



UNIVERSITÀ POLITECNICA DELLE MARCHE
Repository ISTITUZIONALE

Durability of Mitral Valve Bioprostheses: A Meta-Analysis of Long-Term Follow-up Studies

This is the peer reviewed version of the following article:

Original

Durability of Mitral Valve Bioprostheses: A Meta-Analysis of Long-Term Follow-up Studies / Malvindi, P. G.; Mastro, F.; Kowalewski, M.; Ringold, M.; Margari, V.; Suwalski, P.; Speziale, G.; Paparella, D.. - In: ANNALS OF THORACIC SURGERY. - ISSN 0003-4975. - 109:2(2020), pp. 603-611. [10.1016/j.athoracsur.2019.07.024]

Availability:

This version is available at: 11566/301663 since: 2024-12-03T16:19:05Z

Publisher:

Published

DOI:10.1016/j.athoracsur.2019.07.024

Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. The use of copyrighted works requires the consent of the rights' holder (author or publisher). Works made available under a Creative Commons license or a Publisher's custom-made license can be used according to the terms and conditions contained therein. See editor's website for further information and terms and conditions.

This item was downloaded from IRIS Università Politecnica delle Marche (<https://iris.univpm.it>). When citing, please refer to the published version.

(Article begins on next page)

The Annals of Thoracic Surgery

Durability of Mitral Valve Bioprostheses: A meta-analysis of long-term follow-up studies

--Manuscript Draft--

Manuscript Number:	ANNALS-19-00043R4
Article Type:	Review Article
Section/Category:	Adult Cardiac
Keywords:	mitral valve; Mitral valve replacement; prosthesis
Manuscript Classifications:	Mitral valve; Mitral valve replacement; Prosthesis
Corresponding Author:	Pietro Giorgio Malvindi, M.D., Ph.D Ospedale Santa Maria Bari, ITALY
First Author:	Pietro Giorgio Malvindi, M.D., Ph.D
Order of Authors:	Pietro Giorgio Malvindi, M.D., Ph.D Florinda Mastro, MD Mariusz Kowalewski, MD Margot Ringold, MD Vito Margari, MD Piotr Suwalski, MD, PhD Giuseppe Speziale, MD, PhD Domenico Paparella, MD
Manuscript Region of Origin:	ITALY
Abstract:	<p>Background. Porcine and pericardial valves exhibited similar freedom from structural valve deterioration after aortic valve replacement. Limited data exists regarding their durability at long-term follow-up in the mitral position.</p> <p>Methods. A literature search was performed through online databases. Papers reporting freedom from tissue valve deterioration after mitral valve replacement with a follow-up longer than five years were retrieved. Four porcine valves (Carpentier-Edwards, Hancock, Hancock II, Mosaic) and one pericardial prosthesis (Carpentier-Edwards) were the objects of the study. The structural valve deterioration rate (SVD) per year was calculated for each type of prosthesis. Kaplan-Meier curves and log-rank test analysis were performed to compare the long-term durability of porcine and pericardial valves.</p> <p>Results. Forty full-text papers including more than 15,000 patients were considered for the meta-analysis. Porcine valves were generally implanted in younger patients in the first period after their introduction. The mean age of the patients receiving a mitral bioprosthesis increased from 50 to 70 years over the decades. In patients operated after 1980 who had similar mean age at the time of implant, freedom from SVD was higher in the group of porcine valves with Mosaic prosthesis, showing the lowest rate of SDV. Long-term survival was higher for Mosaic porcine and Carpentier pericardial valves.</p> <p>Conclusions. In surgical populations that underwent mitral valve replacement after 1980 with new generation tissue valves and similar mean age at the implant time, we found, at long-term follow up, a higher freedom from SVD in the group of porcine prostheses.</p>

Durability of Mitral Valve Bioprostheses: A meta-analysis of long-term follow-up studies

Running head: durability of mitral valve bioprostheses

Pietro Giorgio Malvindi, MD, PhD¹, Florinda Mastro, MD², Mariusz Kowalewski, MD^{3,4,5}, Margot Ringold, MD², Vito Margari, MD¹, Piotr Suwalski, MD, PhD³, Giuseppe Speziale, MD, PhD⁶, Domenico Paparella, MD^{1,2}

1- GVM Care & Research, Department of Cardiovascular Surgery, Santa Maria Hospital, Bari – Italy

2- Department of Emergency and Organ Transplant, University of Bari Aldo Moro, Bari – Italy

3- Department of Cardiac Surgery, Central Clinical Hospital of the Ministry of Interior, Centre of Postgraduate Medical Education, Warsaw - Poland

4- Cardiothoracic Research Centre, Innovative Medical Forum, Bydgoszcz – Poland

5- Cardio-Thoracic Surgery Department, Heart and Vascular Centre, Maastricht University Medical Centre, Maastricht – The Netherland

6- GVM Care & Research, Department of Cardiovascular Surgery, Anthea Hospital, Bari – Italy

Presented at the STS 55th Annual Meeting, San Diego 27th-29th January 2019

Classification: mitral valve, mitral valve replacement, prosthesis

Word count: 5998

Corresponding author:

D Paparella

Santa Maria Hospital

Via de Ferrariis 22

70124, Bari–Italy

e-mail:domenico.paparella@uniba.it

Abstract

Background. Porcine and pericardial valves exhibited similar freedom from structural valve deterioration after aortic valve replacement. Limited data exists regarding their durability at long-term follow-up in the mitral position.

Methods. A literature search was performed through online databases. Papers reporting freedom from tissue valve deterioration after mitral valve replacement with a follow-up longer than five years were retrieved. Four porcine valves (Carpentier-Edwards, Hancock, Hancock II, Mosaic) and one pericardial prosthesis (Carpentier-Edwards) were the objects of the study. The structural valve deterioration rate (SVD) per year was calculated for each type of prosthesis. Kaplan-Meier curves and log-rank test analysis were performed to compare the long-term durability of porcine and pericardial valves.

Results. Forty full-text papers including more than 15,000 patients were considered for the meta-analysis. Porcine valves were generally implanted in younger patients in the first period after their introduction. The mean age of the patients receiving a mitral bioprosthesis increased from 50 to 70 years over the decades. In patients operated after 1980 who had similar mean age at the time of implant, freedom from SVD was higher in the group of porcine valves with Mosaic prosthesis, showing the lowest rate of SDV. Long-term survival was higher for Mosaic porcine and Carpentier pericardial valves.

Conclusions. In surgical populations that underwent mitral valve replacement after 1980 with new generation tissue valves and similar mean age at the implant time, we found, at long-term follow up, a higher freedom from SVD in the group of porcine prostheses.

Abstract word count: 245

Biological prosthetic heart valves were introduced for clinical use in the 1970s in order to overcome thromboembolic complications and the need for anticoagulation associated with mechanical prostheses. However, since their introduction, SVD has been the main drawback of tissue valves. During the following decades, several ameliorations have been proposed that address the treatment of biologic tissue, the assembling techniques and the stent properties, in order to provide better haemodynamic performances and longer durability. In this light, the introduction of pericardial prostheses was seen as a significant step toward better long-term outcomes (1).

Increasing evidence from long-term follow-up studies involving several types of tissue valves reported no significant difference concerning the durability between porcine and pericardial valves in the aortic position (2,3). Fewer data exist regarding mitral valve prostheses with mixed and conflicting conclusions as to whether there is any advantage in the use of pericardial valve over a porcine prosthesis (4,5,6,7). These results were affected by the choice of different prosthesis models and, in many cases, the presentation of limited follow-up time. Therefore, we retrieved long-term follow-up data of the durability of the most used and most studied tissue valves in the attempt to compare the SVD risk of porcine and pericardial prostheses in the mitral position.

Material and Methods

Literature search

A literature search was performed through online databases (i.e., PubMed, Cochrane, and Researchgate) about valve replacement in the mitral position with a biological prosthesis. The following keywords were used: *bioprosthesis; biological prosthesis; mitral valve replacement; mitral valve; porcine valve; pericardial valve.*

We identified 1,570 papers. We applied the following:

Inclusion criteria:

- 1) Papers on adult human subjects;
- 2) Written in English, French, and Spanish;
- 3) No restriction regarding the date of publication;

4) Providing evidence of at least one of these variables: diagnosis of SVD and reoperation due to SVD;

5) Focusing on the following prostheses:

- Pericardial: Carpentier-Edwards prosthesis (Edwards Lifesciences, Irvine, CA);
- Porcine: Carpentier-Edwards prosthesis 6625 and Carpentier-Edwards suprannular prosthesis 6650 (Edwards Lifesciences, Irvine, CA); Hancock prosthesis, Hancock II prosthesis, Mosaic prosthesis (Medtronic. Inc, Minneapolis, MN)

6) Presenting data with follow-ups longer than five years.

Exclusion criteria:

1) In vitro or animal studies;

2) Research on a cadaver;

3) Paediatric subjects;

4) Case reports, commentaries, or letters to the editor;

5) Analysis of the results of different mitral bioprostheses (i.e., Sorin/Livanova bioprosthesis, Medtronic pericardial, St Jude bioprosthesis, transcatheter valves);

6) Cardiac surgery excluding mitral operation.

Two independent reviewers (F.M. and M.R.) selected the studies for the inclusion and, among these, extracted studies and patients' characteristics of interest and relevant outcomes; divergences were resolved by consensus after discussion with three other reviewers (P.G.M., V.M. and D.P.).

The data extracted includes the following:

- Study period, number of patients, type of prosthesis, definition of SVD, modes of diagnosis of SVD, mean/median follow-up, and completeness of follow-up;
- Patients' characteristics: populations' mean age, gender, etiology, type of lesion of mitral valve disease, history of atrial fibrillation, redo cases, and associated procedures;
- Outcomes: early mortality, survival, and freedom from SVD of mitral prostheses.

Supplemental Figure 1 represents a search flow chart according to the rules specified by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (8); Supplemental Table 1 reports the PRISMA checklist.

Meta-analysis

STATA MP v13.0 software (StataCorp, College Station, TX) was used for all computations. The results are expressed as pooled untransformed proportions (hazard ratios (HR)) with 95% confidence intervals (CIs). First, analyses of the overall pooled HRs for the primary outcome and freedom from SVD over the complete follow-up period up to a maximum of 20 years were performed. Published estimates, if available, were verified and used in the meta-analysis. In case the crude respective HRs were not available from original studies, these were digitized using Engauge Digitizer 9.5 (Mark Mitchell, Torrance, CA, USA) and reconstructed as time-to-event data of individual studies using Cox regression and the algorithm specified by Guyot et al. (9) up to the longest available follow-up across all trials.

Second, concordance between the original and reconstructed time-to-event curves was assessed visually. The intraclass correlation coefficient for the concordance of HRs calculated from reconstructed data and the published HRs was determined; scatterplots were inspected visually, and the mean ratio of calculated and published HRs along with the 95% CI was determined. For the overall analysis, the longest follow-up was considered; conversely, for comparative analyses (e.g., comparison of different valve types for the endpoint SVD), we chose the most extended common follow-up duration to construct KM curves. The proportional hazard assumption was further examined after fitting a Cox model stratified by trial. The statistical inconsistency test $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the chi-square statistic and df is its degrees of freedom, was used to assess heterogeneity (10). Because of the high degree of heterogeneity anticipated among the non-randomized trials, an inverse variance (DerSimonian-Laird) random-effects model was applied as a more conservative approach for observational data accounting for between- and within-study variability. Heterogeneity was determined with estimates indicating a small (< 40%), a moderate (40–60%), and a large (> 60%) extent of heterogeneity and additionally assessed for endpoint freedom from SVD visually by constructing a funnel plot and by Egger's regression approach.

