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

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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.

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Running head: durability of mitral valve bioprostheses

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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.

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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] x 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 (DerSimmonian-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 ± 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: I2 = 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.

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Table 1. Populations' data

Valve types	**CE pericardial Overall 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

~∑(mean age*number of patients)/ ∑number of patients

#∑(mean FU*number of patients)/ ∑number of patients

Table 2. Data of populations operated after 1980

Valve types	**CE pericardial Overall pericardial**	**Overall porcine**	**CE porcine**	**Hancock II**	**Mosaic**
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

~∑(mean age*number of patients)/ ∑number of patients

#∑(mean FU*number of patients)/ ∑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.

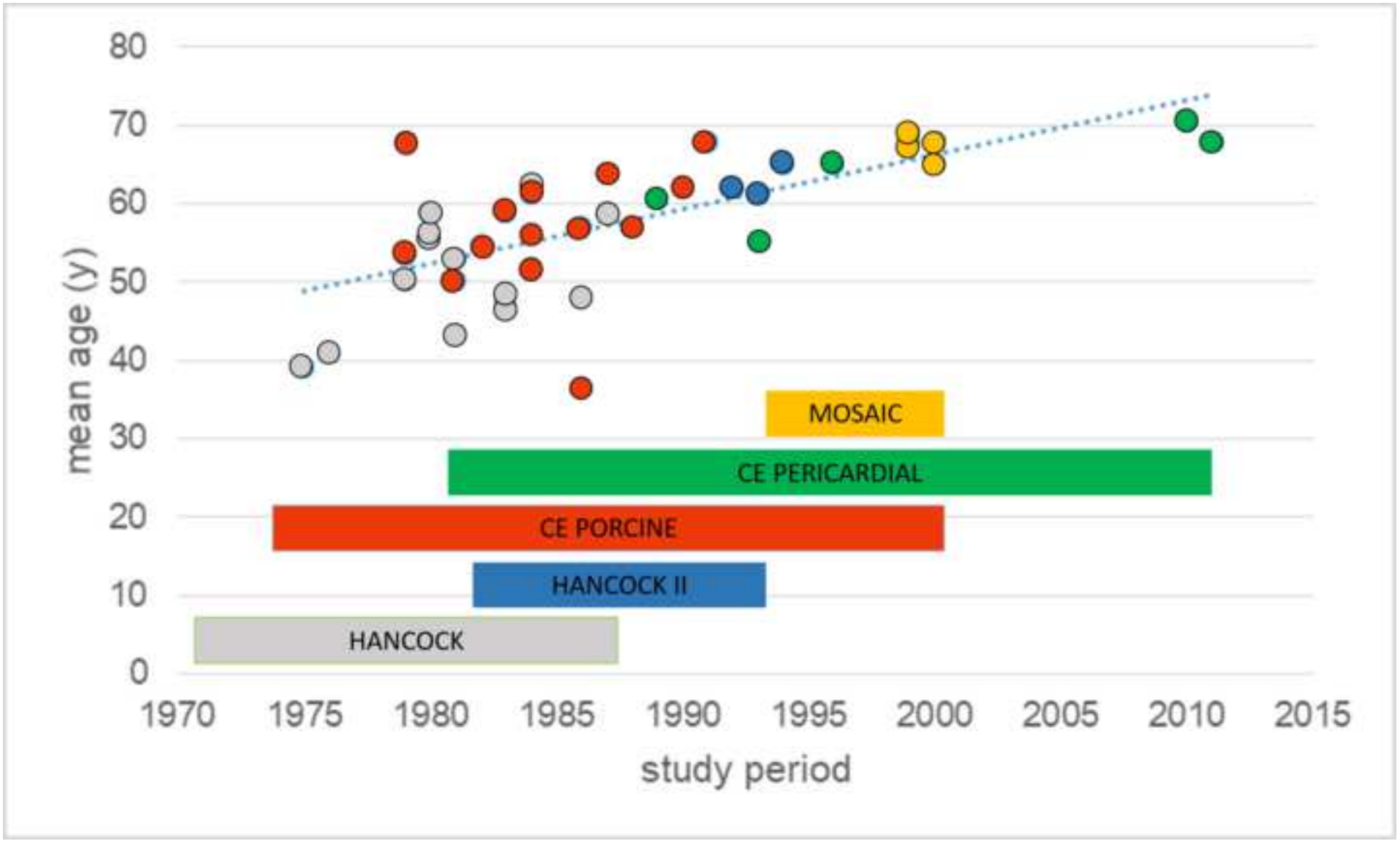
Supplemental figure 1. Flow chart of literature search according to PRISMA guidelines

