (mean gradient greater than 40 mmHg) were combined with dynamic ones (gradient increase greater than 30 mmHg) (Bassano et al., 2018).

As discussed in the limitations of this Thesis, there was no protocol in our center where it was recommended to perform a basal echocardiogram after the intervention in all patients. Some surgeons requested an echocardiogram before hospital discharge, and others did not. After analyzing the clinical medical records in our series, in approximately 50% of the cases, there was no basal echocardiographic study before hospital discharge, and in many of those that had been performed, the images had not been recorded and the report was very brief, limiting itself to say "normal functional prosthesis". For this reason, when we designed this study, we decided to use as a diagnostic criterion of SVD the presence of severe stenosis (mean transprosthetic gradient > 40 mmHg), severe insufficiency, or the combination of moderate prosthetic stenosis (mean gradient 30- 40 mmHg) with moderate insufficiency. Like other authors (Issa et al., 2018), we did not stage the severity of the SVD. However, it was treated as a dichotomous parameter, and it was considered that the bioprostheses with isolated moderate stenosis or isolated moderate insufficiency did not present SVD.

As already mentioned in the methods and the limitations of this discussion, many of our patients were elderly, and long-term follow-up was performed by primary care physicians, so we lack echocardiographic studies and specialized clinical evaluation. Many cases of SVD would likely be left undiagnosed so that the actual rate of SVD was much higher than what we have observed. This circumstance is increased by the fact that the rate of asymptomatic SVD is much higher in elderly patients than in younger age groups (Rodriguez-Gabella et al., 2017).

On the other hand, due to the lack of a basal study before hospital discharge, we do not know the mean postoperative gradient immediately after the intervention in our patients and the degree of actual mismatch. It is possible that the postoperative gradient in some cases was high, especially considering that a moderate mismatch was calculated from the data provided by the manufacturer in 43.8% of the cases that received a Mitroflow bioprosthesis. According to this data, it

is logical to think that the initial postoperative gradient was high due to the reduced EOAI of the prosthesis. In this case, a high gradient observed statically in the postoperative period cannot necessarily be identified with bioprosthetic stenosis secondary to SVD but could theoretically be a non-structural mismatch dysfunction.

The absence of clear and consensual criteria for the diagnosis of SVD makes it inappropriate to compare the durability of different bioprostheses if the same methods are not used to demonstrate the presence of SVD. For example, if the presence of SVD is considered only when patients are symptomatic and reoperation is necessary, the rate of SVD will be lower than if an echocardiogram is performed in asymptomatic patients and a mean gradient > 40 mmHg is demonstrated. It is very likely that in the case of periodic studies are carried out in asymptomatic patients and with mean gradient increases > 10 mmHg, so the number of patients is raised high and, therefore, the rate of SVD is even higher. This means that according to the diagnostic criteria used to diagnose SVD, low or high rates can be observed and consequently conclude that the durability of the same bioprosthesis depends on the one who quantifies it, and this relativism can involve healthcare professionals in the struggle between bioprostheses manufacturers to achieve a greater market share.

Reading the published scientific literature suggests that for more than four decades there has been no particular interest either on the part of manufacturers or professionals in defining and agreeing on homogeneous and unequivocal criteria for the diagnosis of SVD that allow a scientific comparison of durability of the different bioprostheses (Fatima et al., 2019) (Rodriguez-Gabella et al., 2017). However, as a result of the expansion of transcatheter prostheses, the competition between different manufacturers to demonstrate the superior durability of their products has forced healthcare professionals to agree on homogeneous and unequivocal criteria for the diagnosis of SVD.

Thus, in 2017 the European Society of Cardiology, the European Society for Cardio-thoracic Surgery, and the European Association of

Percutaneous Cardiovascular Interventions published a consensus paper on the standardized definition of SVD for both surgically implanted prostheses and transcatheter prostheses (Capodanno et al., 2017). In this document, one of the fundamental recommendations is the need to know the transprosthetic gradients in the early postoperative period by echocardiography to rule out the presence of mismatch and establish the baseline parameters such as repeat the study after 6 months, one year and then every year although the patient is asymptomatic.

This paper divides the SVD into two main sections: morphological SVD and hemodynamic SVD. It considers that there is morphological SVD when in the imaging tests, there are suggestive findings of deterioration such as thickening or anomalies of the mobility of the leaflets, regurgitation, calcification, etc. Hemodynamic SVD is typified based on Doppler findings and is, in turn, classified into moderate SVD and severe SVD.

Moderate hemodynamic SVD is considered to exist when any of the following criteria are met:

a) mean transprosthetic gradient > 20 mmHg and < 40 mmHg.
b) gradient increase > 10mmHg and < 20 mmHg over postoperative baseline values.
c) intra-prosthetic insufficiency of new appearance or that worsens > 1/4 concerning the basal values.

Severe hemodynamic SVD is considered when any of the following circumstances are met:

a) mean transprosthetic gradient > 40 mmHg.
b) mean gradient increase > 20 mmHg over baseline.
c) severe intra-prosthetic insufficiency or worsening over baseline > 2/4.

For the first time, this document introduces the concept of bioprosthetic valve failure, hereinafter BVF, which it defines as the negative consequence for the patient of bioprosthesis deterioration. The BVF integrates the SVD (the etiology) with its clinical consequences and is considered as the main parameter to be studied in the long-term follow-up in patients with bioprostheses.