The studies were stratified a priori based on the valve type used (Carpentier-Edwards pericardial prosthesis, Carpentier-Edwards porcine prosthesis, Hancock prosthesis, Hancock II prosthesis and Mosaic prosthesis); event rates with 95% CIs derived from an analysis with adjusted models by person years, a measure incorporating trial duration, were used as summary statistics in order to better account for potential differences in the duration of the study. Absolute events rates were expressed as incident events per year. Whenever a single study reported median values and interquartile ranges instead of the mean \pm SD, the latter were approximated as described by Wan et al. (10). Sensitivity analyses were performed by excluding single studies from analyses, one at a time, and repeating the calculations. A two-tailed P value of less than 0.05 was considered statistically significant for all statistical tests employed.

The analysis protocol has been uploaded to the PROSPERO registry.

Results

Study selection

One thousand three hundred and forty-two records did not fulfill the inclusion criteria and were removed. The remaining 228 papers were assessed for eligibility, and another 183 studies were excluded mainly because they were consecutive separate analyses from the same center/experience/database. Further, five full-text papers were not entered in the final meta-analysis after the evaluation of the type and quality of data. In most of these cases, it was not possible to retrieve the SVD rate or freedom from SVD for the lone mitral bioprosthesis (i.e., papers with patients operated for aortic and mitral valve replacement) or SVD was studied in association with the interval time of age without providing the mean or median age of each subgroup.

Finally, 40 papers provided more than 15,000 patients for our study; in three cases, cumulative results for Hancock and Carpentier-Edwards porcine valves were reported; we used this data for the analysis between porcine groups vs. pericardial group. Table 1 provides a summary of the population data involved in the analysis. Supplemental Table 2 lists the 40 full-text papers considered for the meta-analysis.

SVD definition

In 23 of the 40 selected papers, SVD was defined according to the “Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations” of the STS/AATS committee published in 1988 (16) and in the following updated versions published in 1996 (18). The latter statement reports the following: “Structural valvular deterioration includes operated valve dysfunction or deterioration exclusive of infection or thrombosis as determined by reoperation, autopsy, or clinical investigation. The term structural deterioration refers to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components (eg, leaflets, chordae) of an operated valve”. The importance of imaging assessment has been better underlined in the following guidelines published in 2008 (65), “Clinical investigation should include periodic echocardiographic surveillance. Substantially increased regurgitation or stenosis of the operated valve over time should be reported with quantitative or semiquantitative methods”. Only one paper defined SVD according to this statement. Seven papers defined “degeneration”, “bio-degeneration”, and “primary tissue failure”, which were generally described as the presence of leaflet tear, stretching or creeping of the stent, or valvular obstruction by leaflet fibrosis or calcification. In the remaining 10 papers, a clear definition of intrinsic prosthesis failure was not reported; six of these full-texts were published before 1988.

SVD diagnosis

The papers included in the analysis provided a different characterization of SVD diagnosis (see Supplemental Table 2). Seventeen studies reported SVD diagnosis based on operative (i.e., explanted prostheses) or autopsy findings. In 23 cases, SVD diagnosis was based on clinical and/or imaging data or reoperation and autopsy findings. Among these papers, five studies clearly included SVD diagnosis based on ultrasound assessment even though patients were symptomatic or ultimately underwent a reoperation (34,39,40,48,50).

Long-term durability and survival

There was a trend through the decades to offer a bioprosthesis to older patients with a 20-year difference in mean age between study populations coming from the 1970s and the 1990s. Figure 1 illustrates the distribution

of mean patients' age according to study periods and models of prostheses. Details about mean age at the implantation time and mean follow-up time were reported in Table 1. Supplemental Figure 2 provides data about freedom from SVD for each type of prosthesis.

The analysis of patient populations operated after 1980 (table 2 for details) included Carpentier-Edwards porcine valves, Hancock II, Mosaic, and Carpentier-Edwards pericardial.

Freedom from SVD at 10-year and 15-year follow-ups were 84% and 67% for Carpentier-Edwards porcine, 84% and 66% for Hancock II, 93% and 80% for Mosaic, and 91% and 61% for Carpentier-Edwards pericardial valves (Figure 2). A high degree of heterogeneity was observed: $I^2 = 99.3\%$, $P < 0.001$; Egger's test: 10.14 (7.99–12.30); $P < 0.0001$ (Supplemental Figure 3). Considering the maximum follow-up of 15 years, there was no difference between Hancock II and Carpentier-Edwards porcine [HR 1.04 (0.86–1.25), $p = 0.688$] and Hancock II and Carpentier-Edwards pericardial [HR 0.97 (0.79–1.18), $p = 0.733$]. Mosaic valves demonstrated better durability: Hancock II vs. Mosaic HR 2.15 (1.54–2.99), $p < 0.001$; Carpentier-Edwards porcine vs. Mosaic HR 2.08 (1.54–2.81), $p < 0.001$; Carpentier-Edwards pericardial vs. Mosaic HR 2.22 (1.63–3.03), $p < 0.001$. Carpentier-Edwards porcine valves showed a lower risk of SVD compared to Carpentier-Edwards pericardial [HR 0.61 (0.53–0.69), $p < 0.001$].

Similar results were obtained through analyzing the series which included patients operated after 1980 and the papers reporting SVD diagnosis based on clinical and/or imaging data and/or operative and autopsy findings (Supplemental Figure 4). Supplemental Figure 5 shows a comparison between porcine and pericardial groups.

Survival curves for each prosthesis are shown in Figure 3: Hancock II vs. Carpentier-Edwards porcine: HR 0.83 (0.73–0.94), $p = 0.004$; Hancock II vs. Carpentier-Edwards pericardial: HR 1.33 (1.16–1.54), $p < 0.001$; Hancock II vs. Mosaic: HR 2.20 (1.84–2.63), $p < 0.001$; Carpentier-Edwards porcine vs. Carpentier-Edwards pericardial: HR 1.51 (1.36–1.67), $p < 0.001$; Carpentier-Edwards porcine vs. Mosaic: HR 2.35 (2.02–2.72), $p < 0.001$; Carpentier-Edwards pericardial vs. Mosaic: HR 1.51 (1.29–1.77), $p < 0.001$.

Owing to the sensitivity of the study, each single study was deleted, one at a time, and calculations repeated. However, no change in direction nor magnitude of the effects was demonstrated.

Comment

Mitral valve surgery has been increasingly performed over the last decade. Although valve repair has been reported feasible and effective in most patients, it is, of course, dependent on the etiology of valve pathologies and the pathogenic mechanisms leading to valve insufficiency (51). In the real-world practice, valve replacement represents more than 40% of procedures on the mitral valve (52); this finding has been constant over the last few years and involves patients with a mean age of 65 years (53). Similar to aortic valve replacement (54), we have assisted a progressive increase in the adoption of tissue valves over mechanical prostheses for mitral replacement (51,55). Even though the aging of the surgical population certainly played an important role, this trend also involved patients younger than 65 years (54). The expectation of better haemodynamic and longer durability derived by newer technologies and techniques of tissue treatment may have partly driven this shift to a preference towards biologic implants. Particularly, the introduction and progressive ameliorations of pericardial prostheses have been perceived as a step forward towards better outcomes.

However, at least for valve durability, scientific evidence does not support this assumption. Several papers, including a recent meta-analysis of long-term studies (2,3,5,7,56), found no difference in primary tissue failure, SVD or reoperation between porcine and pericardial valves in the aortic position. Insufficient data exists regarding mitral valve replacement. Few studies compared the durability of porcine and pericardial prostheses after mitral valve replacement, and included cohorts of patients with different age range at the implant time (7) and populations from different eras (5).

As underlined by Figure 1, we demonstrated that there was a trend over time towards a higher mean age in patients who received a mitral bioprosthesis, which translated in the 20-year mean age gap between patients undergoing mitral valve replacement in the early 1970s and patients operated in the last two decades. There are three reasons for this finding: a) adoption of mechanical prostheses in younger patients soon after the first pieces of evidence of early failure of tissue valves associated with lower age; b) the progressive spread, from the 1980s, of repair techniques in the treatment of degenerative mitral regurgitation that generally affects a younger population; and c) the aging of the global cardiac surgery population. Because patient's age at the implantation time is a well-recognized risk factor for tissue valve failure/SVD (17,19,24,29,48,49), someone

could reasonably argue about a protective age effect on longer durability of prostheses implanted in older patients in the surgical series of the 1980s–1990s and over.

Alongside differences in patients' age, another important aspect regards the introduction in the same period of anticalcification treatment, low-pressure fixation and flexible stents aiming better performances and longer durability. In order to overcome these limitations, we thought that the selection of a particular cut-off of patients' age or the exclusion of some series according to the types of prosthesis implanted would have been arbitrary and probably would not have intercepted the changes in surgical indication and medical management. Therefore, we looked at the surgical experiences coming from the 1980s and the following decades and found that these series included populations of patients with similar age, 64 years for porcine and 65 years for pericardial. The porcine prostheses implanted over this period were second generation Hancock II and Carpentier-Edwards and third generation Mosaic valves. The exclusion of Hancock valves that are no longer used provided a more relevant picture for the contemporary practice. A direct comparison of outcomes between old and newer technologies is difficult due to many clinical and historical variables (i.e., patients' characteristics, associated medical therapy and anticoagulation therapy protocols); however, the study of modalities of failure could suggest whether any proposed amelioration had a positive impact on valve durability. Pericardial valves fail in more than 75% of the cases because of calcification-related leaflets deterioration (4,20,48,57), a process starting already in the first decade and leading to progressive leaflet degeneration usually complicated by prosthesis stenosis. Porcine valves present similar degeneration in a minority of the cases (far less than 50%) (4,15,21), while more commonly they are affected by calcified leaflets complications or non-calcium-related leaflets tears and dehiscence (50–75% of the cases) (4,7,15,58,59,60,61). These latter mechanical/stress-induced lesions (24,33), also highlighted by finite-element analyses and histological studies (62,63,64), have been invariably reported in porcine prostheses implanted in mitral position (58,59). Its occurrence after a mean period of 8 to 10 years after implant, as seen in long-term observational studies including first generation porcine valves (4,5,7,12,13,15,24,25,33), may explain the divergence of SVD curves between pericardial and porcine mitral prostheses. Modalities of failure changed over time, as seen with the introduction of “reduced trimming” for the Carpentier-Edwards 6650 (20) and the tissue treatment for Hancock II (58). Mosaic valve represents a further evolution, and no leaflet tear or disruption have been reported in long-term follow-up series (41). These shreds of evidence are still limited and derived from studies

that have a maximum follow-up of 5 years (39,40,50), with few patients followed for more than 15 years (41) and including populations with higher mean age compared to the other prostheses. However, alongside an outstanding durability, these papers also reported a satisfactory long-term survival in Mosaic valve recipients, thus including a high proportion of patients at risk of developing prosthesis degeneration during the observational period and providing noteworthy imaging follow-ups besides clinical and surgical findings.

A highly variable panel of definitions regarding valve failure and different methodology approaches could be expected while attempting analysis of papers published across four decades. We found, however, that most of the studies aligned with the definition of SVD provided in the STS/AATS guidelines (16,18,65). Diagnosis of SVD was derived from clinical evaluation, or as described at surgical explant or autopsy. Seventeen of the analyzed full-texts reported freedom from SVD at the explant, while 23 papers provided results of freedom from SVD diagnosis including clinical, ultrasound, operative and autopsy findings. The evaluation of valve deterioration based only on the surgical explant of the prosthesis may underestimate the incidence of a clinically relevant SVD and may not account for patients with known SVD considered not fit or at high risk for reoperation. Consequently, we performed an analysis restricted to papers reporting an endpoint of durability characterized by a more comprehensive SVD diagnosis (i.e., clinical, imaging and explant findings). The results confirmed the findings from the general analysis and supported the evidence that, throughout the selected experiences, a reoperation was almost invariably performed in all the patients diagnosed with mitral prosthesis SVD.