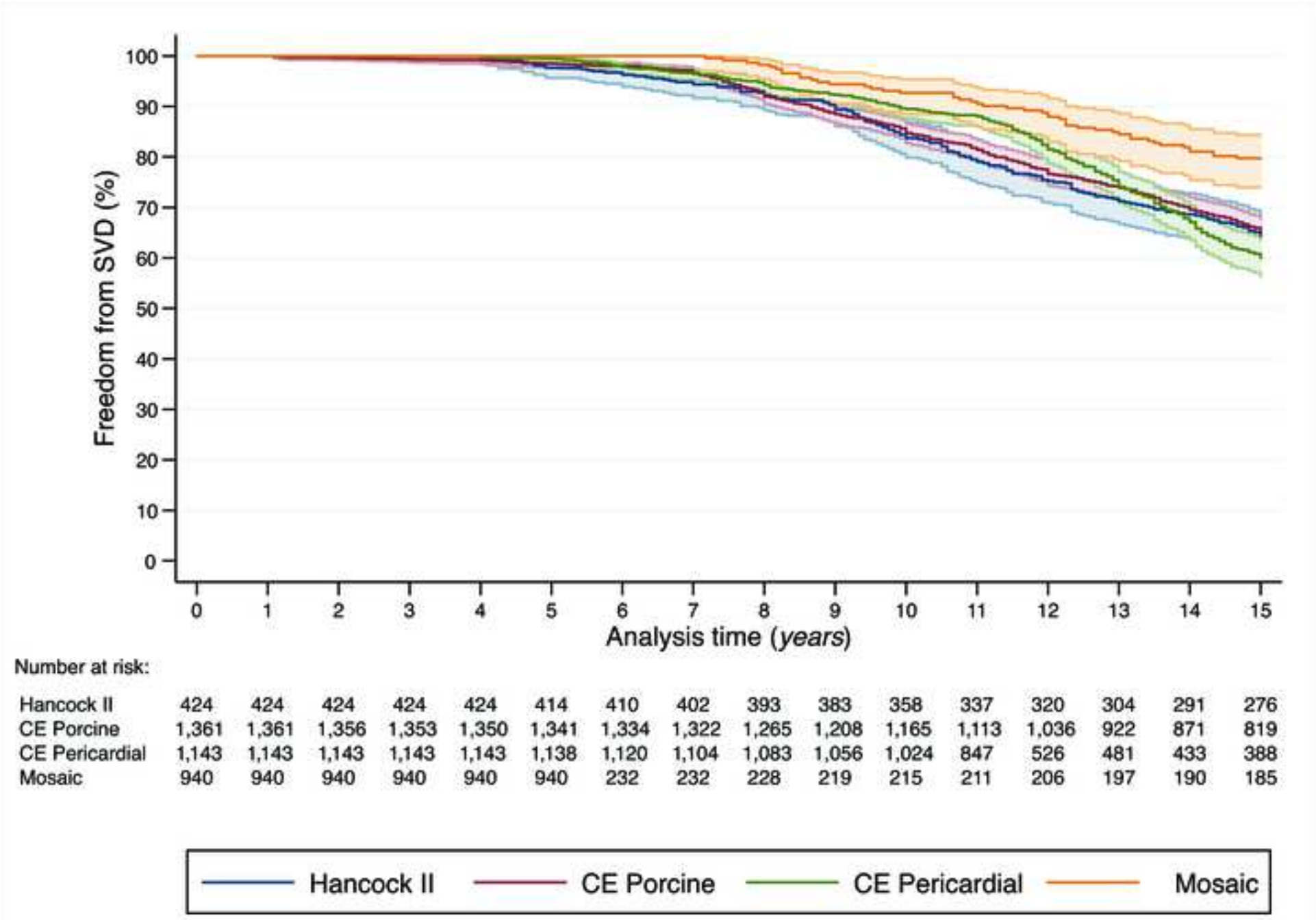
Supplemental figure 2. Freedom from structural valve deterioration at 10-year and 15-year was 72% and 38% for Hancock, 84% and 66% for Hancock II, 78% and 51% for Carpentier-Edwards porcine, 93% and 80% for Mosaic, 91% and 61% for Carpentier-Edwards pericardial valve. Freedom from SVD for pericardial (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).