Importantly, BVF can be a consequence of SVD but can also be secondary to thrombosis, endocarditis, or other forms of non-structural deterioration. The BVF includes some of the following findings:

a) Bioprosthetic dysfunction observed at autopsy and probably related to the cause of death.
b) Valve-related death defined as any death caused by valve dysfunction in the absence of autopsy.
c) Valve reoperation.
d) Severe hemodynamic SVD.

One year after this document was published, in 2018, the VIVID group (Valve in Valve International Data) published another document on the standardized definition of SVD to allow comparability of the degeneration rate between the different bioprostheses, ensuring that the need for reintervention was a very poor surrogate endpoint for calculating the rate of SVD (Dvir et al., 2018).

The VIVID group defines SVD as an intrinsic acquired anomaly of the bioprosthesis due to deterioration of the leaflets or the supporting structures that results in thickening, calcification, tearing or rupture of the prosthesis materials and eventually resulting in valvular hemodynamic dysfunction manifested as stenosis or insufficiency. Other functional abnormalities of bioprostheses such as mismatch, periprosthetic regurgitation, and abnormal implantation are not included within the concept of SVD because there is no involvement of the valve tissue. Even though they are not structural abnormalities they can be associated with early SVD.

The VIVID group paper establishes for the first time a systematic staging of SVD based on prosthetic lesions and not on the clinical condition of the patient. In this way, the concept of SVD ceases to be dichotomous to become a continuous variable, similar to the valvular disease on the native valves. This classification into stages of severity is associated with a specific recommendation for treatment. Three stages of SVD are defined:

Stage 0: no significant alterations from the immediate implantation.

Stage 1: morphological abnormalities of leaflets without hemodynamic changes.

Stage 2S: moderate stenosis. It must include an increase in the mean transprosthetic gradient > 10 mmHg. Many bioprostheses present an immediate gradient between 15-19 mmHg due to mismatch. Therefore, it is crucial to document the morphological abnormalities of leaflets.

Stage 2R: Moderate intra-prosthetic regurgitation.

Stage 2RS: Moderate prosthetic stenosis and regurgitation. If it is symptomatic, it can be considered for reoperation.

Stage 3: Severe stenosis or severe regurgitation. If it is symptomatic, it should be considered for reoperation.

From an echocardiographic point of view, a bioprosthesis is considered to have normal hemodynamics when the mean gradient is less than 20 mmHg, or the gradient increments are < 10 mmHg. Stenosis is moderate when the mean gradient is 20- 40 mmHg and the mean gradient increments are 10- 20 mmHg, and it is severe when the mean gradient is > 40 mmHg or the gradient increments are > 20 mmHg.

These new standardized definitions of SVD published in the last three years (Capodanno et al., 2017) (Dvir et al., 2018) advise the performance of a basal echocardiographic study after the intervention

and a routine annual echocardiographic follow-up in all patients, including asymptomatic ones, to identify the hemodynamic abnormalities. This recommendation could be in contradiction with the guidelines of valvular disease that do not advise performing echocardiograms during the first five years unless there are symptoms or alarming signs (Baumgartner et al., 2017). For this reason, the new definitions of SVD consider that the annual echocardiogram after discharge may be overlooked in asymptomatic patients with bioprostheses who have been on the market for years and have demonstrated excellent durability (Dvir et al., 2018).

5.3. INCIDENCE OF STRUCTURAL VALVE DETERIORATION

After what has been stated in this discussion, it can be affirmed that the true incidence of SVD in bioprostheses is unknown due to the variability of the definition of SVD, the postoperative follow-up protocols, the quality of cardiac imaging laboratories and the methodology to communicate the results. On the other hand, the mathematical calculation of the incidence rate of SVD varies depending on whether it is actual (accumulated) or actuarial data (e.g. Kaplan-Meier). It is estimated that patients undergoing aortic valve replacement by biological prosthesis have a 10-year mortality rate that is close to 70% (Nitsche et al., 2020) (Rodriguez-Gabella et al., 2017) (Glaser et al., 2019) (Puvimanasinghe et al., 2001). Logically, this high mortality exerts a competing effect against the risk of SVD, and for this reason the usual actuarial analyzes used to calculate the risk of SVD may be inappropriate unless statistical tools are used to correct competing risks.

There are historical studies where it is shown that not all bioprostheses behave in the same way, neither from the hemodynamic point of view nor concerning durability (Rodriguez-Gabella et al., 2017) (Fatima et al., 2019). The classic example is the St. Jude Toronto SPV unsupported porcine prosthesis with excellent hemodynamic performance and

durability up to 5 years after implantation but with a very high SVD rate at 15 years (Christ et al., 2015). This means that good results in the medium term cannot always be extrapolated to the long term. A minimum follow-up of 10 years is considered necessary to establish the expected durability for a bioprosthesis.

In the case of our work, with an average age of patients of 77 years, it makes no sense to propose longer follow-ups since, as explained, life expectancy is less than 10 years (Puvimanasinghe et al., 2001). In fact, the percentage of patients survived more than 10 years after the intervention was 10%.