The pathogenetic mechanisms of failure could influence the timing of SVD diagnosis as a sudden tear of a leaflet may hesitate in acute symptoms of mitral regurgitation while a progressive calcification may cause delayed symptoms of mitral stenosis. Unfortunately, sparse data was available in terms of ultrasound evaluation from the studies included in our analyses. Possibly, a more extended period of patients' observation and evaluation of SVD based on routine imaging follow-ups could further affect the estimate of degeneration in favor of porcine valves compared to pericardial mitral prostheses.

Mortality is a competing risk factor for SVD; poor survival and inclusion of elderly patients could underestimate the risk of valve failure since it occurs in a non-linear pattern with an acceleration after the first

decade. These elements could represent possible biases for all the papers evaluated and then included in our analysis.

In surgical populations that underwent mitral valve replacement after 1980 with new generation tissue valves and similar mean age at the implant time, we found, at long-term follow-up, a higher freedom from SVD in the group of porcine prostheses. The inclusion of cohorts of patients presenting difference in demographic characteristics, preoperative features and early and long-term survival, as well as operated on diverse surgical and medical eras, does not allow a direct comparison of durability of different tissue valves. Other underlying mechanisms remain to be studied and elucidated, including patients' selection, the timing of surgery and the effect of improved haemodynamic. The lower survival rate in patients with Hancock II and Carpentier-Edwards porcine valves could have resulted in an underestimation of the degeneration of these prostheses when compared with Carpentier-Edwards pericardial and Mosaic porcine valves. On the other hand, a slightly higher age at the implant and more appropriate surgical and medical protocols could have reasonably contributed, in association with new achievements in valve design and manufacture, to the improved outcomes in patients who received a Mosaic prosthesis. Despite all these limitations, the evidence derived from more recent experiences and modern practice provided the lowest rate of SVD and a satisfactory long-term survival and represented the most reliable picture of the contemporary results in patients undergoing mitral valve replacement. These last findings should be regarded so far as the long-term durability reference to emerging surgical and non-surgical technologies in mitral valve surgery.

References

- 1 - Pellerin M, Mihaileanu S, Couëttil JP, et al. Carpentier-Edwards pericardial bioprosthesis in aortic position: long-term follow-up 1980 to 1994. *Ann Thorac Surg* 1995;60:S292-5
- 2 - Wang M, Furnary AP, Li H, Grunkmeier GL. Bioprosthetic aortic valve durability: a meta-regression of published studies. *Ann Thorac Surg* 2017;104:1080-7
- 3 - Hickey GL, Grant SW, Bridgewater B, et al. A comparison of outcomes between bovine pericardial and porcine valves in 38040 patients in England and Wales over 10 years. *Eur J Cardiothorac Surg* 2015;47:1067-74
- 4 - Jamieson WR, Marchand MA, Pelletier CL, et al. Structural valve deterioration in mitral replacement surgery: comparison of Carpentier-Edwards supra-annular porcine and perimount pericardial bioprostheses. *J Thorac Cardiovasc Surg* 1999;118:297-305
- 5 - Grunkmeier GL, Furnary AP, Wu Y, Wang L, Starr A. Durability of pericardial versus porcine bioprosthetic heart valves. *J Thorac Cardiovasc Surg* 2012;144:1381-6
- 6 - Chaudhry MA, Raco L, Muriithi EW, Bernacca GM, Tolland MM, Wheatley DJ. Porcine versus pericardial bioprostheses: eleven-year follow up of prospective randomized trial. *J Heart Valve Dis* 2000;9:429-37
- 7 - Pelletier LC, Carrier M, Leclerc Y, Lepage G, deGuise P, Dyrda I. Porcine versus pericardial bioprostheses: a comparison of late results in 1593 patients. *Ann Thorac Surg* 1989;47:352-61
- 8 - Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;169:467-473
- 9 - Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;1:12:9
- 10 - Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560
- 11 - Wan X, Wang W, Liu J et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14:135

- 12 - Al-Khaja N, Belhoul A, Larsson S, Roberts D. Eleven years' experience with Carpentier-Edwards biological valves in relation to survival and complications. *Eur J Cardiothorac Surg* 1989;3:305-311
- 13 – Bernal JM, Rabasa JM, Lopez R, Nistal JF, Mufiiz R, Revuelta JM. Durability of the Carpentier-Edwards Porcine Bioprosthesis: Role of Age and Valve Position. *Ann Thorac Surg* 1995;60:S248-52
- 14 - Soots G, Stankowiak C, Warembourg H Jr, et al. Durability of the Carpentier-Edwards porcine bioprosthesis in aortic or mitral positions. 10 years' results on 458 surgically treated cases. *Ann Chir* 1989;43:616-23
- 15 – Akins CW, Carroll DL, Buckley MJ, Daggett WM, Hilgenberg AD, Austen WG. Late results with Carpentier-Edwards porcine bioprosthesis. *Circulation* 1990;82(5 Suppl):IV65-74
- 16 - Edmunds LH Jr, Cohn LH, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. *Ann Thorac Surg* 1988;46:257-9
- 17 - Jamieson WR, Burr LH, Janusz MT, et al. Carpentier-Edwards standard and supraannular porcine bioprostheses: comparison of technology. *Ann Thorac Surg* 1999;67:10 –7
- 18 - Edmunds LH Jr, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. The American Association for Thoracic Surgery, Ad Hoc Liaison Committee for standardizing definitions of prosthetic heart valve morbidity. *Ann Thorac Surg* 1996;62:932–5
- 19 - Fiane AE, Saatvedt K, Svennevig JL. Carpentier-Edwards bioprosthesis. Experiences of 17 years with analysis of risk factors of early mortality. *Scand Cardiovasc J.* 1997;31(1):39-44
- 20 - Jamieson WR, Gudas VM, Burr LH, et al. Mitral valve disease: if the mitral valve is not reparable/failed repair, is bioprosthesis suitable for replacement? *Eur J Cardiothorac Surg* 2009;35:104-10
- 21 - Yamak B, Sener E, Kiziltepe U, Mavitas B, Tasdemir O, Bayazit K. Late results of mitral valve replacement with Carpentier-Edwards high profile bioprosthesis in young adults. *Eur J Cardiothorac Surg* 1995;9:335-41

- 22 - Louagie Y, Noirhomme P, Aranguis E, et al. Use of the Carpentier-Edwards porcine bioprosthesis: assessment of a patient selection policy. *J Thorac Cardiovasc Surg* 1992;104:1013-24
- 23 - Geha AS, Holter AR, Langou RA, Laks H, Hammond GL. Dysfunction and thromboembolism associated with cardiac valve xenografts in adults. *Circulation* 1981;64:II172-7
- 24 - Jones EL, Weintraub WS, Craver JM, et al. Ten-year experience with the porcine bioprosthetic valve: interrelationship of valve survival and patient survival in 1,050 valve replacements. *Ann Thorac Surg* 1990;49:370-83; discussion 383-4
- 25 - Fann JI, Miller DC, Moore KA, et al. Twenty-year clinical experience with porcine bioprostheses. *Ann Thorac Surg* 1996;62:1301-11
- 26 - Perier P, Deloche A, Chauvaud S, et al. A 10-year comparison of mitral valve replacement with Carpentier-Edwards and Hancock porcine bioprostheses. *Ann Thorac Surg* 1989;48:54-9
- 27 - Burr LH, Jamieson WR, Munro AI, et al. Structural valve deterioration in elderly patient populations with the Carpentier-Edwards standard and supra-annular porcine bioprostheses: a comparative study. *J Heart Valve Dis* 1992;1:87-91
- 28 - Cobanoglu A, Jamieson WR, Miller DC, et al. A tri-institutional comparison of tissue and mechanical values using a patient-oriented definition of "treatment failure". *Ann Thorac Surg* 1987;43:245-53
- 29 - Cohn LH, Collins JJ Jr, DiSesa VJ, et al. Fifteen-year experience with 1678 Hancock porcine bioprosthetic heart valve replacements. *Ann Surg* 1989;210:435-42
- 30 - Bortolotti U, Milano A, Mazzucco A, et al. Extended follow-up of the standard Hancock porcine bioprosthesis. *J Card Surg* 1991;6:544-9
- 31 - Gallo I, Nistal F, Artiñano E. Six- to ten-year follow-up of patients with the Hancock cardiac bioprosthesis. Incidence of primary tissue valve failure. *J Thorac Cardiovasc Surg* 1986;92:14-20
- 32 - Bernal JM, Rabasa JM, Cagigas JC, Echevarria JR, Carrion MF, Revuelta JM. Valve-related complications with the Hancock I porcine bioprosthesis. A twelve- to fourteen-year follow-up study. *J Thorac Cardiovasc Surg* 1991;101:871-80

- 33 - Burdon TA, Miller DC, Oyer PE, et al. Durability of porcine valves at fifteen years in a representative North American patient population. *J Thorac Cardiovasc Surg* 1992;103:238-51
- 34 - Kawachi Y, Tanaka J, Tominaga R, Kinoshita K, Tokunaga K. More than ten years' follow-up of the Hancock porcine bioprosthesis in Japan. *J Thorac Cardiovasc Surg* 1992;104:5-13
- 35 - Bortolotti U, Milano A, Mossuto E, Mazzaro E, Thiene G, Casarotto D. Porcine valve durability: a comparison between Hancock standard and Hancock II bioprostheses. *Ann Thorac Surg* 1995;60:S216-20
- 36 - Martinell J, Fraile J, Artiz V, Moreno J, Rábago G. Long-term comparative analysis of the Björk-Shiley and Hancock valves implanted in 1975. *J Thorac Cardiovasc Surg* 1985;90:741-9
- 37 - Milano A, Bortolotti U, Mazzucco A, et al. Mitral valve replacement with the Hancock, Björk-Shiley and Lillehei-Kaster prostheses. A comparison based on a 15-year follow-up. *Eur J Cardiothorac Surg* 1989;3:312-9
- 38 - Rizzoli G, Bottio T, Thiene G, Toscano G, Casarotto D. Long-term durability of the Hancock II porcine bioprosthesis. *J Thorac Cardiovasc Surg* 2003;126:66-74
- 39 - Thomson DJ, Jamieson WR, Dumesnil JG, et al. Medtronic Mosaic porcine bioprosthesis: midterm investigational trial results. *Ann Thorac Surg* 2001;71:S269-72
- 40 - Fradet GJ, Bleese N, Burgess J, Cartier PC. Mosaic valve international clinical trial: early performance results. *Ann Thorac Surg* 2001;71:S273-7
- 41 - Rieß FC, Fradet G, Lavoie A, Legget M. Long-Term Outcomes of the Mosaic Bioprosthesis. *Ann Thorac Surg* 2018;105:763-769
- 42 - Hartz RS, Fisher EB, Finkelmeier B, et al. An eight-year experience with porcine bioprosthetic cardiac valves. *J Thorac Cardiovasc Surg* 1986;91:910-7
- 43 - Cohn LH, Allred EN, Cohn LA, et al. Early and late risk of mitral valve replacement. A 12 year concomitant comparison of the porcine bioprosthetic and prosthetic disc mitral valves. *J Thorac Cardiovasc Surg* 1985;90:872-81