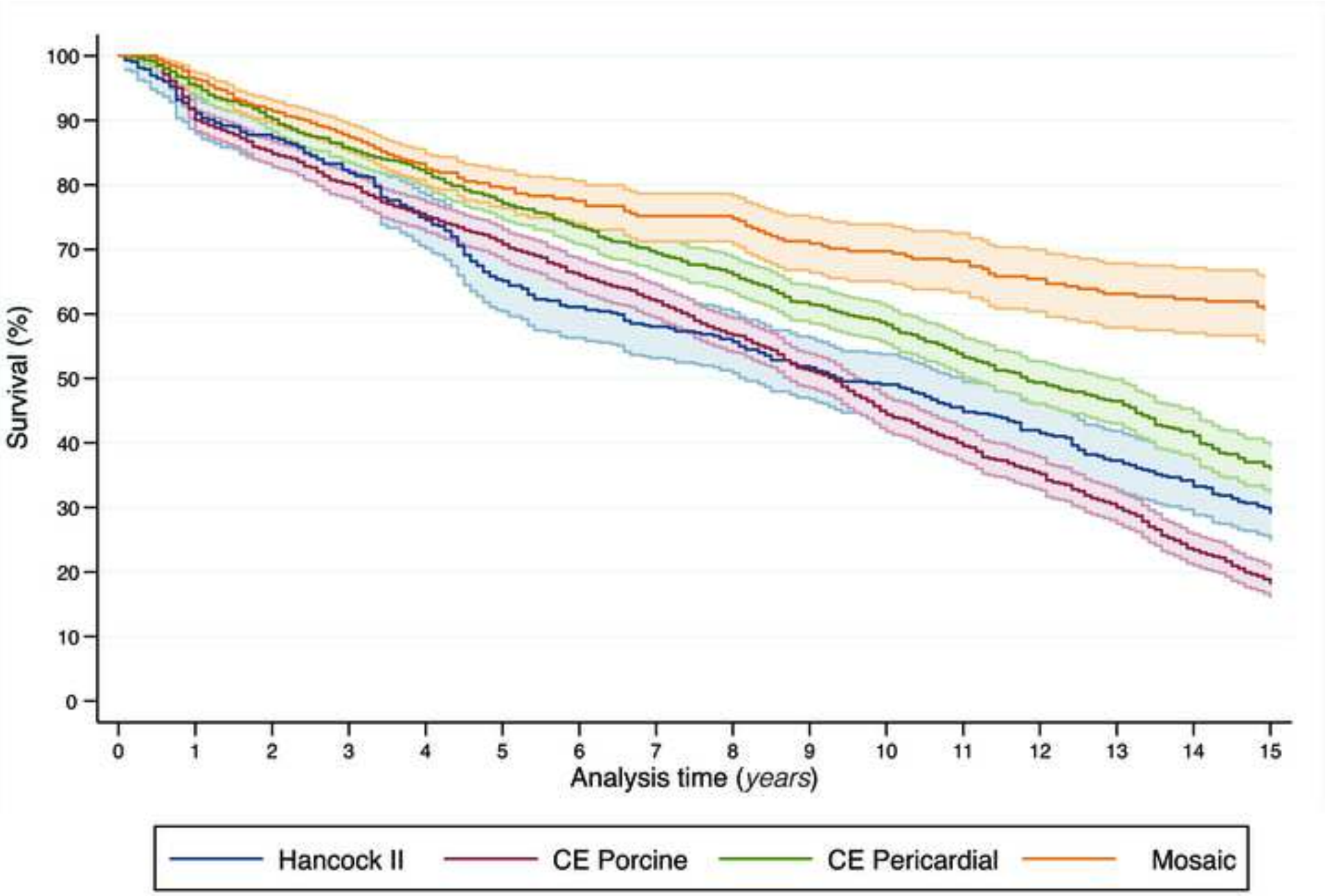
Supplemental figure 3. Heterogeneity funnel plot.

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=NA; CE porcine vs CE pericardial: HR 0.52(0.45-0.61), p<0.001; Carpentier-Edwards vs Mosaic: HR NA, p=NA; Carpentier-Edwards vs Mosaic: HR NA, p=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.







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

Running head: durability of mitral valve bioprostheses

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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] x 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 (DerSimmonian-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 ± 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: I2 = 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.

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Table 1. Populations' data

Valve types	**CE pericardial Overall 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

~∑(mean age*number of patients)/ ∑number of patients

#∑(mean FU*number of patients)/ ∑number of patients

Table 2. Data of populations operated after 1980

Valve types	**CE pericardial Overall pericardial**	**Overall porcine**	**CE porcine**	**Hancock II**	**Mosaic**
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

~∑(mean age*number of patients)/ ∑number of patients

#∑(mean FU*number of patients)/ ∑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=NA; CE porcine vs CE pericardial: HR 0.52(0.45-0.61), p<0.001; Carpentier-Edwards vs Mosaic: HR NA, p=NA; Carpentier-Edwards vs Mosaic: HR NA, p=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.