SUPPLEMENTAL MATERIAL
Data S1.

Supplemental Methods

Ethics Statement
The ethics committee was not involved on account of the retrospective nature of the study. All patients gave consent for the use of their data for research at the University Hospital.

Patient Cohort
Single-centre study of patients requiring reoperation for degenerative bioprostheses at Broussais-Hospital/Georges Pompidou European Hospital in Paris, (Chair: Professor Alain Carpentier). Professor A. Carpentier has developed the concept of valvular heart bioprostheses and overseen the development of several generations of porcine and bovine bioprostheses. Moreover, a large number of cases have undergone initial evaluation studies at this center.

Patients’ characteristics before 1985 (1975-1980 and 1980-1985) and a number of implanted bioprostheses in the mitral or aortic position in the Broussais Hospital have already been reported in the literature. Due to a mean longevity of heart valve bioprostheses of 10 years, the period 1985-1997 corresponded to CE-2nd/3rd generation bioprostheses that were implanted at the institution mainly between 1975 and 1985. Unlike the 2nd-CE generation of bioprostheses made from one pig, the 3rd-CE was manufactured using the cusps of two pigs with a view to improving the hemodynamics. New generations of CE-bioprostheses made from xenogenic bovine pericardium have been implanted since 1980 and have almost totally replaced porcine bioprostheses since 1985. Chemical fixation by glutaraldehyde is still the main
reticulating reagent. Patients’ clinical conditions were not taken into account for the choice between a porcine or bovine bioprosthesis and, after 1985, almost all patients received the new generation of bovine bioprostheses.

All patients reoperated for degenerative porcine bioprostheses during the 13-year period from January 1985 to December 1997 were eligible for the study and mainly comprised patients from our institution.

In addition, we included all patients reoperated on from January 1998 to January 2014 who had a porcine bioprosthesis with exceptional longevity (≥ 13 years). Since most porcine bioprostheses were implanted before 1985, we have a total follow-up period of 29 years for most of them.

Criteria for inclusion: a degenerative porcine bioprosthesis that needs replacement during this period because of bioprosthetic valve dysfunction due to intrinsic structural valve deterioration (i.e. bioprosthesis degeneration (SVD)). Excluded are bioprosthetic replacements for other causes of valvular dysfunction such as nonstructural valve deterioration (i.e. any abnormality not intrinsic to the valve itself such as para-prosthetic regurgitation, malposition)\textsuperscript{51}, endocarditis or thrombosis. The cause of valve replacement and the type of intrinsic structural valve anomalies were prospectively specified by the surgeon at the time of bioprosthesis replacement, with observations on the presence of calcification, pannus, tears or perforations. A standardized classification of bioprosthesis valve degeneration in the aortic position has been recently proposed and excludes bioprosthesis thrombosis\textsuperscript{9,51,52}. In a recent prospective study evaluating 25 years of Carpentier-Edwards bovine bioprostheses in the aortic position, the causes for valvular replacement were revealed to be: SVD (73%), endocarditis (15%), nonstructural dysfunction (11%), and thrombosis (exceptional)\textsuperscript{3}.
Additional recent factors that lead to accelerated bioprosthetic valve dysfunction, such as patient prosthesis mismatch or the small size of some prostheses, were not specifically investigated. In the case of multiple bioprosthesis implants, only degenerative bioprostheses were considered. Some cases of early failure or intermediate longevity in the new generation of bovine bioprostheses were explanted during this period (1985-1998) and analysed separately.

**Study variables**

The main outcome variable was the interval between valve implantation and explantation (longevity) and the type of SVD. The main risk factor of interest was the patient’s blood type (ABO and rhesus) and was retrospectively collected. Other known classical risk factors for structural degeneration of bioprostheses, and for which data were prospectively collected at replacement, were as follows: patient’s age at the moment of implantation, sex, valve location and number of bioprostheses implanted initially. Some additional risk factors in bioprosthesis degeneration, especially in the aortic position, have also been reported recently and include factors that increase hemodynamic stress (large body surface area, small prosthesis size, prosthesis-patient mismatch, left ventricle hypertrophy) and cardiovascular risk factors such as smoking, hypertension, metabolic syndrome, diabetes mellitus, dyslipidemia. Chronic dialyses and hyperparathyroidism have also been shown to be associated with early structural valve degeneration, although patients presenting these characteristics are rare in this study.

The only type of bioprosthetic degeneration that has been well studied is that caused by calcification; while the roles of pannus, tears or perforations are mostly unknown. None of these factors have been shown to be related to patient ABO blood group and could
therefore not explain the different levels of bioprosthesis degeneration between the different ABO blood groups.