- 44 - Czer LS, Matloff JM, Chaux A, DeRobertis MA, Gray RJ. Comparative clinical experience with porcine bioprosthetic and St. Jude valve replacement. *Chest* 1987;91:503-14
- 45 - Murakami T, Eishi K, Nakano S, et al. Aortic and mitral valve replacement with the Carpentier-Edwards pericardial bioprosthesis: 10-year results. *J Heart Valve Dis* 1996;5:45-9
- 46 - Poirer NC, Pelletier LC, Pellerin M, Carrier M. 15-year experience with the Carpentier-Edwards pericardial bioprosthesis. *Ann Thorac Surg* 1998;66:S57-61
- 47 - Marchand M, Aupart M, Norton R, et al. Twelve-year experience with Carpentier-Edwards PERIMOUNT pericardial valve in the mitral position: a multicenter study. *J Heart Valve Dis* 1998;7:292-8
- 48 - Bourguignon T, Bouquiaux-Stablo AL, Loardi C, et al. Very late outcomes for mitral valve replacement with the Carpentier-Edwards pericardial bioprosthesis: 25-year follow-up of 450 implantations. *J Thorac Cardiovasc Surg* 2014;148:2004-2011
- 49 - David TE, Ivanov J, Armstrong S, Feindel CM, Cohen G. Late results of heart valve replacement with the Hancock II bioprosthesis. *J Thorac Cardiovasc Surg* 2001;121:268-77
- 50 - Eichinger WB, Botzenhardt F, Gunzinger R, et al. European experience with the Mosaic bioprosthesis. *J Thorac Cardiovasc Surg* 2002;124:333-9
- 51 - Gammie JS, Chikwe J, Badhwar V, et al. Isolated Mitral Valve Surgery: The Society of Thoracic Surgeons Adult Cardiac Surgery Database Analysis. *Ann Thorac Surg* 2018;106:716-727
- 52 - Jacobs JP, Shahian DM, D'Agostino RS, et al. The Society of Thoracic Surgeons National Database 2018 Annual Report. *Ann Thorac Surg* 2018;106:1603-1611
- 53 - 12. The Society for Cardiothoracic Surgery in Great Britain & Ireland. Blue Book Online. <http://www.bluebook.scts.org>
- 54 - Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. *J Thorac Cardiovasc Surg* 2015;149:1262-9.e3

- 55 - Goldstone AB, Chiu P, Baiocchi M, et al. Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. *N Engl J Med* 2017;377:1847-1857
- 56 - Ganapathi AM, Englum BR, Keenan JE, et al. Long-Term Survival After Bovine Pericardial Versus Porcine Stented Bioprosthetic Aortic Valve Replacement: Does Valve Choice Matter? *Ann Thorac Surg* 2015;100:550-9
- 57 - Marchand MA, Aupart MR, Norton R, et al. Fifteen-year experience with the mitral Carpentier-Edwards PERIMOUNT pericardial bioprosthesis. *Ann Thorac Surg* 2001;71:S236-9
- 58 - Bottio T, Thiene G, Pettenazzo E, et al. Hancock II bioprosthesis: a glance at the microscope in mid-long-term explants. *J Thorac Cardiovasc Surg* 2003;126:99-105
- 59 - Bottio T, Valente M, Rizzoli G, et al. Commissural dehiscence: a rare and peculiar cause of porcine valve structural deterioration. *J Thorac Cardiovasc Surg* 2006;132:1017-22
- 60 - Naqvi TZ, Siegel RJ, Buchbinder NA, et al. Echocardiographic and pathologic features of explanted Hancock and Carpentier-Edwards bioprosthetic valves in the mitral position. *Am J Cardiol* 1999;84:1422-7
- 61 - Bloomfield P, Kitchin AH, Wheatley DJ, Walbaum PR, Lutz W, Miller HC. A prospective evaluation of the Bjork-Shiley, Hancock, and Carpentier-Edwards heart valve prostheses. *Circulation* 1986;73:1213-1222
- 62 - Sabbah HN, Hamid MS, Stein PD. Mechanical stresses on closed cusps of porcine bioprosthetic valves: correlation with sites of calcification. *Ann Thorac Surg* 1986;42:93-96
- 63 - Sabbah HN, Hamid MS, Stein PD. Estimation of mechanical stresses on closed cusps of porcine bioprosthetic valves: effects of stiffening, focal calcium and focal thinning. *Am J Cardiol* 1985;55:1091-1096
- 64 - Stein PD, Kemp SR, Riddle JM, Lee MW, Lewis JW, Magilligan DJ. Relation of calcification to torn leaflets of spontaneously degenerated porcine bioprosthetic valves. *Ann Thorac Surg* 1985;40:175-180
- 65 - Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *Ann Thorac Surg* 2008;85:1490-5

Table 1. Populations' data

Valve types	CE pericardial	Overall porcine	CE porcine	Hancock	Hancock II	Mosaic
Series (n.)	5	34	18	11	2	4
Patients (n.)	1143	14072	7026	4829	424	940
Mean age~ (y)	65.2	57.7	59.5	53.2	63.6	68.0
Early mortality (%)	4.7	8.9	9	10	8.7	3.7
Mean FU# (y)	6.42	6.29	5.97	7.28	7.52	3.90

~ $\sum(\text{mean age} \times \text{number of patients}) / \sum \text{number of patients}$

$\sum(\text{mean FU} \times \text{number of patients}) / \sum \text{number of patients}$

Table 2. Data of populations operated after 1980

Valve types	CE pericardial	Overall porcine	CE porcine	Hancock	Mosaic
	Overall pericardial			II	
Series (n.)	5	9	3	2	4
Patients (n.)	1143	2725	1361	424	940
Mean age~ (y)	65.2	64.1	61.5	63.5	68.0
Early mortality (%)	4.7	7.6	9.9	8.7	3.7
Mean FU# (y)	6.42	5.84	6.53	7.41	3.90

~ $\sum(\text{mean age} \times \text{number of patients}) / \sum \text{number of patients}$

$\sum(\text{mean FU} \times \text{number of patients}) / \sum \text{number of patients}$

Figure legends

Figure 1. Distribution of mean age at the implantation time according to study periods (x axis) and types of tissue valve.

Figure 2. Freedom from SVD according to each prosthesis from series including populations of patients operated after 1980.

Figure 3. Kaplan-Meier curves of survival for porcine and pericardial valves implanted after 1980.

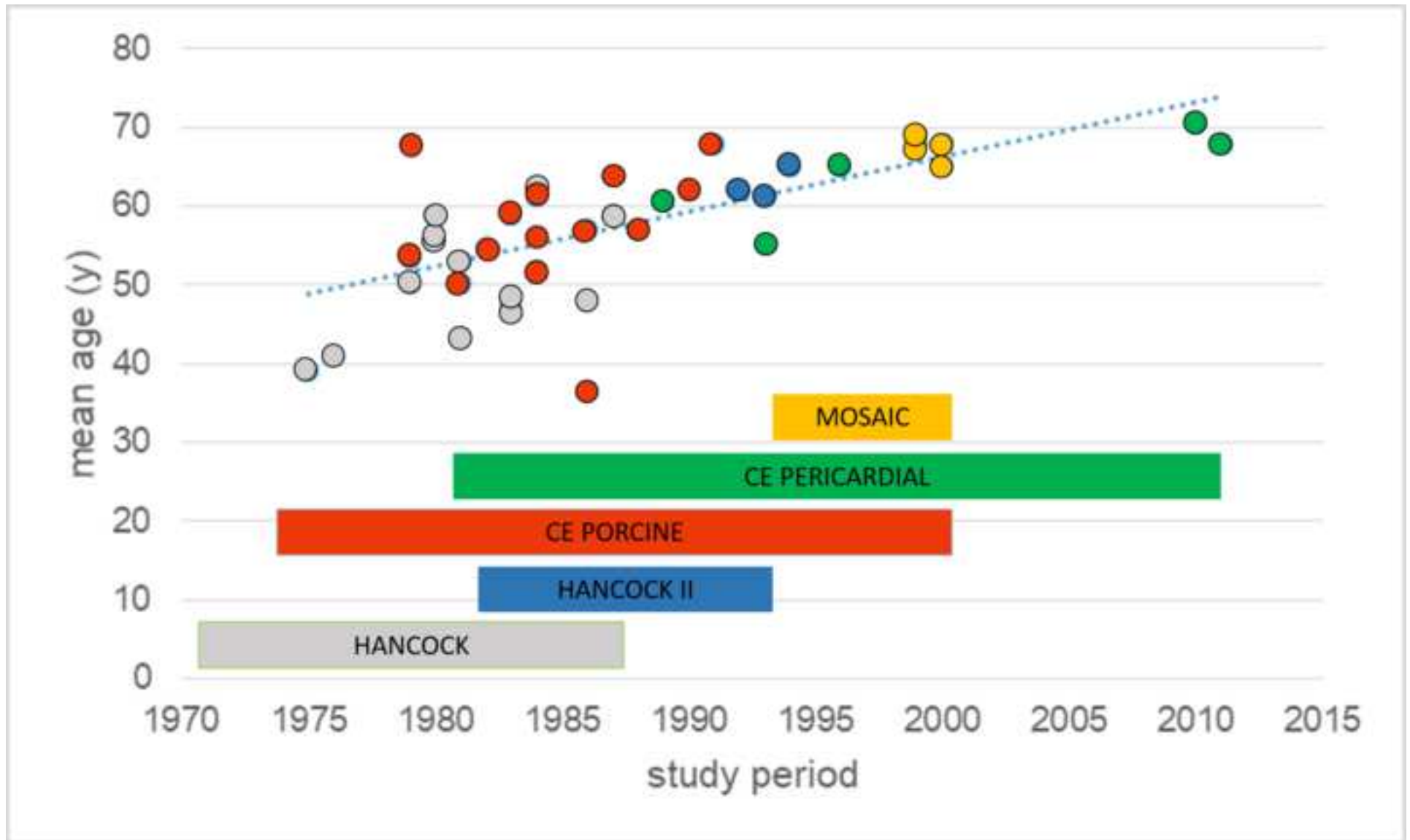
Supplemental figure 1. Flow chart of literature search according to PRISMA guidelines

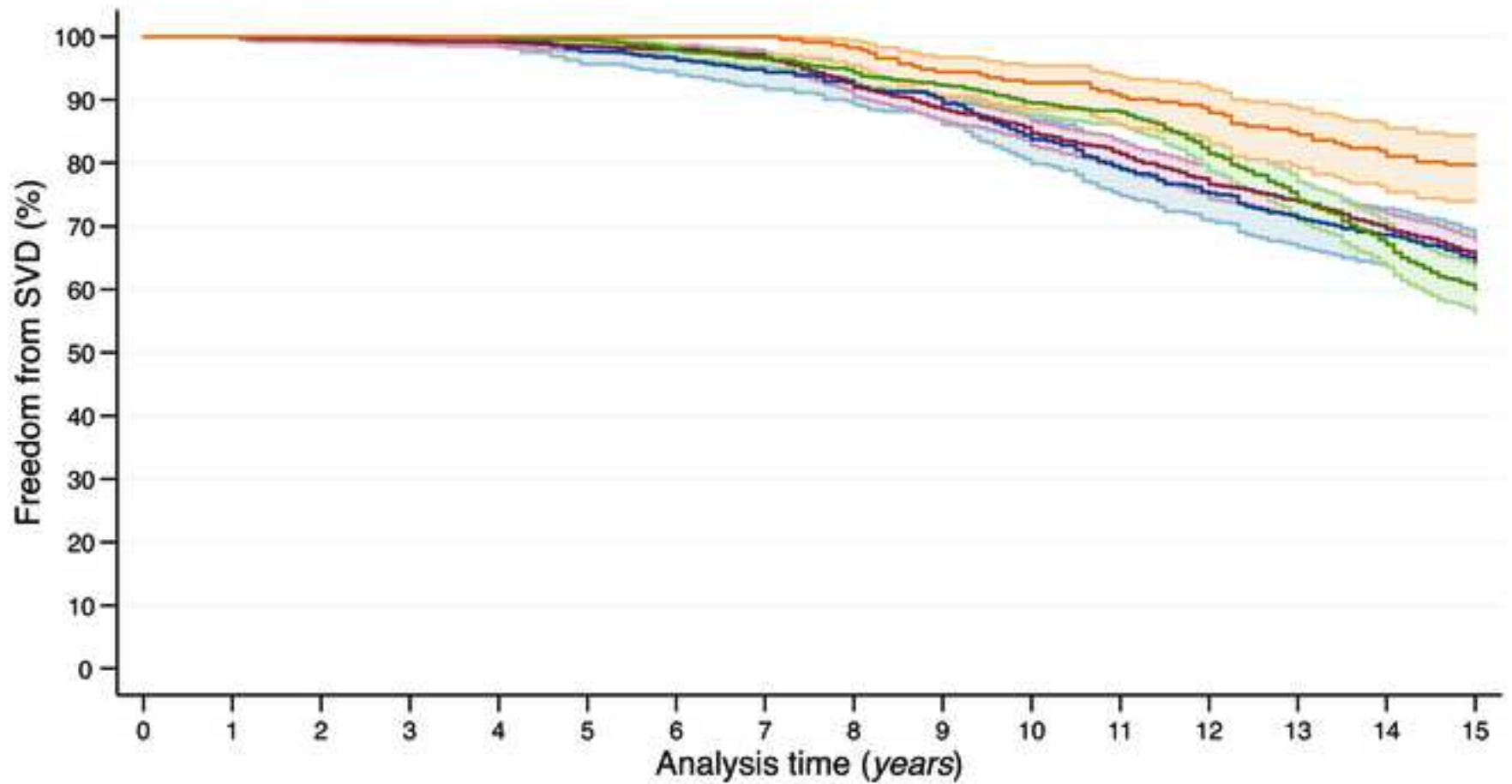
Supplemental figure 2. Freedom from structural valve deterioration at 10-year and 15-year was 72% and 38% for Hancock, 84% and 66% for Hancock II, 78% and 51% for Carpentier-Edwards porcine, 93% and 80% for Mosaic, 91% and 61% for Carpentier-Edwards pericardial valve. Freedom from SVD for pericardial (mean age 65.2 years) and porcine (mean age 57.7 years) valves was 91% and 74% respectively at 10-year, 61% and 50% respectively at 15-year follow-up; log-rank test pericardial vs porcine $p < 0.001$ (HR 0.72; CI: 0.65-0.79).