The diagnosis of SVD based on the number of patients referred for reoperation in most of the studies published before 2017 places the SVD rate at 10 years below 10% for practically all bioprostheses on the market. Thus, for example, the Carpentier Edwards SAV supra-annular porcine prosthesis presents an SVD rate of 5.4% at 10 years (Jamieson et al., 2005), the Mitroflow prosthesis 5.1% at 10 years (Yankah et al., 2008), Hancock II prosthesis 2.4% at 10 years (David et al., 2010), the Carpentier Edwards Perimount pericardial prosthesis 3.9% at 10 years (Forcillo et al., 2013) and the Biocor bioprosthesis 7.9% at 10 years (Guenzinger et al., 2015).

We should make two comments regarding these SVD figures. The first is that these are global values where patients of all ages are included. In younger subgroups, the durability of the prostheses is lower, while in patients > 70 years of age, in some series, the SVD is around 1%. A second comment is that these are studies carried out before 2017, the date on which were published the new guidelines for the diagnosis of SVD based on defined echocardiographic criteria and that, in some cases, as we will see later, has motivated radical changes in the rate of SVD in some types of prostheses.

5.4. PREDICTORS STRUCTURAL DETERIORATION

The SVD is the main limiting factor for the durability of bioprostheses. The precise mechanism of SVD is unknown, but it probably includes thickening or rupture of tissue due to mechanical stress and abnormal flow on the surface of the leaflet, rupture of collagen fibers, and tissue calcification (Nitsche et al., 2020).

The hemodynamic impact of SVD has led to a new concept, which is the term valve hemodynamic deterioration (VHD) (Nitsche et al., 2020). Within the VHD in pericardial bioprostheses, prosthetic stenosis is the most common finding and is due to calcification (65%) followed by insufficiency due to leaflet rupture (23%) and double injury (12%) (Nitsche et al., 2020).

Several factors related to SVD have been observed that can be classified into two large groups: prosthesis-dependent factors and patient-dependent factors.

Some of the factors related to the prosthesis include the position of the prosthesis, the prosthetic size, the presence of mismatch, and the design of some bioprostheses (Rodriguez-Gabella et al., 2017).

Bioprostheses in the mitral position present SVD earlier than those implanted in the aortic position because the stress of closure by systolic intraventricular pressure is much higher than aortic closure at diastolic pressure.

As for prosthetic size, it is accepted that small-size prostheses (Nos. 19 and 21) degenerate earlier than large-size prostheses (No. 23 and higher). In our study, we observed a tendency towards an SVD in the smaller prosthetic sizes. Of the 35 prostheses with SVD, a total of 30 corresponded to sizes Nos. 19 + 21 and five to size No. 23. We could not demonstrate statistically significant differences, probably due to the sample size (Rodriguez-Gabella et al., 2017) (Nielsen et al., 2016) (Nitsche et al., 2020) (Piccardo et al., 2016).

The disproportion between the size of the prosthesis and the theoretical valve area of the patient, called mismatch and defined in the introduction of this Thesis, is considered a non-structural prosthetic deterioration responsible for iatrogenic stenosis and a high mean transprosthetic gradient from the moment of implantation. Although the mismatch itself is not SVD, it can favor its appearance due to the hemodynamic stress that the transprosthetic pressure gradient causes on the prosthesis leaflets, favoring their thickening and calcification (Nitsche et al., 2020) (Rodriguez-Gabella et al., 2017) (Blasi et al., 2020).

In the absence of a basal echocardiographic study within 30 days of the intervention, it may be difficult to distinguish whether a transprosthetic gradient is due to mismatch or secondary to SVD. In general, if the morphology of the leaflets is normal, it is considered that the high gradient may be most likely due to mismatch (Dvir et al., 2018).

In our series, we observed moderate or severe mismatch in 44% of the patients who received a Mitroflow prosthesis however, although we were unable to demonstrate an association between mismatch and SVD.

In relation to the design of the bioprosthesis, some models have shown earlier structural deterioration than others, such as the Toronto porcine unsupported prosthesis (Christ et al., 2015) and the Mitroflow prosthesis (Sénage et al., 2014). Regarding the latter, it has been invoked that the absence of anticalcification treatment of the latter may be responsible for the higher rate of structural deterioration (Sénage et al., 2014). However, the introduction of anticalcification treatment to the Mitroflow design does not seem to have substantially modified its durability (Bassano et al., 2018). One of the main findings of our work is the high SVD rate of the Mitroflow bioprosthesis, and we will address this issue in a more specific way in point 5.7 of this discussion.

When it comes to patient-related factors, they include age, high blood pressure, renal failure, obesity, smoking, diabetes, and dyslipidemia (Rodriguez-Gabella et al., 2017) (Nitsche et al., 2020).

Age is a determining factor in the early onset of SVD. So, the younger the patient, the greater the probability of presenting SVD, and the older the patient, the less. Numerous studies have shown this association that we were also able to observe in our series.

High blood pressure can accelerate the onset of SVD due to increased diastolic stress of closure of the prosthesis. Regarding renal failure, it has been observed that the alteration of calcium and phosphorus metabolism in these patients can favor an early calcification of the bioprosthesis, the main finding in SVD of bovine pericardial bioprostheses. In our work, we did not observe an association between AH and SVD. On the contrary, we were able to demonstrate an association between renal failure and atrial fibrillation with SVD. The interpretation of these findings should be made with caution. After hospital discharge, many of our patients did not receive specialized cardiology care. We were able to observe that when they presented an episode of heart failure that required hospital admission, on some occasions, an echocardiogram was requested to know the status of the bioprosthesis. There was no protocol, and the performance of the echocardiogram depended on the responsible physician during admission. It is possible that the higher rate of SVD that we observed in patients with renal failure and atrial fibrillation could be related to a closer specialized follow-up or other clear symptomatology that facilitated the performance of more echocardiographic examinations and, therefore, a greater number of diagnoses of SVD.