**Data collection**

A prospective database for bioprosthetic heart valves has been developed since 1985. Thus, from 1985 to 1998, data was collected prospectively and valve information recorded in the operating room. Data on the type of bioprosthesis alteration was prospectively reported by the surgeon in the operating room, so that we now have information for the main criteria (pannus/calcification/tears/perforation) for most degenerative bioprostheses (913 out of 963). Other additional information collected included factors contributing to bioprosthesis replacement (e.g. thrombosis, endocarditis, non-dysfunction valve), date of implantation, longevity, site of implantation and number, origin (bovine or porcine) and type of bioprosthesi...
**Statistical analysis**

We obtained frequency distributions for all study variables, for all replaced valves, and for all patients. For the main outcome variable, i.e. valve longevity, discrete categories were defined: the approximate lower and upper deciles were isolated (early and late failure), and the remainder was split into 3 classes, resulting in the following 5 longevity categories (years): 0-5.9, 6-8.9, 9-11.9, 12-14.9 and 15-28. We cross-tabulated the 5-levels of longevity variable with ABO and rhesus blood types. This analysis suggested that the three middle categories were homogenous, so for simplicity we continued the analysis with a 3-level longevity variable (0-5.9, 6-14.9, 15-28). We cross-tabulated this variable with blood types and other valve and patient characteristics. We did not choose the class of longevity initially, but these classes of longevity appear to be clinically relevant\(^3\).

Categorial data were examined as percentage ± SD and compared by \(\chi^2\) test or Fisher's exact test as appropriate. All variables used in the univariate analysis were entered into the multivariate models. A \(p\) value of \(\leq 0.05\) was considered statistically significant. A multivariate logistic regression model was used to identify the independent predictors of structural bioprosthesis degeneration. Only bioprosthesis patients with known ABO blood group were included in the multivariate analyses.

The analyses were conducted using SPSS-version18 or the statistical software system SEM (Silex Development, Mirefleurs, France).
**Supplemental Results**

**Patient and valve characteristics**

Between 1985 and 1998, 854 porcine bioprostheses were explanted from 641 patients. From 1998 to 2014, 32 additional porcine bioprostheses with longevity ≥ 13 years were removed (total 886). The blood group was retrospectively found for 736 out of 886 patients and longevity information was available for 564 out of 886, while the important ‘age at implantation’ factor was available for 559 of the cohort.

Not surprisingly, most patients (89.3%) in this group with porcine bioprostheses needing surgical replacement were ≤ 60yrs at implantation. We focus our attention on this group with porcine bioprostheses implanted before the age of 60 because it is over-represented and corresponds to the group of bioprosthesis patients that needs major clinical improvements. Most of the patients with bioprostheses implanted at 60 years or before will need to be re-operated after a period of 25 years for degenerative bioprosthesis\(^4\). SVD data collected was available for 29 years so that we assume we have an unbiased full spectrum of bioprosthesis degenerative type anomalies for several periods of longevity.

We have a group of 500 porcine bioprostheses that were implanted before the patients were 60 years old and for which most variables, especially the type of alteration, were known. This group thus constitutes our study cohort. However, in this cohort, information on the ABO blood group was missing for 79 bioprosthesis patients.

During the period 1987-1998, we also explanted 82 bovine bioprostheses with intermediate and short longevity and 62 BP implanted when patients were ≤ 60yrs.
Demographic data and porcine valve characteristics are shown in Table 1. Types of explanted porcine bioprostheses were as follows: CE-2nd 49.9%, 3rd 33.8%, CE-1st 2.7%, other porcine bioprostheses 13.6%. 20.1% of patients had had more than one porcine bioprosthesis. Mean age at implantation was 38.6±12.6 years, the time lapsed before reoperation for degenerative porcine bioprosthesis was 9.9 years ±3.4 [0-28] and the quartiles were 8/10/12 years. Most valves lasted between 6 and 15 years. About 15.6% failed before 7 years and another 10.6% failed after ≥15 years. In our group of patients re-operated for failing bioprostheses, many factors known to be predictive for lower longevity, such as mitral site of implantation (60.9%), younger age or multiple bioprostheses (20.1%), were over-represented compared with the initial population at the time of implantation 43-45 46, 47 48. In this failing group, the number of young patients ≤ 35 years old at implantation (39.4%) was very high.

The prevalence of ABO in this small cohort was: A: 34.2%, 95% CI +/- 4.5; B: 15.7%, 95% CI +/- 3.5; AB: 6.7%, 95% CI, +/- 2.4; O: 43.5%, 95% CI +/- 4.7; and Rhesus (-): 9.7%, 95% CI +/- 2.8. Prevalence of ABO blood group in France or in Caucasian populations is around 45% for Group A, 43% for Group O, 9% for Group B, 3% for Group AB 105. Thus the distribution by blood group matched the expected prevalence for blood group O, the incidence was higher for blood groups B and AB, and slightly lower for blood group A.