Supplemental figure 3. Heterogeneity funnel plot.

Supplemental figure 4. Kaplan-Meier curves of freedom from SVD for porcine and pericardial valves implanted after 1980 according to SVD diagnosis including clinical, imaging and explant findings. Hancock II vs Carpentier-Edwards porcine: HR 1.35(0.99-1.84), $p = 0.053$; Hancock II vs Carpentier-Edwards pericardial: HR 1.11(0.81-1.53), $p = 0.518$; Hancock II vs Mosaic: HR NA, $p = \text{NA}$; CE porcine vs CE pericardial: HR 0.52(0.45-0.61), $p < 0.001$; Carpentier-Edwards vs Mosaic: HR NA, $p = \text{NA}$; Carpentier-Edwards vs Mosaic: HR NA, $p = \text{NA}$. The analysis of Mosaic valve is limited at 7 years because the paper with a longer FU, up to 16 years, by Rieß et al.(41) reported the SVD diagnosis purely as explant at redo operation.

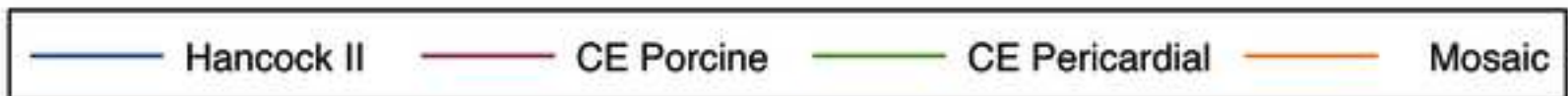
Supplemental figure 5. Freedom from SVD for porcine and pericardial valves implanted after 1980.

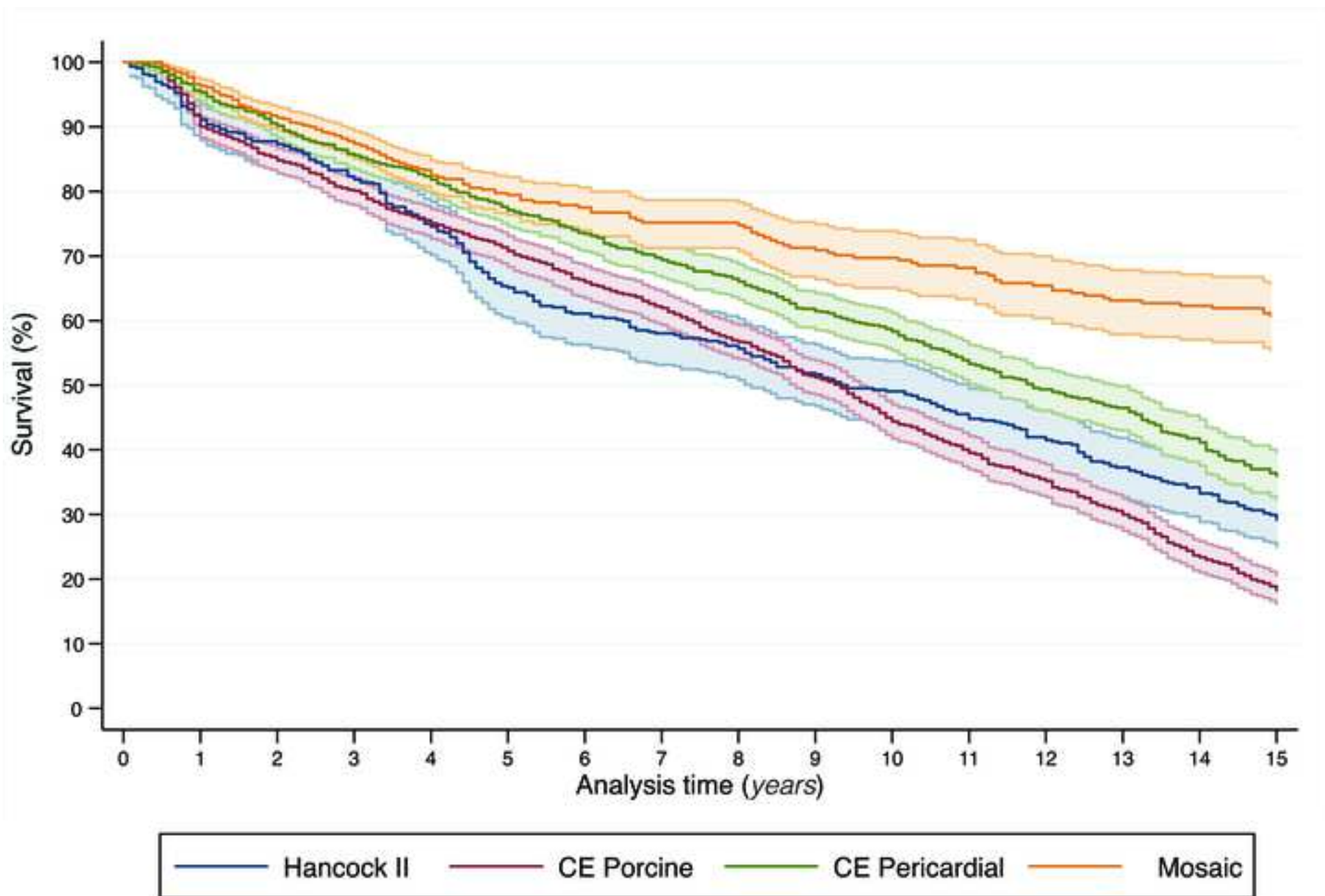





Number at risk:

Hancock II	424	424	424	424	424	414	410	402	393	383	358	337	320	304	291	276
CE Porcine	1,361	1,361	1,356	1,353	1,350	1,341	1,334	1,322	1,265	1,208	1,165	1,113	1,036	922	871	819
CE Pericardial	1,143	1,143	1,143	1,143	1,143	1,138	1,120	1,104	1,083	1,056	1,024	847	526	481	433	388
Mosaic	940	940	940	940	940	940	232	232	228	219	215	211	206	197	190	185







Click here to access/download

**Supplemental/Appendix material (suppl. tables, figures,
etc.)**

suppl table 1.doc





Click here to access/download

**Supplemental/Appendix material (suppl. tables, figures,
etc.)**

suppl table 2 revision3.docx






Click here to access/download

**Supplemental/Appendix material (suppl. tables, figures,
etc.)**

Suppl Figure 1.tif






Click here to access/download

**Supplemental/Appendix material (suppl. tables, figures,
etc.)**

Supplemental figure 2.tif





Click here to access/download

**Supplemental/Appendix material (suppl. tables, figures,
etc.)**

supplemental figure 3.tif





Click here to access/download

**Supplemental/Appendix material (suppl. tables, figures,
etc.)**

supplemental figure 4.tif





Click here to access/download

**Supplemental/Appendix material (suppl. tables, figures,
etc.)**

supplemental figure 5.tif



Title: Durability of Mitral Valve Bioprostheses: A meta-analysis of long-term follow-up studies**Running head:** durability of mitral valve bioprostheses

Pietro Giorgio Malvindi, MD, PhD¹, Florinda Mastro, MD², Mariusz Kowalewski, MD^{3,4,5}, Margot Ringold, MD², Vito Margari, MD¹, Piotr Suwalski, MD, PhD³, Giuseppe Speziale, MD, PhD⁶, Domenico Paparella, MD^{1,2}

1- GVM Care & Research, Department of Cardiovascular Surgery, Santa Maria Hospital, Bari – Italy

2- Department of Emergency and Organ Transplant, University of Bari Aldo Moro, Bari – Italy

3- Department of Cardiac Surgery, Central Clinical Hospital of the Ministry of Interior, Centre of Postgraduate Medical Education, Warsaw - Poland

4- Cardiothoracic Research Centre, Innovative Medical Forum, Bydgoszcz – Poland

5- Cardio-Thoracic Surgery Department, Heart and Vascular Centre, Maastricht University Medical Centre, Maastricht – The Netherland

6- GVM Care & Research, Department of Cardiovascular Surgery, Anthea Hospital, Bari – Italy

Presented at the STS 55th Annual Meeting, San Diego 27th-29th January 2019

Classification: mitral valve, mitral valve replacement, prosthesis**Word count:** 5988

Corresponding author:

D Paparella

Santa Maria Hospital

Via de Ferrariis 22

70124, Bari–Italy

Tel: 00390805040111

e-mail:domenico.paparella@uniba.it

Abstract

Background. Porcine and pericardial valves exhibited similar freedom from structural valve deterioration after aortic valve replacement. Limited data exists regarding their durability at long-term follow-up in the mitral position.

Methods. A literature search was performed through online databases. Papers reporting freedom from tissue valve deterioration after mitral valve replacement with a follow-up longer than five years were retrieved. Four porcine valves (Carpentier-Edwards, Hancock, Hancock II, Mosaic) and one pericardial prosthesis (Carpentier-Edwards) were the objects of the study. The structural valve deterioration rate (SVD) per year was calculated for each type of prosthesis. Kaplan-Meier curves and log-rank test analysis were performed to compare the long-term durability of porcine and pericardial valves.

Results. Forty full-text papers including more than 15,000 patients were considered for the meta-analysis. Porcine valves were generally implanted in younger patients in the first period after their introduction. The mean age of the patients receiving a mitral bioprosthesis increased from 50 to 70 years over the decades. In patients operated after 1980 who had similar mean age at the time of implant, freedom from SVD was higher in the group of porcine valves with Mosaic prosthesis, showing the lowest rate of SDV. Long-term survival was higher for Mosaic porcine and Carpentier pericardial valves.

Conclusions. In surgical populations that underwent mitral valve replacement after 1980 with new generation tissue valves and similar mean age at the implant time, we found, at long-term follow up, a higher freedom from SVD in the group of porcine prostheses.

Abstract word count: 245

Introduction

Biological prosthetic heart valves were introduced for clinical use in the 1970s in order to overcome thromboembolic complications and the need for anticoagulation associated with mechanical prostheses. However, since their introduction, SVD has been the main drawback of tissue valves. During the following decades, several ameliorations have been proposed that address the treatment of biologic tissue, the assembling techniques and the stent properties, in order to provide better haemodynamic performances and longer durability. In this light, the introduction of pericardial prostheses was seen as a significant step toward better long-term outcomes (1).