5.5. STRUCTURAL DETERIORATION AND CLINICAL IMPACT

Aortic valve replacement provokes a reduction in life expectancy (Glaser et al., 2019). The average survival in patients aged 75- 85 years is estimated to be 6 years (Foroutan et al., 2016) (Puvimanasinghe et al., 2001). Some factors related to long-term survival after aortic valve replacement by a bioprosthesis have been identified: age at the time of intervention, renal failure, presence of coronary artery disease, the combination of myocardial revascularization with valve replacement, COPD, left ventricular ejection fraction, diabetes, atrial fibrillation, mismatch and, of course, SVD (Tjang et al., 2007) (Di Eusanio et al., 2011) (Javadzadegan et al., 2013) (Nitsche et al., 2020) (Rodriguez-Gabella et al., 2017) (Nielsen et al., 2016) (Sénage et al., 2014) (Díaz et al., 2017).

The relationship between the rate of SVD, late mortality, and reoperation is complex due to the dissociation between echocardiographic studies, symptoms, and the need for reoperation.

First, as we have seen, the absence of serial echocardiographic studies and the definition itself makes it impossible to identify all patients with SVD.

Second, not all patients diagnosed with SVD are operated on either because the patient is asymptomatic, refuses the intervention, or there are contraindications for it. It is estimated that the percentage of patients diagnosed with SVD who are re-operated varies between 100% and 20% (Nitsche et al., 2020) (Rodriguez-Gabella et al., 2017) (Díaz et al., 2017). Of the 35 patients diagnosed with SVD in our study, 56% were re-operated, and the rest received medical treatment. Logically, the more patients with SVD are re-operated, the lower the mortality due to the SVD. Therefore, the more difficult it will be to demonstrate a statistical association between SVD and survival, especially when the sample size is small (Nitsche et al., 2020).

The third is the problem of symptomatology in patients with SVD. On the one hand, in elderly patients, the presence of SVD without symptoms is much more frequent than in younger ones (Rodriguez-Gabella et al., 2017), and this may condition the lower number of echocardiographic examinations in this population and therefore the lower number of confirmed diagnoses of SVD. The absence of symptoms in elderly patients with severe SVD can reach 30% of cases, so the determination of plasma levels of NT-proBNP can be a useful tool in these cases (Issa et al., 2018). On the other hand, we have patients with heart failure not attributed to SVD. One of the frequent causes of late death in patients with a bioprosthesis is heart failure not related to the prosthesis (Blasco-Lucas et al., 2017) (De Paulis et al., 2017). In our study, up to 10.4% of late deaths were labeled by their responsible physicians, such as chronic, refractory, or congestive heart failure. Most of these patients died in hospital, but very few underwent an echocardiographic study. Hence, the status of the bioprosthesis at the time of death is unknown. It is possible that heart failure in some of these cases could be caused by SVD that went unnoticed. However, it is true that these were elderly patients with multiple pathologies.

In a recent study of late deceased patients with aortic bioprostheses, it has been observed that they have a higher risk of admission for heart failure and endocarditis when the cause of death is SVD (Waziri et al., 2019). This leads once again to an impact on the need for periodic echocardiographic follow-up starting five years after the intervention to identify patients with SVD, and then carefully question the symptomatology they present, since in many cases as they are elderly, the limitation of physical activity makes them remain with few symptoms.

5.6. TREATMENT OF STRUCTURAL VALVE DETERIORATION

The current guidelines of the ESC/EACTS (Baumgartner et al., 2017) recommend re-operate patients with symptoms who present SVD with "significant gradient" or severe insufficiency. In asymptomatic patients, reoperation can be considered if there is a low surgical risk.

In the paper of the VIVID group, the SVD treatment recommendations are systematized according to the evolutionary stage and taking into account the surgical risk. In patients at stage 2RS, reoperation is recommended if they are symptomatic. In contrast, in asymptomatic patients, a clinical evaluation is advised every 3- 6 months and repeat the echocardiogram every 6 months. In patients at stage 3, reoperation is recommended if they are symptomatic. In asymptomatic patients with preserved ventricular function, a clinical evaluation is recommended every 3- 6 months and a repeat of the echocardiogram every 6 months.

As we have previously discussed, 44% of our patients diagnosed with SVD were not re-operated. All were elderly patients with comorbidities, and some of them had some degree of cognitive deterioration. In this sense, the multidisciplinary evaluation of each particular case should serve as a compass to not deprive any patient of improving his quality of life while also avoiding futile efforts.

5.7. THE STRUCTURAL DETERIORATION OF THE MITROFLOW BIOPROSTHESIS

As we have seen in the introduction to this Thesis, the bioprosthesis Mitroflow 12A introduced to the market in 1992 (Sorin Group Canada Inc., Mitroflow Division, Burnaby, Canada) is a bioprosthesis composed of flexible polypropylene housing, coated with braided polyester, a silicone sewing ring covered by polyester and a continuous band of bovine pericardium fixed externally on the housing to

maximize the valve orifice. The LX model, introduced in 2010, incorporates small changes such as the pre-fixation of the veils with glutaraldehyde instead of post-fixation to facilitate their apposition on the housing. Neither of the two models has an anticalcification treatment in its fabrication. From a practical point of view, we will include them under the heading Mitroflow. The main theoretical advantage of the Mitroflow bioprosthesis lies in its hemodynamic profile, certain flexibility of its polymer housing, and reduced sewing ring size, which makes it, a priori, an ideal substitute for small aortic rings.