**Risks of porcine SVD by pannus**

Pannus were present in 42.4% of SVD (CI 95%, [38.1%-46.7%]) (see Table 2 and Table S1). Using univariate analysis, we identified several risk factors such as increased risk with longevity ($p=0.0036$) and bioprosthesis type (less frequent in more recent PB)($p=0.08$). Interestingly, we
observed a possible association indicating an increased risk of pannus in A-group: OR 1.24 [0.99-1.56] (p=0.064)(p=ns). Risk of pannus for A-group for PBs with different classes of longevity was as follows: short longevity: OR 1.15 [0.66-2.01] (p=0.61), intermediate longevity: OR 1.25 [0.96-1.63] (p=0.092) and, for the group with the longest longevity: OR 1.06 [0.59-1.89] (p=0.85).

Using Multivariate analysis, the risks for pannus were found to be associated with: longevity: OR 2.01 [1.81-2.21] (p=0.00031) and possibly, although not statistically significant, A-group: OR 1.50 [0.99-2.26] (p=0.054)(p=ns).

**Risks of porcine SVD by calcification**

Calcification was present in 38.8% of SVDs (CI 95%, [34.5-43.1%]) (see table 3 and Table S2). Using univariate analysis, we identified the classical risk factors such as younger age at implantation (p=0.00097), site (p=0.0041), and multiple bioprostheses (p=0.021). Higher longevity was surprisingly associated with a lower risk of calcification (p=0.034). We also identified two new additional risk factors for calcification related to ABO blood group: the A-group factor was associated with a decreased risk: OR 0.74 [0.56-0.96] (p=0.024), while the B-antigen showed a possible association with an increased risk: OR 1.28 [0.97-1.67] (p=0.076)(p=ns).

Using multivariate analysis, and including A-group as a variable, we identified several risks for calcification: age at implantation: OR 0.81 (p=0.014), valve number: OR 1.75 (p=0.039), longevity: OR 0.65 (p=0.087) and, compared with B blood group patients, there was a decreased calcification propensity in A-group patients: OR 0.67 [0.45-0.89] (p=0.087), although it was not statistically significant. The same multivariate analysis, with the presence of B-antigen, showed that this last factor was again associated with an increased risk of calcification: OR 1.34 [1.09-1.59], although it was not statistically significant (p=0.25).
Risks of porcine SVD by tears

Tears were present in 57.2% of SVDs (CI 95%, [53.4-62.0]) (see Table 4 and Table S3). Using univariate analysis, we identified several risks of tears such as: site of implantation ($p=0.012$), multiple prostheses ($p=0.024$), and tendency for types of bioprosthesis ($p=0.096$). The incidence of tears decreased with longevity ($p=0.083$). The influence of mechanical factors, with repetitive stimulations, is known to increase with longevity. Thus, tears did not appear to be the sole variable directly related to mechanical factors. In addition, we found that A-group was globally associated with an increased risk of tears: A-group: OR 1.17 [0.98-1.71] ($p=0.078$), especially for bioprostheses with intermediate longevity: OR 1.30 [1.07-1.57] ($p=0.0091$), but not for bioprostheses with a short longevity: OR 1.03 [0.85-1.24] ($p=0.97$) ($p=ns$) or a long longevity: OR 0.77 [0.41-1.45] ($p=0.42$) ($p=ns$).

Using multivariate analysis, only two factors were identified as being associated with the risk of tears: PB types: OR 0.79 ($p=0.014$) and A-group: OR 1.61 [1.39-1.83] ($p=0.026$) while the number of valves was no longer statistically significant ($p=0.082$).

Risks of porcine SVD through perforations

Perforations were the least frequent anomaly in relation to SVDs (10.5%, CI 95%, [7.8-13.2]) (Table 5 and Table S4). Using univariate analysis did not enable us to identify any classical factor for SVD. The only factors that we found to be associated with perforations were new factors that we found associated with blood group characteristics. There was a possible association with an increased risk of perforations in B-group: OR 1.79 [0.95-3.39] ($p=0.072$) ($p=ns$) and A-antigen was associated with a possible decreased risk: OR 0.56 [0.30-1.05] ($p=0.071$) ($p=ns$). The association of the presence of A-antigen and the risk of perforation was as follows for the different classes of
 PB: short longevity: OR 0.23 [0.04-1.33] \(p=0.19\)\((p=ns)\), intermediate longevity: OR 0.76 [0.36-1.58] \(p=0.46\), and high longevity: OR 1.18 [0.22-6.37] \(p=0.76\)(\(p=ns\)).

Separate multivariate analyses, which included all other variables not related to blood type and one variable that was related to blood type, found several risk factors associated with blood type: B-group with an increased risk: OR 2.21 [1.83-2.59] \(p=0.043\) and, for another analysis, a decreased risk in the presence of the A-antigen: OR 0.53 [0.17-0.89] \(p=0.076\)(\(p=ns\)).

**Development of new scoring system for porcine SVD**

We developed two new indicators: the first described the presence of calcification or perforations and was positive in 48.9% of the patients, while the second described the presence of tears or pannus and was positive in 84.2% of the patients (Table S6).