Increasing evidence from long-term follow-up studies involving several types of tissue valves reported no significant difference concerning the durability between porcine and pericardial valves in the aortic position (2,3). Fewer data exist regarding mitral valve prostheses with mixed and conflicting conclusions as to whether there is any advantage in the use of pericardial valve over a porcine prosthesis (4,5,6,7). These results were affected by the choice of different prosthesis models and, in many cases, the presentation of limited follow-up time. Therefore, we retrieved long-term follow-up data of the durability of the most used and most studied tissue valves in the attempt to compare the SVD risk of porcine and pericardial prostheses in the mitral position.

Material and Methods

Literature search

A literature search was performed through online databases (i.e., PubMed, Cochrane, and Researchgate) about valve replacement in the mitral position with a biological prosthesis. The following keywords were used: *bioprosthesis; biological prosthesis; mitral valve replacement; mitral valve; porcine valve; pericardial valve.*

We identified 1,570 papers. We applied the following:

Inclusion criteria:

- 1) Papers on adult human subjects;
- 2) Written in English, French, and Spanish;

- 3) No restriction regarding the date of publication;
- 4) Providing evidence of at least one of these variables: diagnosis of SVD and reoperation due to SVD;
- 5) Focusing on the following prostheses:
 - Pericardial: Carpentier-Edwards prosthesis (Edwards Lifesciences, Irvine, CA);
 - Porcine: Carpentier-Edwards prosthesis 6625 and Carpentier-Edwards suprannular prosthesis 6650 (Edwards Lifesciences, Irvine, CA); Hancock prosthesis, Hancock II prosthesis, Mosaic prosthesis (Medtronic. Inc, Minneapolis, MN)
- 6) Presenting data with follow-ups longer than five years.

Exclusion criteria:

- 1) In vitro or animal studies;
- 2) Research on a cadaver;
- 3) Paediatric subjects;
- 4) Case reports, commentaries, or letters to the editor;
- 5) Analysis of the results of different mitral bioprostheses (i.e., Sorin/Livanova bioprosthesis, Medtronic pericardial, St Jude bioprosthesis, transcatheter valves);
- 6) Cardiac surgery excluding mitral operation.

Two independent reviewers (F.M. and M.R.) selected the studies for the inclusion and, among these, extracted studies and patients' characteristics of interest and relevant outcomes; divergences were resolved by consensus after discussion with three other reviewers (P.G.M., V.M. and D.P.).

The data extracted includes the following:

- Study period, number of patients, type of prosthesis, definition of SVD, modes of diagnosis of SVD, mean/median follow-up, and completeness of follow-up;

- Patients' characteristics: populations' mean age, gender, etiology, type of lesion of mitral valve disease, history of atrial fibrillation, redo cases, and associated procedures;
- Outcomes: early mortality, survival, and freedom from SVD of mitral prostheses.

Supplemental Figure 1 represents a search flow chart according to the rules specified by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (8); Supplemental Table 1 reports the PRISMA checklist.

Meta-analysis

STATA MP v13.0 software (StataCorp, College Station, TX) was used for all computations. The results are expressed as pooled untransformed proportions (hazard ratios (HR)) with 95% confidence intervals (CIs). First, analyses of the overall pooled HRs for the primary outcome and freedom from SVD over the complete follow-up period up to a maximum of 20 years were performed. Published estimates, if available, were verified and used in the meta-analysis. In case the crude respective HRs were not available from original studies, these were digitized using Engauge Digitizer 9.5 (Mark Mitchell, Torrance, CA, USA) and reconstructed as time-to-event data of individual studies using Cox regression and the algorithm specified by Guyot et al. (9) up to the longest available follow-up across all trials.

Second, concordance between the original and reconstructed time-to-event curves was assessed visually. The intraclass correlation coefficient for the concordance of HRs calculated from reconstructed data and the published HRs was determined; scatterplots were inspected visually, and the mean ratio of calculated and published HRs along with the 95% CI was determined. For the overall analysis, the longest follow-up was considered; conversely, for comparative analyses (e.g., comparison of different valve types for the endpoint SVD), we chose the most extended common follow-up duration to construct KM curves. The proportional hazard assumption was further examined after fitting a Cox model stratified by trial. The statistical inconsistency test $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the chi-square statistic and df is its degrees of freedom, was used to assess heterogeneity (10). Because of the high degree of heterogeneity anticipated among the non-randomized trials, an inverse variance (DerSimonian-Laird) random-effects model was applied as a more

conservative approach for observational data accounting for between- and within-study variability. Heterogeneity was determined with estimates indicating a small (< 40%), a moderate (40–60%), and a large (> 60%) extent of heterogeneity and additionally assessed for endpoint freedom from SVD visually by constructing a funnel plot and by Egger's regression approach.

The studies were stratified a priori based on the valve type used (Carpentier-Edwards pericardial prosthesis, Carpentier-Edwards porcine prosthesis, Hancock prosthesis, Hancock II prosthesis and Mosaic prosthesis); event rates with 95% CIs derived from an analysis with adjusted models by person years, a measure incorporating trial duration, were used as summary statistics in order to better account for potential differences in the duration of the study. Absolute events rates were expressed as incident events per year. Whenever a single study reported median values and interquartile ranges instead of the mean \pm SD, the latter were approximated as described by Wan et al. (10). Sensitivity analyses were performed by excluding single studies from analyses, one at a time, and repeating the calculations. A two-tailed P value of less than 0.05 was considered statistically significant for all statistical tests employed.

The analysis protocol has been uploaded to the PROSPERO registry.

Results

Study selection

One thousand three hundred and forty-two records did not fulfill the inclusion criteria and were removed. The remaining 228 papers were assessed for eligibility, and another 183 studies were excluded mainly because they were consecutive separate analyses from the same center/experience/database. Further, five full-text papers were not entered in the final meta-analysis after the evaluation of the type and quality of data. In most of these cases, it was not possible to retrieve the SVD rate or freedom from SVD for the lone mitral bioprosthesis (i.e., papers with patients operated for aortic and mitral valve replacement) or SVD was studied in association with the interval time of age without providing the mean or median age of each subgroup.

Finally, 40 papers provided more than 15,000 patients for our study; in three cases, cumulative results for Hancock and Carpentier-Edwards porcine valves were reported; we used this data for the analysis between

porcine groups vs. pericardial group. Table 1 provides a summary of the population data involved in the analysis. Supplemental Table 2 lists the 40 full-text papers considered for the meta-analysis.

SVD definition

In 23 of the 40 selected papers, SVD was defined according to the “Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations” of the STS/AATS committee published in 1988 (16) and in the following updated versions published in 1996 (18). The latter statement reports the following: “Structural valvular deterioration includes operated valve dysfunction or deterioration exclusive of infection or thrombosis as determined by reoperation, autopsy, or clinical investigation. The term structural deterioration refers to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components (eg, leaflets, chordae) of an operated valve”. The importance of imaging assessment has been better underlined in the following guidelines published in 2008 (65), “Clinical investigation should include periodic echocardiographic surveillance. Substantially increased regurgitation or stenosis of the operated valve over time should be reported with quantitative or semiquantitative methods”. Only one paper defined SVD according to this statement. Seven papers defined “degeneration”, “bio-degeneration”, and “primary tissue failure”, which were generally described as the presence of leaflet tear, stretching or creeping of the stent, or valvular obstruction by leaflet fibrosis or calcification. In the remaining 10 papers, a clear definition of intrinsic prosthesis failure was not reported; six of these full-texts were published before 1988.

SVD diagnosis

The papers included in the analysis provided a different characterization of SVD diagnosis (see Supplemental Table 2). Seventeen studies reported SVD diagnosis based on operative (i.e., explanted prostheses) or autopsy findings. In 23 cases, SVD diagnosis was based on clinical and/or imaging data or reoperation and autopsy findings. Among these papers, five studies clearly included SVD diagnosis based on ultrasound assessment even though patients were symptomatic or ultimately underwent a reoperation (34,39,40,48,50).

Long-term durability and survival

There was a trend through the decades to offer a bioprosthesis to older patients with a 20-year difference in mean age between study populations coming from the 1970s and the 1990s. Figure 1 illustrates the distribution of mean patients' age according to study periods and models of prostheses. Details about mean age at the implantation time and mean follow-up time were reported in Table 1. Supplemental Figure 2 provides data about freedom from SVD for each type of prosthesis.

The analysis of patient populations operated after 1980 (table 2 for details) included Carpentier-Edwards porcine valves, Hancock II, Mosaic, and Carpentier-Edwards pericardial.

Freedom from SVD at 10-year and 15-year follow-ups were 84% and 67% for Carpentier-Edwards porcine, 84% and 66% for Hancock II, 93% and 80% for Mosaic, and 91% and 61% for Carpentier-Edwards pericardial valves (Figure 2). A high degree of heterogeneity was observed: $I^2 = 99.3\%$, $P < 0.001$; Egger's test: 10.14 (7.99–12.30); $P < 0.0001$ (Supplemental Figure 3). Considering the maximum follow-up of 15 years, there was no difference between Hancock II and Carpentier-Edwards porcine [HR 1.04 (0.86–1.25), $p = 0.688$] and Hancock II and Carpentier-Edwards pericardial [HR 0.97 (0.79–1.18), $p = 0.733$]. Mosaic valves demonstrated better durability: Hancock II vs. Mosaic HR 2.15 (1.54–2.99), $p < 0.001$; Carpentier-Edwards porcine vs. Mosaic HR 2.08 (1.54–2.81), $p < 0.001$; Carpentier-Edwards pericardial vs. Mosaic HR 2.22 (1.63–3.03), $p < 0.001$. Carpentier-Edwards porcine valves showed a lower risk of SVD compared to Carpentier-Edwards pericardial [HR 0.61 (0.53–0.69), $p < 0.001$].

Similar results were obtained through analyzing the series which included patients operated after 1980 and the papers reporting SVD diagnosis based on clinical and/or imaging data and/or operative and autopsy findings (Supplemental Figure 4). Supplemental Figure 5 shows a comparison between porcine and pericardial groups.

Survival curves for each prosthesis are shown in Figure 4: Hancock II vs. Carpentier-Edwards porcine: HR 0.83 (0.73–0.94), $p = 0.004$; Hancock II vs. Carpentier-Edwards pericardial: HR 1.33 (1.16–1.54), $p < 0.001$; Hancock II vs. Mosaic: HR 2.20 (1.84–2.63), $p < 0.001$; Carpentier-Edwards porcine vs. Carpentier-Edwards pericardial: HR 1.51 (1.36–1.67), $p < 0.001$; Carpentier-Edwards porcine vs. Mosaic: HR 2.35 (2.02–2.72), $p < 0.001$; Carpentier-Edwards pericardial vs. Mosaic: HR 1.51 (1.29–1.77), $p < 0.001$.

Owing to the sensitivity of the study, each single study was deleted, one at a time, and calculations repeated. However, no change in direction nor magnitude of the effects was demonstrated.

Comment

Mitral valve surgery has been increasingly performed over the last decade. Although valve repair has been reported feasible and effective in most patients, it is, of course, dependent on the etiology of valve pathologies and the pathogenic mechanisms leading to valve insufficiency (51). In the real-world practice, valve replacement represents more than 40% of procedures on the mitral valve (52); this finding has been constant over the last few years and involves patients with a mean age of 65 years (53). Similar to aortic valve replacement (54), we have assisted a progressive increase in the adoption of tissue valves over mechanical prostheses for mitral replacement (51,55). Even though the aging of the surgical population certainly played an important role, this trend also involved patients younger than 65 years (54). The expectation of better haemodynamic and longer durability derived by newer technologies and techniques of tissue treatment may have partly driven this shift to a preference towards biologic implants. Particularly, the introduction and progressive ameliorations of pericardial prostheses have been perceived as a step forward towards better outcomes.

However, at least for valve durability, scientific evidence does not support this assumption. Several papers, including a recent meta-analysis of long-term studies (2,3,5,7,56), found no difference in primary tissue failure, SVD or reoperation between porcine and pericardial valves in the aortic position. Insufficient data exists regarding mitral valve replacement. Few studies compared the durability of porcine and pericardial prostheses after mitral valve replacement, and included cohorts of patients with different age range at the implant time (7) and populations from different eras (5).