In healthy individuals, the size of the aortic annulus is related to body surface area, age, gender, and height (Gutgesell & French, 1991) (Cassottana et al., 1997) (Cohen et al., 1995) (Capps et al., 2000). Using Doppler echocardiography, it has been observed in healthy volunteers that the aortic effective valve area at rest is around 1.33 cm^2/m^2, having demonstrated a correlation between the valve area and the body surface (Gutgesell & French, 1991).

The concept of the small aortic annulus is a surgical term used in patients who are candidates for aortic valve replacement. Traditionally, an aortic annulus is considered small when it is less than 21 mm for a supported bioprosthesis and less than 19 mm for a bidisc mechanical prosthesis. Logically, these sizes are arbitrary and should be related to body surface area, age, and level of physical activity (Ghosh et al., 1998). Taking this into account, we can define the aortic annulus as the one that does not allow the implantation of a prosthesis with an effective orifice area indexed greater than 0.85 cm^2/m^2.

More than 50% of patients with a small aortic annulus are elderly women. The fibrosis and calcification of the annulus associated with advanced age or simply the presence of a very small annulus determine that the prosthesis that adapts to that annulus is small. The Mitroflow prosthesis, as we have mentioned, is the ideal substitute for this type of small annulus. It is no coincidence that in our series, as in other published works, the proportion of Mitroflow prostheses of sizes No.

19 and No. 21 and the number of women with Mitroflow prostheses is higher than that of other prostheses such as the Carpentier (Nielsen et al., 2016) (Blasco-Lucas et al., 2017).

It could be argued that for a patient with a small annulus, it is indifferent to implant a Mitroflow size No. 19 than a Carpentier same size. However, this is not the case. According to the manufacturer of the Mitroflow prosthesis, the external diameter (the non-compressible part) is 18.5 mm, and the size of the sewing ring is 21 mm. In the case of the Carpentier prosthesis, the diameter of the metal housing is 19 mm to which it would be necessary to add at least 1 mm of the braided polyester coating, which results in an external diameter (the non-compressible part) of 20 mm and the diameter of the sewing ring is 24 mm. This means that a size 19 Mitroflow prosthesis is objectively smaller and more flexible than a size 19 Carpentier. It seems incongruous, but it is a reality.

For this reason, it is easier to implant a Mitroflow No. 19 prosthesis in a patient with a 19 mm aortic annulus than to implant a Carpentier No. 19 prosthesis in the same patient. The same is the case for the rest of the sizes. Furthermore, it may happen that in a specific patient, it is easy to safely implant a size 19 Mitroflow prosthesis. However, in the same patient, it is impossible to implant a size 19 Carpentier prosthesis. On the other hand, the sewing ring of the Mitroflow prosthesis is less voluminous. Also, due to the flexibility of the polypropylene housing, it is very easy to tie, avoiding interference with the coronary ostium. In this regard, it is worth mentioning that was observed in four patients of the Carpentier group who died in the immediate postoperative period, an interference of the right coronary ostium with the prosthetic ring and it was found that in two cases, after tying a Carpentier size 21 prosthesis, that the prosthetic ring could interfere with the right ostium. It was decided intraoperatively to explant this prosthesis and implant a size No. tying19 Mitroflow prosthesis.

The reason why the Mitroflow prosthesis has been so successful is that it allowed the simple and safe implantation of a prosthesis with

reasonable hemodynamic performance in small aortic annulus without the need for annulus enlargement in elderly patients with high surgical risk. Another different issue is the durability of the Mitroflow bioprosthesis, as we will see below.

The durability of the Mitroflow bioprosthesis, being inferior to that of other prostheses, is one of the issues that have generated the most controversy, and that has not yet been fully resolved. The results published in the literature are disparate and, to some extent, contradictory. However, this is logical when we take into account that the definition of SVD varies considerably from one study to another.

Some authors have shown for the Mitroflow bioprosthesis a very low actuarial rate of SVD, defined in terms of the need for reintervention, of 28.2% in patients older than 70 years at 20 years (Yankah et al., 2008), 21.8% at 18 years (The Italian study on the Mitroflow postoperative results (ISTHMUS), 2011), 95% and 92% in patients between 75- 79 years of age at 10 and 15 years respectively (Minami et al., 2005), 6% at 10 years (Jamieson et al., 2009), 11% at 10 years (Sjögren et al., 2006), 2% and 7% at 5 and 8 years respectively (Blasi et al., 2020) and 11% at 8 years (García-Bengochea et al., 2006).