Using univariate analysis, the calcification or perforations factor was found to be associated with site \(p=0.0052\), age at implantation \(p=0.017\), and number of valves \(p=0.092\) and was also significantly associated with some ABO variables: blood type (i.e. general distribution) \(p=0.021\), blood type B: OR 1.36 [1.06-1.75] \(p=0.016\), blood type A: OR 0.75 [0.60-0.94] \(p=0.012\), A antigen: OR 0.79 [0.64-0.97] \(p=0.028\), and B antigen: OR 1.27 [1.01-1.60] \(p=0.039\). Following multivariate analysis, in addition to longevity, the site and blood type B were significantly associated with calcifications or perforations: OR 1.78 [1.51-2.05] \(p=0.035\). The same multivariate analysis was also conducted for B antigen: OR 1.6 [1.36-1.84] \(p=0.041\), for blood group A: OR 0.72 [0.46-0.88] \(p=0.067\), and A antigen: OR 0.72 [0.52-0.92] \(p=0.12\)(\(p=ns\)).

The risk factors for the presence of tears or pannus, as determined by univariate analysis, were: valve replaced \(p=0.0000061\), bioprosthesis type \(p=0.002\) and blood type A: OR 1.11 [1.02-1.22] \(p=0.014\) (Table 7). Following multivariate analysis, only two factors were shown to
be associated with the presence of pannus or tears: valve replacement: OR 0.37 [0.14-0.97] 
\( (p=0.000022) \) and blood group A: OR 2.03 [1.71-2.35] \( (p=0.021) \) (Table 7).

**Risks for specific porcine SVD**

In our study, two anomalies were present during SVD in 50.3% of cases.

The bioprosthesis presented only one type of SVD in 49.7% of cases as follows: isolated pannus 18%, isolated calcification 11.2%, isolated tears 17.8%, isolated perforations 2.4%.

In 50.3% of cases, two anomalies were associated with each other: pannus with tears 15.8%, pannus with calcification 6.8%, pannus with perforation 1.2%, calcification with tears 18%, calcification with perforation 1.4%, tears with perforation 5.8%.

While most pannus/calcification/tear/perforation factors were statistically highly negatively associated with each other, one pair was not associated: perforations with tears \( (p=0.48) \).

Furthermore, weaker correlations were revealed between tears/calcification: OR 0.70 [0.56-0.88] \( (p=0.0016) \), pannus/tears: OR 0.43 [0.35-0.52] \( p<0.0000001 \), pannus/calcification: OR 0.29 [0.22-0.38] \( p<0.0000001 \), pannus/perforations: OR 0.24 [0.13-0.41] \( p=0.00000055 \), and calcification/perforation: OR 0.30 [0.17-0.53] \( p=0.000026 \).

Following numerous univariate analyses to compare the different blood group variables and types of SVD associations, ABO blood groups were shown to be associated with very few of them: again there was a possible decreased incidence of isolated calcification in A-group patients: OR 0.54 [0.28-1.04] \( (p=0.064)(p=ns) \); an increased incidence of pannus with tears in A-group patients: OR 1.71 [1.08-2.69] \( p=0.021 \); and, while the pannus is normally more prevalent in A blood group, there was an increase in the prevalence of the pannus with calcification in B-group: OR 2.42 [1.16-5.05] \( p=0.036 \) and B-antigen: OR 2.13 [1.05-4.31] \( p=0.037 \).
Interestingly, while the A-group was associated with pannus in general, when we considered the specific risk of “isolated pannus”, the A-group was not significantly associated: OR 1.06 [0.71-1.60] (p=0.77).

Risk of pannus with tears increased for A-group in bioprostheses with short longevity: OR 1.93 [1.18-3.16] (p=0.0091), but not for those with intermediate longevity: OR 1.67 [0.50-5.50] (p=0.64) or the high longevity: OR 0.58 [0.16-2.05] (p=0.60).

By conducting separate multivariate analyses, which included all classical risk factors for SVD (i.e. such as age at implantation, male sex, site, number of valves, bioprosthesis types, longevity), one type of specific SVD and one variable related to blood type, the A-group variable was found to be significantly associated with pannus with tears: OR 1.73 [1.48-1.98] (p=0.037) but not with the group of isolated calcification: OR 0.65 [0.26-1.04] (p=0.17). For SVD by pannus with calcification, multivariate analysis revealed B-group to be the only factor statistically associated: OR 3.0 [2.54-3.46] (p=0.025), while the B-antigen showed a weaker association: OR 2.24 [1.81-2.67] (p=0.077).

**Potential link between ABO blood group and bovine SVD**

During the study period, some new generations of bovine bioprostheses with short (<7 years) or intermediate longevity (7-15 yrs) were explanted (n=82) and analyzed separately. Only the 62 bovine bioprostheses implanted before the patient was 60 years old were considered. In this small group of degenerative bovine bioprostheses, multiple univariate analyses comparing any type of SVD and any type of ABO blood group variables, found there were no significant statistical associations.