As underlined by Figure 1, we demonstrated that there was a trend over time towards a higher mean age in patients who received a mitral bioprosthesis, which translated in the 20-year mean age gap between patients undergoing mitral valve replacement in the early 1970s and patients operated in the last two decades. There are three reasons for this finding: a) adoption of mechanical prostheses in younger patients soon after the first

pieces of evidence of early failure of tissue valves associated with lower age; b) the progressive spread, from the 1980s, of repair techniques in the treatment of degenerative mitral regurgitation that generally affects a younger population; and c) the aging of the global cardiac surgery population. Because patient's age at the implantation time is a well-recognized risk factor for tissue valve failure/SVD (17,19,24,29,48,49), someone could reasonably argue about a protective age effect on longer durability of prostheses implanted in older patients in the surgical series of the 1980s–1990s and over.

Alongside differences in patients' age, another important aspect regards the introduction in the same period of anticalcification treatment, low-pressure fixation and flexible stents aiming better performances and longer durability. In order to overcome these limitations, we thought that the selection of a particular cut-off of patients' age or the exclusion of some series according to the types of prosthesis implanted would have been arbitrary and probably would not have intercepted the changes in surgical indication and medical management. Therefore, we looked at the surgical experiences coming from the 1980s and the following decades and found that these series included populations of patients with similar age, 64 years for porcine and 65 years for pericardial. The porcine prostheses implanted over this period were second generation Hancock II and Carpentier-Edwards and third generation Mosaic valves. The exclusion of Hancock valves that are no longer used provided a more relevant picture for the contemporary practice. A direct comparison of outcomes between old and newer technologies is difficult due to many clinical and historical variables (i.e., patients' characteristics, associated medical therapy and anticoagulation therapy protocols); however, the study of modalities of failure could suggest whether any proposed amelioration had a positive impact on valve durability. Pericardial valves fail in more than 75% of the cases because of calcification-related leaflets deterioration (4,20,48,57), a process starting already in the first decade and leading to progressive leaflet degeneration usually complicated by prosthesis stenosis. Porcine valves present similar degeneration in a minority of the cases (far less than 50%) (4,15,21), while more commonly they are affected by calcified leaflets complications or non-calcium-related leaflets tears and dehiscence (50–75% of the cases) (4,7,15,58,59,60,61). These latter mechanical/stress-induced lesions (24,33), also highlighted by finite-element analyses and histological studies (62,63,64), have been invariably reported in porcine prostheses implanted in mitral position (58,59). Its occurrence after a mean period of 8 to 10 years after implant, as seen in long-term observational studies including first generation porcine valves (4,5,7,12,13,15,24,25,33), may explain the divergence of SVD

curves between pericardial and porcine mitral prostheses. Modalities of failure changed over time, as seen with the introduction of “reduced trimming” for the Carpentier-Edwards 6650 (20) and the tissue treatment for Hancock II (58). Mosaic valve represents a further evolution, and no leaflet tear or disruption have been reported in long-term follow-up series (41). These shreds of evidence are still limited and derived from studies that have a maximum follow-up of 5 years (39,40,50), with few patients followed for more than 15 years (41) and including populations with higher mean age compared to the other prostheses. However, alongside an outstanding durability, these papers also reported a satisfactory long-term survival in Mosaic valve recipients, thus including a high proportion of patients at risk of developing prosthesis degeneration during the observational period and providing noteworthy imaging follow-ups besides clinical and surgical findings.

A highly variable panel of definitions regarding valve failure and different methodology approaches could be expected while attempting analysis of papers published across four decades. We found, however, that most of the studies aligned with the definition of SVD provided in the STS/AATS guidelines (16,18,65). Diagnosis of SVD was derived from clinical evaluation, or as described at surgical explant or autopsy. Seventeen of the analyzed full-texts reported freedom from SVD at the explant, while 23 papers provided results of freedom from SVD diagnosis including clinical, ultrasound, operative and autopsy findings. The evaluation of valve deterioration based only on the surgical explant of the prosthesis may underestimate the incidence of a clinically relevant SVD and may not account for patients with known SVD considered not fit or at high risk for reoperation. Consequently, we performed an analysis restricted to papers reporting an endpoint of durability characterized by a more comprehensive SVD diagnosis (i.e., clinical, imaging and explant findings). The results confirmed the findings from the general analysis and supported the evidence that, throughout the selected experiences, a reoperation was almost invariably performed in all the patients diagnosed with mitral prosthesis SVD.

The pathogenetic mechanisms of failure could influence the timing of SVD diagnosis as a sudden tear of a leaflet may hesitate in acute symptoms of mitral regurgitation while a progressive calcification may cause delayed symptoms of mitral stenosis. Unfortunately, sparse data was available in terms of ultrasound evaluation from the studies included in our analyses. Possibly, a more extended period of patients’ observation

and evaluation of SVD based on routine imaging follow-ups could further affect the estimate of degeneration in favor of porcine valves compared to pericardial mitral prostheses.

Mortality is a competing risk factor for SVD; poor survival and inclusion of elderly patients could underestimate the risk of valve failure since it occurs in a non-linear pattern with an acceleration after the first decade. These elements could represent possible biases for all the papers evaluated and then included in our analysis.

In surgical populations that underwent mitral valve replacement after 1980 with new generation tissue valves and similar mean age at the implant time, we found, at long-term follow-up, a higher freedom from SVD in the group of porcine prostheses. The inclusion of cohorts of patients presenting difference in demographic characteristics, preoperative features and early and long-term survival, as well as operated on diverse surgical and medical eras, does not allow a direct comparison of durability of different tissue valves. Other underlying mechanisms remain to be studied and elucidated, including patients' selection, the timing of surgery and the effect of improved haemodynamic. The lower survival rate in patients with Hancock II and Carpentier-Edwards porcine valves could have resulted in an underestimation of the degeneration of these prostheses when compared with Carpentier-Edwards pericardial and Mosaic porcine valves. On the other hand, a slightly higher age at the implant and more appropriate surgical and medical protocols could have reasonably contributed, in association with new achievements in valve design and manufacture, to the improved outcomes in patients who received a Mosaic prosthesis. Despite all these limitations, the evidence derived from more recent experiences and modern practice provided the lowest rate of SVD and a satisfactory long-term survival and represented the most reliable picture of the contemporary results in patients undergoing mitral valve replacement. These last findings should be regarded so far as the long-term durability reference to emerging surgical and non-surgical technologies in mitral valve surgery.

Conflict of interest: none declared

Funding statement: no fund

References

- 1 - Pellerin M, Mihaileanu S, Couëttil JP, et al. Carpentier-Edwards pericardial bioprosthesis in aortic position: long-term follow-up 1980 to 1994. *Ann Thorac Surg* 1995;60:S292-5
- 2 - Wang M, Furnary AP, Li H, Grunkmeier GL. Bioprosthetic aortic valve durability: a meta-regression of published studies. *Ann Thorac Surg* 2017;104:1080-7
- 3 - Hickey GL, Grant SW, Bridgewater B, et al. A comparison of outcomes between bovine pericardial and porcine valves in 38040 patients in England and Wales over 10 years. *Eur J Cardiothorac Surg* 2015;47:1067-74
- 4 - Jamieson WR, Marchand MA, Pelletier CL, et al. Structural valve deterioration in mitral replacement surgery: comparison of Carpentier-Edwards supra-annular porcine and perimount pericardial bioprostheses. *J Thorac Cardiovasc Surg* 1999;118:297-305
- 5 - Grunkmeier GL, Furnary AP, Wu Y, Wang L, Starr A. Durability of pericardial versus porcine bioprosthetic heart valves. *J Thorac Cardiovasc Surg* 2012;144:1381-6
- 6 - Chaudhry MA, Raco L, Muriithi EW, Bernacca GM, Tolland MM, Wheatley DJ. Porcine versus pericardial bioprostheses: eleven-year follow up of prospective randomized trial. *J Heart Valve Dis* 2000;9:429-37
- 7 - Pelletier LC, Carrier M, Leclerc Y, Lepage G, deGuise P, Dyrda I. Porcine versus pericardial bioprostheses: a comparison of late results in 1593 patients. *Ann Thorac Surg* 1989;47:352-61
- 8 - Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;169:467-473
- 9 - Guyot P, Ades AE, Ouwers MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;1:12:9
- 10 - Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560

- 11 - Wan X, Wang W, Liu J et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14:135
- 12 - Al-Khaja N, Belhoul A, Larsson S, Roberts D. Eleven years' experience with Carpentier-Edwards biological valves in relation to survival and complications. *Eur J Cardiothorac Surg* 1989;3:305-311
- 13 – Bernal JM, Rabasa JM, Lopez R, Nistal JF, Mufiiz R, Revuelta JM. Durability of the Carpentier-Edwards Porcine Bioprosthesis: Role of Age and Valve Position. *Ann Thorac Surg* 1995;60:S248-52
- 14 - Soots G, Stankowiak C, Warembourg H Jr, et al. Durability of the Carpentier-Edwards porcine bioprosthesis in aortic or mitral positions. 10 years' results on 458 surgically treated cases. *Ann Chir* 1989;43:616-23
- 15 – Akins CW, Carroll DL, Buckley MJ, Daggett WM, Hilgenberg AD, Austen WG. Late results with Carpentier-Edwards porcine bioprosthesis. *Circulation* 1990;82(5 Suppl):IV65-74
- 16 - Edmunds LH Jr, Cohn LH, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. *Ann Thorac Surg* 1988;46:257-9
- 17 - Jamieson WR, Burr LH, Janusz MT, et al. Carpentier-Edwards standard and supraannular porcine bioprostheses: comparison of technology. *Ann Thorac Surg* 1999;67:10 –7
- 18 - Edmunds LH Jr, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. The American Association for Thoracic Surgery, Ad Hoc Liaison Committee for standardizing definitions of prosthetic heart valve morbidity. *Ann Thorac Surg* 1996;62:932–5
- 19 - Fiane AE, Saatvedt K, Svennevig JL. Carpentier-Edwards bioprosthesis. Experiences of 17 years with analysis of risk factors of early mortality. *Scand Cardiovasc J.* 1997;31(1):39-44
- 20 - Jamieson WR, Gudas VM, Burr LH, et al. Mitral valve disease: if the mitral valve is not reparable/failed repair, is bioprosthesis suitable for replacement? *Eur J Cardiothorac Surg* 2009;35:104-10

- 21 - Yamak B, Sener E, Kiziltepe U, Mavitas B, Tasdemir O, Bayazit K. Late results of mitral valve replacement with Carpentier-Edwards high profile bioprosthesis in young adults. *Eur J Cardiothorac Surg* 1995;9:335-41
- 22 - Louagie Y, Noirhomme P, Aranguis E, et al. Use of the Carpentier-Edwards porcine bioprosthesis: assessment of a patient selection policy. *J Thorac Cardiovasc Surg* 1992;104:1013-24
- 23 - Geha AS, Holter AR, Langou RA, Laks H, Hammond GL. Dysfunction and thromboembolism associated with cardiac valve xenografts in adults. *Circulation* 1981;64:III172-7
- 24 - Jones EL, Weintraub WS, Craver JM, et al. Ten-year experience with the porcine bioprosthetic valve: interrelationship of valve survival and patient survival in 1,050 valve replacements. *Ann Thorac Surg* 1990;49:370-83; discussion 383-4
- 25 - Fann JI, Miller DC, Moore KA, et al. Twenty-year clinical experience with porcine bioprostheses. *Ann Thorac Surg* 1996;62:1301-11
- 26 - Perier P, Deloche A, Chauvaud S, et al. A 10-year comparison of mitral valve replacement with Carpentier-Edwards and Hancock porcine bioprostheses. *Ann Thorac Surg* 1989;48:54-9
- 27 - Burr LH, Jamieson WR, Munro AI, et al. Structural valve deterioration in elderly patient populations with the Carpentier-Edwards standard and supra-annular porcine bioprostheses: a comparative study. *J Heart Valve Dis* 1992;1:87-91
- 28 - Cobanoglu A, Jamieson WR, Miller DC, et al. A tri-institutional comparison of tissue and mechanical values using a patient-oriented definition of "treatment failure". *Ann Thorac Surg* 1987;43:245-53
- 29 - Cohn LH, Collins JJ Jr, DiSesa VJ, et al. Fifteen-year experience with 1678 Hancock porcine bioprosthetic heart valve replacements. *Ann Surg* 1989;210:435-42
- 30 - Bortolotti U, Milano A, Mazzucco A, et al. Extended follow-up of the standard Hancock porcine bioprosthesis. *J Card Surg* 1991;6:544-9
- 31 - Gallo I, Nistal F, Artiñano E. Six- to ten-year follow-up of patients with the Hancock cardiac bioprosthesis. Incidence of primary tissue valve failure. *J Thorac Cardiovasc Surg* 1986;92:14-20