In contrast to these studies, there are other studies that, using echocardiographic criteria for the diagnosis of SVD, have shown very reduced durability of the Mitroflow bioprosthesis. With an echocardiographic definition of SVD (increase in transprosthetic gradient > 30mmHg with an EOA < 1cm^2 or insufficiency > 2/4) Sénage observed an actuarial rate of SVD at 5 years, which is very early degeneration of this prosthesis (Sénage et al., 2014). Other studies, also using echocardiographic criteria for the diagnosis of SVD, demonstrated an SVD rate of 25% at 9 years for sizes 19 and 21(De Paulis et al., 2017), 4.6% and 32.1% at 5 and 9 years respectively (Ius et al., 2017), 40% at 10 years (Blasco-Lucas et al., 2017) 5% and 45% at 5 and 10 years respectively (Alvarez et al., 2009), and 7% at 5 years, worsening in the presence of mismatch (Bassano et al., 2018), 4.2%, 15.7% and 30% at 5, 8 and 10 years respectively increasing and 40% at

5 years for prostheses of sizes 19 and 21 (Díaz et al., 2017).

In addition to population-based follow-up studies, some studies carried out on explanted dysfunctional Mitroflow prostheses demonstrated the presence of extensive and early calcification, even in patients older than 65 years, with stenosis due to rigidity of leaflets being the primary mechanism of hemodynamic dysfunction in the Mitroflow prosthesis (Luk et al., 2015).

The aforementioned articles, published from 2014, raised serious doubts about the durability of the Mitroflow bioprosthesis. However, it was the three works discussed below that led to its definitive withdrawal from the market in 2017.

Nielsen carried out an observational study at the request of surgeons at the Odense Hospital in Denmark, where he compared survival and the need for reoperation of the Mitroflow prosthesis with the Carpentier, demonstrating that the Mitroflow prosthesis was associated with an increased risk of death or reoperation, although he clarified that the difference between both prostheses disappeared when the size of the bioprosthesis housing was taken into account (instead of the nominal size of the prosthesis), indicating that the reason for the performance of the Mitroflow prosthesis could be related to the housing size. This last observation recalls what we previously commented: the non-compressible rigid housing of the Mitroflow prosthesis is smaller than the non-compressible rigid housing of the Carpentier prosthesis for the same nominal size (Nielsen et al., 2014).

Hickey published in the Journal JAMA Internal Medicine (Hickey et al., 2017) the National Registry of Valvular Prostheses in the United Kingdom where a greater risk was demonstrated for patients with a Mitroflow bioprosthesis.

In May 2017, the British NHS Medicines and Healthcare Products Regulatory Agency issued an alert to all hospitals about the risk of early SVD in the Mitroflow Bioprosthesis, especially in the smaller sizes

(Nos. 19 and 21) (The British NHS Medicines and Healthcare Products Regulatory Agency, 2017).

We have seen the disparity of results that have been published regarding the durability of the Mitroflow bioprosthesis. We cannot doubt the scientific honesty of the researchers in terms of praise or criticism of this bioprosthesis. As we mentioned previously, the way to define SVD and the heterogeneity of the studied populations can explain conflicting findings and make it difficult to make comparisons. Precisely the interest in knowing the real performance of this prosthesis in our environment was one of the reasons that encouraged us to carry out this Doctoral Thesis.

Recently, other papers have been published where the results about the rate of SVD in the Mitroflow bioprosthesis are neither as good as those initially reported nor as low as those that led to its withdrawal from the market.

Using echocardiographic criteria, Lootens has observed an actuarial rate of SVD of 6.2% at 12 years in patients older than 75 years and considers that the poor results of this prosthesis are due to an inadequate selection of patients since, in his opinion, early dysfunction occurs when small prostheses are implanted that can generate mismatch, especially in younger patients (Lootens et al., 2017).

Issa has observed actuarial rates of SVD of 6%, 13%, and 17% at 10 years for prostheses sizes Nos. 23- 29, 21, and 19, respectively, using echocardiographic criteria for the diagnosis of SVD (Issa et al., 2018). In our environment, Mosquera has demonstrated an actuarial rate of SVD of 30% at 12 years using echocardiographic criteria, without esteeming worse results in prostheses size No. 19 (Mosquera et al., 2016).

In our study, we decided to apply the echocardiographic criteria for the diagnosis of SVD, and we observed an actuarial rate of SVD of the Mitroflow prosthesis of 3.2% and 40% at 5 and 12 years respectively.

These are SVD values similar to those reported in our environment (Mosquera et al., 2016) (Blasco-Lucas et al., 2017). In the hypothetical case that we had defined SVD based on the patients referred for reoperation for structural dysfunction, we would have observed an actuarial rate of SVD of 1.3% and 11.8% at 5 and 12 years. It is clear that in the same cohort, we can follow very different rates of SVD depending on the used diagnostic criteria for SVD. Our results are very similar to those of Piccardo, who observed an actuarial rate of diagnosed SVD by echocardiography of 23% and 44% at 10 and 15 years and an actuarial rate of re-operated SVD of 1% and 5% at 10 and 15 years, respectively (Piccardo et al., 2016).

5.8. COMPARATIVE STUDY BETWEEN MITROFLOW AND CARPENTIER BIOPROSTHESES

As we have seen, it is practically impossible to compare the durability of the different bioprosthesis models. Most of the published comparative studies are observational rather than randomized with great variability in the patient's basal characteristics, surgical technique, management, and follow-up.

Some studies have compared the Mitroflow prosthesis with the Carpentier in the long term, showing a survival rate of 25% at 12 years, slightly lower for the Mitroflow prosthesis (Nielsen et al., 2016). In this work, SVD is defined as relevant stenosis or insufficiency at the time of reoperation. The rate of SVD is around 88% for the Mitroflow prosthesis and 99% for the Carpentier at 12 years, with the most obvious differences being in sizes Nos. 19 and 21 (Nielsen et al., 2016). An essential data of this work is that the age, percentage of women, small prostheses (Nos. 19 and 21), previous surgery, and EuroSCORE all are higher in the group of patients who received a Mitroflow prosthesis than in the Carpentier group. It does not seem strange that comparing different groups, the results of mortality and SVD are different.