By associating the different porcine bioprostheses (n=500; age of implantation ≤60yrs) with the 62 new-generation bioprostheses (also implanted ≤60yrs), it appeared that, for the first time using
univariate analysis, the rare AB blood group was significantly associated with certain types of SVD. Considering the AB blood group, we did not find such a correlation for porcine bioprostheses alone. There was a significant association for the AB blood group for increases in the presence of isolated calcification: OR 2.10 [1.14-3.86] (p=0.017) (Table S5) and a decrease in the presence of pannus or tears: OR 0.87 [0.75-1.00] (p=0.044).

By conducting multivariate analyses, which included all the risk factors and the type of porcine or bovine bioprosthesis, for isolated calcification, the following associations were revealed: for AB-group: OR 2.74 [2.30-3.18] (p=0.035), and BB versus PB: OR 1.97 [2.30-3.18] (p=0.28) (Table S6). Multivariate analysis also revealed the following associations for risks of pannus or tears: AB-group: OR 0.37 [0.07-0.67] (p=0.03), BB versus PB: OR 0.53 [0.28-0.78] (p=0.28).

A summary of the main results are presented in Figures 1 and 2.
Table S1. Risks for SVD by pannus for porcine bioprostheses implanted at age ≤ 60 years.

|                          | All Porcine Bioprostheses n=500 | SVD without Pannus n=288 (57.6%) | SVD with Pannus n=212 (42.4%) | Univariate Analysis |
|--------------------------|----------------------------------|----------------------------------|--------------------------------|---------------------|
|                          |                                  |                                  |                                | OR (95%CI)         |
|                          |                                  |                                  |                                | P-value             |
| Male sex                 | 268 (54.6%)                      | 160 (55.9%)                      | 108 (52.7%)                    | 0.93 [0.75-1.14]   |
| Age at implantation      |                                  |                                  |                                | 0.47                |
| [7-20]                   | 24 (5.2%)                        | 18 (6.6%)                        | 6 (3.2%)                       | 1.0 (reference)     |
| [20-30]                  | 110 (23.9%)                      | 64 (23.5%)                       | 46 (24.5%)                     | 1.67 [0.87-3.23]   |
| [30-40]                  | 98 (21.3%)                       | 56 (20.6%)                       | 42 (22.3%)                     | 1.71 [0.89-3.31]   |
| [40-50]                  | 114 (24.7%)                      | 64 (23.5%)                       | 50 (26.6%)                     | 1.75 [0.92-3.34]   |
| [50-60]                  | 114 (24.7%)                      | 70 (25.7%)                       | 44 (23.4%)                     | 1.54 [0.79-3.03]   |
| Longevity                |                                  |                                  |                                | 0.50                |
| [0-7]                    | 73 (15.9%)                       | 55 (20.3%)                       | 18 (9.6%)                      | 1.0 (reference)     |
| [7-15]                   | 338 (73.5%)                      | 194 (71.3%)                      | 144 (76.6%)                    | 1.73 [1.19-2.52]   |
| [15-28]                  | 49 (10.6%)                       | 23 (8.4%)                        | 26 (13.8%)                     | 2.15 [1.35-3.44]   |
| Valve replaced, n (%)    |                                  |                                  |                                | 0.22                |
| Mitral                   | 304 (60.9%)                      | 167 (58.0%)                      | 137 (64.9%)                    | 1.0 (reference)     |
| Aortic                   | 188 (37.7%)                      | 115 (39.9%)                      | 73 (34.6%)                     | 1.11 [0.95-1.30]   |
| Tricuspid or pulmonary   | 7 (1.4%)                         | 6 (2%)                           | 1 (0.5%)                       | 1.56 [0.91-2.67]   |
| Number of valves replaced, n (%) |                                  |                                  |                                | 0.31                |
| 1                        | 399 (79.9%)                      | 224 (77.8%)                      | 175 (82.9)                     | 1.0 (reference)     |
| 2                        | 94 (18.8%)                       | 59 (20.5%)                       | 35 (16.6%)                     | 1.12 [0.93-1.35]   |
| 3                        | 6 (1.3%)                         | 5 (1.7%)                         | 1 (0.5%)                       | 1.48 [0.83-2.65]   |
| Blood type, n (%)        |                                  |                                  |                                | 0.22                |
| A                        | 143 (34.2%)                      | 74 (30.3%)                       | 69 (39%)                       | 1.0 (reference)     |
| B                        | 66 (15.7%)                       | 38 (15.6%)                       | 28 (15.8%)                     | 0.8 [0.63-1.20]    |
| AB                       | 28 (6.7%)                        | 18 (7.4%)                        | 10 (5.7%)                      | 0.73 [0.45-1.19]   |
| O                        | 183 (43.5%)                      | 114 (46.7%)                      | 69 (39%)                       | 0.78 [0.60-1.00]   |
| Blood type A (versus other) | 143 (34.0%)                      | 74 (30.3%)                       | 69 (38.9%)                     | 1.24 [0.99-1.56]   |
| Blood type B (versus other) | 66 (15.7%)                       | 38 (15.6%)                       | 28 (15.8%)                     | 1.01 [0.74-1.37]   |
| Blood type AB (versus other) | 28 (6.7%)                        | 18 (7.4%)                        | 10 (5.6%)                      | 0.84 [0.52-1.37]   |
| Blood type O (versus other) | 183 (43.5%)                      | 114 (46.7%)                      | 69 (38.9%)                     | 0.83 [0.66-1.05]   |
| Antigen A, n (%)         |                                  |                                  |                                | 0.20                |