- 32 - Bernal JM, Rabasa JM, Cagigas JC, Echevarria JR, Carrion MF, Revuelta JM. Valve-related complications with the Hancock I porcine bioprosthesis. A twelve- to fourteen-year follow-up study. *J Thorac Cardiovasc Surg* 1991;101:871-80
- 33 - Burdon TA, Miller DC, Oyer PE, et al. Durability of porcine valves at fifteen years in a representative North American patient population. *J Thorac Cardiovasc Surg* 1992;103:238-51
- 34 - Kawachi Y, Tanaka J, Tominaga R, Kinoshita K, Tokunaga K. More than ten years' follow-up of the Hancock porcine bioprosthesis in Japan. *J Thorac Cardiovasc Surg* 1992;104:5-13
- 35 - Bortolotti U, Milano A, Mossuto E, Mazzaro E, Thiene G, Casarotto D. Porcine valve durability: a comparison between Hancock standard and Hancock II bioprostheses. *Ann Thorac Surg* 1995;60:S216-20
- 36 - Martinell J, Fraile J, Artiz V, Moreno J, Rábago G. Long-term comparative analysis of the Björk-Shiley and Hancock valves implanted in 1975. *J Thorac Cardiovasc Surg* 1985;90:741-9
- 37 - Milano A, Bortolotti U, Mazzucco A, et al. Mitral valve replacement with the Hancock, Björk-Shiley and Lillehei-Kaster prostheses. A comparison based on a 15-year follow-up. *Eur J Cardiothorac Surg* 1989;3:312-9
- 38 - Rizzoli G, Bottio T, Thiene G, Toscano G, Casarotto D. Long-term durability of the Hancock II porcine bioprosthesis. *J Thorac Cardiovasc Surg* 2003;126:66-74
- 39 - Thomson DJ, Jamieson WR, Dumesnil JG, et al. Medtronic Mosaic porcine bioprosthesis: midterm investigational trial results. *Ann Thorac Surg* 2001;71:S269-72
- 40 - Fradet GJ, Bleese N, Burgess J, Cartier PC. Mosaic valve international clinical trial: early performance results. *Ann Thorac Surg* 2001;71:S273-7
- 41 - Rieß FC, Fradet G, Lavoie A, Legget M. Long-Term Outcomes of the Mosaic Bioprosthesis. *Ann Thorac Surg* 2018;105:763-769
- 42 - Hartz RS, Fisher EB, Finkelmeier B, et al. An eight-year experience with porcine bioprosthetic cardiac valves. *J Thorac Cardiovasc Surg* 1986;91:910-7

- 43 - Cohn LH, Allred EN, Cohn LA, et al. Early and late risk of mitral valve replacement. A 12 year concomitant comparison of the porcine bioprosthetic and prosthetic disc mitral valves. *J Thorac Cardiovasc Surg* 1985;90:872-81
- 44 - Czer LS, Matloff JM, Chaux A, DeRobertis MA, Gray RJ. Comparative clinical experience with porcine bioprosthetic and St. Jude valve replacement. *Chest* 1987;91:503-14
- 45 - Murakami T, Eishi K, Nakano S, et al. Aortic and mitral valve replacement with the Carpentier-Edwards pericardial bioprosthesis: 10-year results. *J Heart Valve Dis* 1996;5:45-9
- 46 - Poirer NC, Pelletier LC, Pellerin M, Carrier M. 15-year experience with the Carpentier-Edwards pericardial bioprosthesis. *Ann Thorac Surg* 1998;66:S57-61
- 47 - Marchand M, Aupart M, Norton R, et al. Twelve-year experience with Carpentier-Edwards PERIMOUNT pericardial valve in the mitral position: a multicenter study. *J Heart Valve Dis* 1998;7:292-8
- 48 - Bourguignon T, Bouquiaux-Stablo AL, Loardi C, et al. Very late outcomes for mitral valve replacement with the Carpentier-Edwards pericardial bioprosthesis: 25-year follow-up of 450 implantations. *J Thorac Cardiovasc Surg* 2014;148:2004-2011
- 49 - David TE, Ivanov J, Armstrong S, Feindel CM, Cohen G. Late results of heart valve replacement with the Hancock II bioprosthesis. *J Thorac Cardiovasc Surg* 2001;121:268-77
- 50 - Eichinger WB, Botzenhardt F, Gunzinger R, et al. European experience with the Mosaic bioprosthesis. *J Thorac Cardiovasc Surg* 2002;124:333-9
- 51 - Gammie JS, Chikwe J, Badhwar V, et al. Isolated Mitral Valve Surgery: The Society of Thoracic Surgeons Adult Cardiac Surgery Database Analysis. *Ann Thorac Surg* 2018;106:716-727
- 52 - Jacobs JP, Shahian DM, D'Agostino RS, et al. The Society of Thoracic Surgeons National Database 2018 Annual Report. *Ann Thorac Surg* 2018;106:1603-1611
- 53 - 12. The Society for Cardiothoracic Surgery in Great Britain & Ireland. Blue Book Online. <http://www.bluebook.scts.org>

- 54 - Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. *J Thorac Cardiovasc Surg* 2015;149:1262-9.e3
- 55 - Goldstone AB, Chiu P, Baiocchi M, et al. Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. *N Engl J Med* 2017;377:1847-1857
- 56 - Ganapathi AM, Englum BR, Keenan JE, et al. Long-Term Survival After Bovine Pericardial Versus Porcine Stented Bioprosthetic Aortic Valve Replacement: Does Valve Choice Matter? *Ann Thorac Surg* 2015;100:550-9
- 57 - Marchand MA, Aupart MR, Norton R, et al. Fifteen-year experience with the mitral Carpentier-Edwards PERIMOUNT pericardial bioprosthesis. *Ann Thorac Surg* 2001;71:S236-9
- 58 - Bottio T, Thiene G, Pettenazzo E, et al. Hancock II bioprosthesis: a glance at the microscope in mid-long-term explants. *J Thorac Cardiovasc Surg* 2003;126:99-105
- 59 - Bottio T, Valente M, Rizzoli G, et al. Commissural dehiscence: a rare and peculiar cause of porcine valve structural deterioration. *J Thorac Cardiovasc Surg* 2006;132:1017-22
- 60 - Naqvi TZ, Siegel RJ, Buchbinder NA, et al. Echocardiographic and pathologic features of explanted Hancock and Carpentier-Edwards bioprosthetic valves in the mitral position. *Am J Cardiol* 1999;84:1422-7
- 61 - Bloomfield P, Kitchin AH, Wheatley DJ, Walbaum PR, Lutz W, Miller HC. A prospective evaluation of the Bjork-Shiley, Hancock, and Carpentier-Edwards heart valve prostheses. *Circulation* 1986;73:1213-1222
- 62 - Sabbah HN, Hamid MS, Stein PD. Mechanical stresses on closed cusps of porcine bioprosthetic valves: correlation with sites of calcification. *Ann Thorac Surg* 1986;42:93-96
- 63 - Sabbah HN, Hamid MS, Stein PD. Estimation of mechanical stresses on closed cusps of porcine bioprosthetic valves: effects of stiffening, focal calcium and focal thinning. *Am J Cardiol* 1985;55:1091-1096
- 64 - Stein PD, Kemp SR, Riddle JM, Lee MW, Lewis JW, Magilligan DJ. Relation of calcification to torn leaflets of spontaneously degenerated porcine bioprosthetic valves. *Ann Thorac Surg* 1985;40:175-180

65 - Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *Ann Thorac Surg* 2008;85:1490-5

Table 1. Populations' data

Valve types	CE pericardial	Overall porcine	CE porcine	Hancock	Hancock II	Mosaic
Series (n.)	5	34	18	11	2	4
Patients (n.)	1143	14072	7026	4829	424	940
Mean age~ (y)	65.2	57.7	59.5	53.2	63.6	68.0
Early mortality (%)	4.7	8.9	9	10	8.7	3.7
Mean FU# (y)	6.42	6.29	5.97	7.28	7.52	3.90

~ $\sum(\text{mean age} \times \text{number of patients}) / \sum \text{number of patients}$

$\sum(\text{mean FU} \times \text{number of patients}) / \sum \text{number of patients}$

Table 2. Data of populations operated after 1980

Valve types	CE pericardial	Overall porcine	CE porcine	Hancock	Mosaic
	Overall pericardial			II	
Series (n.)	5	9	3	2	4
Patients (n.)	1143	2725	1361	424	940
Mean age~ (y)	65.2	64.1	61.5	63.5	68.0
Early mortality (%)	4.7	7.6	9.9	8.7	3.7
Mean FU# (y)	6.42	5.84	6.53	7.41	3.90

~ $\sum(\text{mean age} \times \text{number of patients}) / \sum \text{number of patients}$

$\sum(\text{mean FU} \times \text{number of patients}) / \sum \text{number of patients}$

Figure legends

Figure 1. Distribution of mean age at the implantation time according to study periods (x axis) and types of tissue valve.

Figure 2. Freedom from SVD according to each prosthesis from series including populations of patients operated after 1980

Figure 3. Kaplan-Meier curves of survival for porcine and pericardial valves implanted after 1980.

Supplemental figure 1. Flow chart of literature search according to PRISMA guidelines

Supplemental figure 2. Freedom from structural valve deterioration at 10-year and 15-year was 72% and 38% for Hancock, 84% and 66% for Hancock II, 78% and 51% for Carpentier-Edwards porcine, 93% and 80% for Mosaic, 91% and 61% for Carpentier-Edwards pericardial valve. Freedom from SVD for pericardial (mean age 65.2 years) and porcine (mean age 57.7 years) valves was 91% and 74% respectively at 10-year, 61% and 50% respectively at 15-year follow-up; log-rank test pericardial vs porcine $p < 0.001$ (HR 0.72; CI: 0.65-0.79).

Supplemental figure 3. Heterogeneity funnel plot.

Supplemental figure 4. Kaplan-Meier curves of freedom from SVD for porcine and pericardial valves implanted after 1980 according to SVD diagnosis including clinical, imaging and explant findings. Hancock II vs Carpentier-Edwards porcine: HR 1.35(0.99-1.84), $p = 0.053$; Hancock II vs Carpentier-Edwards pericardial: HR 1.11(0.81-1.53), $p = 0.518$; Hancock II vs Mosaic: HR NA, $p = \text{NA}$; CE porcine vs CE pericardial: HR 0.52(0.45-0.61), $p < 0.001$; Carpentier-Edwards vs Mosaic: HR NA, $p = \text{NA}$; Carpentier-Edwards vs Mosaic: HR NA, $p = \text{NA}$. The analysis of Mosaic valve is limited at 7 years because the paper with a longer FU, up to 16 years, by Rieß et al.(41) reported the SVD diagnosis purely as explant at redo operation.

Supplemental figure 5. Freedom from SVD for porcine and pericardial valves implanted after 1980.