In a more recent study in our environment, the Mitroflow and Carpentier prostheses are compared (Blasco-Lucas et al., 2017). Cardiovascular mortality observed at 8 years is higher in the Mitroflow group (25%) than in the Carpentier group (12%), while the cumulative rate of SVD at 9 years is 32% in the Mitroflow prosthesis and 6% in the Carpentier. Again, as in Nielsen's study, age, hypertension, smoking, native endocarditis, EuroSCORE, number of size No. 19 prostheses, and percentage of mismatch are higher in the Mitroflow group.

In our study, we observed higher mortality at 10 years in the group that received a Mitroflow prosthesis (8%) compared to Carpentier (29%). Applying the echocardiographic criteria for the diagnosis of SVD, we observed an actuarial rate of SVD for the Mitroflow prosthesis of 3.2% and 40% at 5 and 10 years, respectively, and for the Carpentier prosthesis 0.8% and 21.8% at the 5 and 10 years respectively. In the case of the Mitroflow prosthesis, these SVD values are similar to those observed in our environment (Mosquera et al., 2016) (Blasco-Lucas et al., 2017). On the contrary, the rate of SVD in the Carpentier prosthesis is higher than that of other studies carried out in Spain that used diagnostic criteria for SVD similar to our work (Blasco-Lucas et al., 2017).

In our work, like Nielsen and Blasco-Lucas, we could also observe that the population of patients who received a Mitroflow prosthesis was older, with more comorbidities, higher surgical risk, percentage of mismatches and percentage of small-size prostheses than the group that received a Carpentier prosthesis.

The published data and our results confirm that there may have been a significant bias when using Mitroflow prostheses with a tendency to implant this prosthesis in elderly patients, with the small annulus, with multiple comorbidities and higher surgical risk. Objectively, surgeons at the time of intervening on their patients preferred to use the Mitroflow prosthesis in this type of patient instead of implanting another type of bioprosthesis with higher durability, such as the Carpentier. The reason for this choice has already been argued

throughout this discussion: the Mitroflow bioprosthesis is smaller than the Carpentier and can be implanted without the need for aortic annulus enlargement in elderly high-risk patients.

The observed data confirm that the durability of the Mitroflow prosthesis is less than the Carpentier. The two questions that remain to be answered are: what would have happened in terms of mortality and durability if a Carpentier prosthesis had been implanted in this group of patients instead of a Mitroflow prosthesis? What would be the results if a randomized comparative study were conducted between the small sizes of the Mitroflow and Carpentier prostheses? (Balsam & DeAnda, 2017).

Nowadays, these questions are of little interest. The Mitroflow prosthesis has disappeared from the market, and its advantages in small aortic rings in elderly patients with high surgical risk have been surpassed by sutureless prostheses and by transcatheter prostheses. In any case, there will always be the possibility of performing a surgical enlargement of the aortic annulus.

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6. CONCLUSIONS

1. The frequency of structural deterioration of bioprostheses in the aortic position in our environment is 4% and 22% at 5 and 10 years, respectively.

2. The Mitroflow bioprosthesis shows earlier and more intense structural deterioration than the Carpentier bioprosthesis.

3. The Mitroflow bioprosthesis is implanted in older patients, with more comorbidities, smaller aortic annulus size, and higher surgical risk than the Carpentier bioprosthesis.

4. The structural deterioration of the prostheses is inversely proportional to the age of the patients.

5. After aortic valve replacement by bioprosthesis, the related factors to higher long-term mortality include age, the presence of atrial fibrillation, the implantation of a Mitroflow bioprosthesis, and chronic renal failure.

6. The size of the implanted prosthesis and the presence of a moderate mismatch between the effective valve orifice of the prosthesis and the patient do not influence long-term evolution.

7. In our environment, there is great heterogeneity in the protocols for clinical and echocardiographic postoperative follow-up in patients with bioprostheses, which makes it impossible to know the rate of structural deterioration both for clinically relevant and asymptomatically.

8. Infectious endocarditis continues to be a relevant complication in patients with valve prostheses, which is why it is necessary to take extreme measures of prophylaxis and consider it in the differential diagnosis of febrile processes in the elderly.

9. Periodic echocardiographic follow-up of patients with bioprostheses, including asymptomatic patients, is necessary to facilitate early diagnosis of structural deterioration.

1. La frecuencia de deterioro estructural de las bioprótesis en posición aórtica en nuestro medio se sitúa en el 4% y el 22% a los 5 y 10 años respectivamente.

2. La bioprótesis Mitroflow presenta un deterioro estructural más precoz e intenso que la bioprótesis Carpentier.

3. La bioprótesis Mitroflow se implanta en pacientes más ancianos, con más comorbilidades, menor tamaño del anillo aórtico y mayor riesgo quirúrgico que la bioprótesis Carpentier.

4. El deterioro estructural de las prótesis es inversamente proporcional a la edad de los pacientes.

5. Después del recambio valvular aórtico por bioprótesis los factores relacionados con una mayor mortalidad a largo plazo incluyen la edad, la presencia de fibrilación auricular, el implante de una bioprótesis Mitroflow y el fallo renal crónico.