|                                | Positive (A or AB) | Negative (B or O) | Antigen B, n (%) | Positive (B or AB) | Negative (A or O) | Rhesus, n (%) | Bioprosthesis type | Multivariate Analysis |
|--------------------------------|--------------------|-------------------|------------------|--------------------|--------------------|---------------|--------------------|----------------------|
|                                | 168 (39.9%)        | 253 (60.1%)       | 253 (60.1%)      | 94 (22.3%)         | 327 (67.7%)       | 380 (90.3%)   | 161 (33.8%)        | 2.01 [1.81-2.21]      |
|                                | 91 (37.3%)         | 153 (62.7%)       | 153 (62.7%)      | 56 (23.0%)         | 118 (77.1%)       | 220 (89.8%)   | 104 (37.4%)        | 1.50 [0.99-2.26]      |
|                                | 77 (43.5%)         | 100 (56.5%)       | 100 (56.5%)      | 38 (21.5%)         | 149 (84.2%)       | 160 (90.9%)   | 57 (28.7%)         | 1.08 [0.73-1.60]      |
|                                |                    |                   |                  |                    |                    | 41 (9.7%)     |                    |                      |
|                                |                    |                   |                  |                    |                    | 25 (10.2%)    |                    |                      |
|                                |                    |                   |                  |                    |                    | 16 (9.1%)     |                    |                      |
|                                |                    |                   |                  |                    |                    |              | CE-3rd             |                      |
|                                |                    |                   |                  |                    |                    |              | CE-2nd             |                      |
|                                |                    |                   |                  |                    |                    |              | CE-1st             |                      |
|                                |                    |                   |                  |                    |                    |              | Other porcine      |                      |
|                                |                    |                   |                  |                    |                    |              | biopr.             |                      |
|                                |                    |                   |                  |                    |                    |              | Bioprosthesis type |                      |

**Values are mean +/- SD or n (% of n).** P values refer to comparisons between SVD without pannus and SVD with pannus.

**SVD:** structural bioprosthesis degeneration

**CE-1st*/CE-2nd*/CE-3rd:* Carpentier Edwards First/Second/Third generation of porcine bioprostheses

Patient numbers by category may be lower than expected due to missing data.
Table S2. Risks for SVD by calcification for porcine bioprostheses implanted at age ≤60 years.

| n=500 | SVD without calcification n=306 (61.2%) | SVD with calcification n=194 (38.8%) | Univariate Analysis |
|-------|--------------------------------------|-------------------------------------|---------------------|
|       | OR (95%CI)                            | P-Value                             |
| Male sex | 156 (52.2%) | 112 (58.3%) | 1.16 [0.93-1.16] | 0.18 |
| Age at implantation | | | | 0.00097 |
| [7-20] | 11 (4.0%) | 13 (7.1%) | 1.0 (reference) | |
| [20-30] | 58 (20.9%) | 52 (28.4%) | 0.87 [0.56-1.35] | |
| [30-40] | 54 (19.5%) | 44 (24.0%) | 0.83 [0.53-1.30] | |
| [40-50] | 74 (26.7%) | 40 (21.9%) | 0.65 [0.40-1.05] | |
| [50-60] | 80 (28.9%) | 34 (18.6%) | 0.55 [0.33-0.92] | |
| Longevity | | | | 0.034 |
| [0-7] | 38 (13.2%) | 41 (21.7%) | 1.0 (reference) | |
| [7-15] | 214 (74.8%) | 132 (69.8%) | 0.74 [0.56-0.96] | |
| [15-28] | 35 (12.0%) | 16 (8.5%) | 0.60 [0.39-0.93] | |
| Valves replaced, n (%) | | | 0.0041 |
| Mitral | 199 (65.2%) | 105 (54.1%) | 1.0 (reference) | |
| Aortic | 105 (34.4%) | 83 (42.8%) | 1.25 [0.96-1.63] | |
| Tricuspid or pulmonary | 1 (0.3%) | 6 (3.1%) | 2.48 [0.31-4.69] | |
| Number of valves replaced, n (%) | | | 0.021 |
| 1 | 253 (83.0%) | 146 (75.3%) | 1.0 (reference) | |
| 2 | 51 (16.7%) | 43 (22.2%) | 1.25 [0.96-1.63] | |
| 3 | 1 (0.3%) | 5 (2.6%) | 2.28 [1.15-4.52] | |
| Blood type, n (%) | | | 0.13 |
| A | 98 (38.1%) | 45 (27.4%) | 1.0 (reference) | |
| B | 35 (13.6%) | 31 (18.9%) | 1.47 [1.03-2.11] | |
| AB | 15 (5.8%) | 13 (7.9%) | 1.45 [0.48-2.39] | |
| O | 109 (42.4%) | 74 (45.1%) | 1.27 [0.95-1.70] | |
| Blood type A (versus other) | 98 (38.1%) | 45 (27.4%) | 0.74 [0.56-0.96] | 0.024 |
| Blood type B (versus other) | 35 (13.6%) | 31 (18.9%) | 1.25 [0.97-1.64] | 0.15 |
| Blood type AB (versus other) | 15 (5.8%) | 13 (7.9%) | 1.21 [0.78-1.88] | 0.40 |
| Blood type O (versus other) | 109 (42.4%) | 74 (45.1%) | 1.07 [0.84-1.36] | 0.58 |
| Antigen A, n (%) | | | 0.82 [0.64-1.06] | 0.13 |
| Positive (A or AB) | 110 (42.8%) | 58 (35.4%) | |
| Negative (B or O) | 147 (57.2%) | 106 (64.6%) | |
| Antigen B, n (%)       |       |       |       |       |
|----------------------|-------|-------|-------|-------|
| Positive (B or AB)   | 50 (19.5%) | 44 (26.8%) | 1.28 [0.97-1.67] | 0.076 |
| Negative (A or O)    | 207 (80.5%) | 120 (73.2%) |       |       |
| Rhesus, n (%)        |       |       | 0.37 [0.59-1.27] | 0.47 |
| Positive             | 235 (91.1%) | 145 (89.0%) |       |       |
| Negative             | 23 (8.9%) | 18 (11.0%) |       |       |
| Bioprosthesis type   |       |       |       | 0.86 |
| CE-3<sup>rd</sup>    | 101 (34.7%) | 60 (32.3%) | 1.0 (reference) |       |
| CE-2<sup>nd</sup>    | 142 (48.8%) | 96 (51.6%) | 1.08 [0.84-1.39] |       |
| CE-1<sup>st</sup>    | 7 (2.4%) | 6 (3.2%) | 1.24 [0.64-2.40] |       |
| Other porcine bio.   | 41 (14.1%) | 24 (12.9%) | 0.99 [0.68-1.44] |       |

| Calcification |       |       |       |       |
|---------------|-------|-------|-------|-------|
| Age at implantation | 0.81 [0.72-0.89] | 0.014 |
| Number of valves | 1.75 [1.54-2.02] | 0.039 |
| Longevity     | 0.65 [0.45-0.85] | 0.041 |
| Blood type A  | 0.67 [0.45-0.89] | 0.087 |
| (versus other) |       |       |       |       |
| Valves replaced| 1.18 [0.99-1.37] | 0.37 |
| Bioprosthesis type | 1.03 [0.94-1.12] | 0.74 |

The total may be below total number of bioprostheses due to missing data.

+ multivariate analyses comparing the same risk factors but with B antigen as a risk factor and no another ABO type variable show that for B antigen OR 1.34 [1.09-1.59] (p=0.25).
Table S3. Risks for SVD by tears for porcine bioprostheses implanted at age ≤60 years.

| n=500 | SVD without tears n=214 (42.8%) | SVD with tears n=286 (57.2%) | Univariate Analysis |
|-------|---------------------------------|------------------------------|---------------------|
|       | OR (95%CI)                      | P-value                      |
| Male sex | 1.04 [0.90-1.21]                | 0.59                          |
| Age at implantation                        | 0.49                          |
| [7-20] | 1.0 (reference)                 |                               |
| [20-30] | 0.94 [0.63-1.38]                |                               |
| [30-40] | 0.98 [0.67-1.44]                |                               |
| [40-50] | 1.10 [0.78-1.55]                |                               |
| [50-60] | 0.99 [0.68-1.44]                |                               |
| Longevity | 0.083                          |                               |
| [0-7] | 1.0 (reference)                 |                               |
| [7-15] | 0.86 [0.73-1.06]                |                               |
| [15-28] | 0.70 [0.51-0.96]                |                               |
| Valves replaced, n (%) | 0.012                          |
| Mitral | 1.0 (reference)                 |                               |
| Aortic | 0.86 [0.73-1.01]                |                               |
| Tricuspid or pulmonary | 0.23 [0.07-0.73]               |
| Number of valves replaced, n (%) | 0.024                          |
| 1 | 2.02 [1.25-3.26]                | 0.002                         |
| 2 | 0.79 [0.67-0.94]                |                               |
| 3 | 1.02 [0.59-1.76]                |                               |
| Blood type, n (%) | 0.39                           |
| A | 1.0 (reference)                 |                               |
| B | 0.83 [0.73-1.06]                |                               |
| AB | 0.81 [0.57-1.16]                |                               |
| O | 0.88 [0.73-1.06]                |                               |
| Blood A vs other | 1.17 [0.98-1.38]               | 0.078                         |
| Blood B vs other | 0.90 [0.71-1.15]               | 0.39                          |
| Blood AB vs other | 0.88 [0.62-1.26]               | 0.49                          |
| Blood O vs other | 0.95 [0.80-1.13]               | 0.55                          |
| Antigen A, n (%) | 1.08 [0.93-1.10]               | 0.28                          |
| Positive (A or AB) | 1.00 [0.88-1.13]               |                               |
| Negative (B or O) | 0.88 [0.72-1.09]               | 0.25                          |
| Antigen B, n (%) | 1.00 [0.88-1.13]               |                               |
| Positive (B or AB) | 1.00 [0.88-1.13]               |                               |
| Negative (A or O) | 1.00 [0.88-1.13]               |                               |
| Bioprosthesi type | Rhesus, n (%) | 95%CI | P-value |
|------------------|---------------|-------|---------|
| Positive         | 167 (91.3%)  | 0.92 [0.70-1.21] | 0.55 |
| Negative         | 16 (8.7%)    |       |         |
| Bioprosthesi type |               |       |         |
| CE-3rd           | 59 (29.4%)   | 1.0 (reference) |       |
| CE-2nd           | 104 (51.7%)  | 1.19 [0.93-1.52] |       |
| CE-1st           | 9 (4.5%)     | 1.89 [1.10-3.24] |       |
| Other porcine bio. | 29 (14.4%) | 1.22 [0.86-1.72] |       |