6. El tamaño de la prótesis implantada y la presencia de desajuste moderado entre el orificio valvular efectivo protésico y el paciente no influyen en la evolución a largo plazo.

7. En nuestro medio existe una gran heterogeneidad en los protocolos de seguimiento postoperatorio clínico y ecocardiográfico en los pacientes portadores de bioprótesis que impide conocer la tasa de deterioro estructural tanto clínicamente relevante como asintomático.

8. La endocarditis infecciosa continúa siendo una complicación relevante en los pacientes portadores de prótesis valvulares por lo que es preciso extremar las medidas de profilaxis y considerarla en el diagnóstico diferencial de los procesos febriles en el anciano.

9.Es preciso realizar un seguimiento periódico ecocardiográfico de los pacientes con bioprótesis incluidos los asintomático para facilitar un diagnóstico precoz del deterioro estructural.

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8. ANNEXES

ANNEX 1

XUNTA DE GALICIA
CONSELLERÍA DE SANIDADE
Secretaría Xeral Técnica

Secretaría Técnica
Comité Autonómico de Ética da Investigación de Galicia
Secretaría Xeral. Consellería de Sanidade
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DITAME DO COMITÉ DE ÉTICA DA INVESTIGACIÓN DE SANTIAGO-LUGO

Juan Manuel Vázquez Lago, Secretario do Comité de Ética da Investigación de Santiago-Lugo

CERTIFICA:

Que este Comité avaliou na súa reunión do día 17/03/2015 o estudo:

Título: Deterioro estructural de las bioprótesis valvulares en posición aórtica: incidencia, factores de riesgo e impacto clínico
Promotor: Angel Luis Fernández González
Tipo de estudo: Outros
Versión:
Código do Promotor:
Código de Rexistro: 2015/209

E, tomando en consideración as seguintes cuestións:

- A pertinencia do estudo, tendo en conta o coñecemento dispoñible, así coma os requisitos legais aplicables, e en particular a Lei 14/2007, de investigación biomédica, o Real Decreto 1716/2011, de 18 de novembro, polo que se establecen os requisitos básicos de autorización e funcionamento dos biobancos con fins de investigación biomédica e do tratamento das mostras biolóxicas de orixe humana, e se regula o funcionamento e organización do Rexistro Nacional de Biobancos para investigación biomédica, a ORDE SAS/3470/2009, de 16 de decembro, pola que se publican as Directrices sobre estudos Posautorización de Tipo Observacional para medicamentos de uso humano, e a Circular nº 07/2004, investigacións clínicas con produtos sanitarios.
- A idoneidade do protocolo en relación cos obxectivos do estudo, xustificación dos riscos e molestias previsibles para o suxeito, así coma os beneficios esperados.
- Os principios éticos da Declaración de Helsinki vixente.
- Os Procedementos Normalizados de Traballo do Comité.

Emite un **INFORME FAVORABLE** para a realización do estudo **polo/a investigador/a do centro:**

Centros	Investigadores Principais
C.H. Universitario de Santiago	Angel Luis Fernández González

En Santiago de Compostela, a 17 de marzo de 2015
O secretario juan.manuel.vazquez.lago@sergas.es

Firmado digitalmente por juan.manuel.vazquez.lago@sergas.es
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Juan M. Vázquez Lago

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O CEI-SL recomenda corrixir a incongruencia atopada na páxina 3 do protocolo, no apartado "Diseño del estudio y metodología" onde no primeiro párrafo se informa "todos los pacientes sometidos a recambio valvular aórtico por bioprótesis en el Complejo Hospitalario Universitario de Santiago de Compostela entre el 1 de Enero de 2010 y el 1 de Enero de 2011" e no 2º párrafo "Los criterios de inclusión en el estudio serán pacientes de ambos sexos sometidos a recambio valvular aórtico por bioprótesis aislado o combinado con revascularización coronaria en el Hospital Clínico Universitario de Santiago entre el 1 de enero de 2000 y el 1 de enero de 2011". Polo tanto cómpre aclarar cal será o período de tempo de inclusión dos participantes.

ANNEX 2

XUNTA DE GALICIA
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COMITÉ DE ÉTICA DA INVESTIGACIÓN DE SANTIAGO-LUGO

Ante a solicitude de D. Ángel Luis Fernández González, Investigador Principal do estudo titulado:

"Deterioro estructural de las bioprótesis valvulares en posición aórtica: incidencia, factores de riesgo e impacto clínico"

Con código de rexistro CAEIG: 2015/209

de incluír como investigador colaborador a D. Zaid Alhamwy en dito estudo.

Resólvese

A inclusión de D. Zaid Alhamwy como investigador.

Para que así conste, asino o presente documento como secretario do CEI-SL e expídese novo ditame anexado no que se inclúe este novo investigador.

En Santiago de Compostela, a 23 de setembro de 2015
O secretario

NOMBRE VAZQUEZ LAGO JUAN MANUEL - NIF 44829259M

Juan M. Vázquez Lago

XUNTA DE GALICIA
CONSELLERÍA DE SANIDADE
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Juan Manuel Vázquez Lago, Secretario do Comité de Ética da Investigación de Santiago-Lugo

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- Os principios éticos da Declaración de Helsinki vixente.
- Os Procedementos Normalizados de Traballo do Comité.

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