### Tears

|                          | Multivariate Analysis |
|--------------------------|-----------------------|
|                          | OR (95%CI)            | P-value |
| Blood A vs other         | 1.61 [1.39-1.83]      | 0.026   |
| Bioprosthesi type        | 0.79 [0.69-0.88]      | 0.014   |
| Number of valves         | 0.66 [0.43-0.89]      | 0.082   |
| Longevity                | 0.84 [0.65-1.03]      | 0.41    |
| Valves replaced          | 0.90 [0.72-1.08]      | 0.60    |

The total may be below total number of bioprostheses due to missing data.
Table 54. Risks for SVD by perforations for porcine bioprostheses implanted at age <60 years.

| n=497 | SVD without perforations n=445 (89,5%) | SVD with perforations n=52 (10.5%) | Univariate Analysis |
|-------|---------------------------------------|----------------------------------|---------------------|
|       |                                       | OR (95%CI)                       | P-value             |
| Male sex | 237 (54.4%) | 31 (56.4%) | 1.07 [0.65-1.78] | 0.78               |
| Age at implantation |                       |                                   | 0.36               |
| [7-20] | 20 (4.7%) | 4 (7.8%) | 1.0 (reference) |                     |
| [20-30] | 104 (24.5%) | 10 (19.6%) | 0.53 [0.18-1.55] |                     |
| [30-40] | 89 (20.9%) | 12 (23.5%) | 0.71 [0.25-2.04] |                     |
| [40-50] | 106 (24.9%) | 14 (27.5%) | 0.70 [0.25-1.97] |                     |
| [50-60] | 106 (24.9%) | 11 (21.6%) | 0.56 [0.19-1.64] |                     |
| Longevity |                     |                                   | 0.71               |
| [0-7] | 67 (16.3%) | 6 (12.0%) | 1.0 (reference) |                     |
| [7-15] | 299 (72.9%) | 39 (78.0%) | 1.40 [0.63-3.15] |                     |
| [15-28] | 44 (10.8%) | 5 (10.0%) | 1.24 [0.40-3.84] |                     |
| Valve replac., n (%) |                       |                                   | 0.41               |
| Mitral | 275 (61.9%) | 31 (56.4%) | 1.0 (reference) |                     |
| Aortic | 162 (36.5%) | 24 (43.6%) | 1.27 [0.73-2.10] |                     |
| Tricusp. or pulm. | 7 (1.6%) | 0 (0.0%) | 0.00               |                     |
| Number of valves replaced, n (%) |                       |                                   | 0.68               |
| 1 | 354 (79.7%) | 45 (81.8%) | 1.0 (reference) |                     |
| 2 | 84 (18.9%) | 10 (18.2%) | 0.94 [0.49-1.80] |                     |
| 3 | 6 (1.4%) | 0 (0.0%) | 0.00               |                     |
| Blood type, n (%) |                       |                                   | 0.13               |
| A | 132 (35.0%) | 11 (25.0%) | 1.0 (reference) |                     |
| B | 55 (14.6%) | 11 (25.0%) | 2.18 [1.01-4.72] |                     |
| AB | 27 (7.2%) | 1 (2.3%) | 0.47 [0.07-3.21] |                     |
| O | 162 (43.0%) | 21 (47.7%) | 1.50 [0.75-2.99] |                     |
| Blood A vs other |                       |                                   | 0.65 [0.34-1.23] | 0.18               |
| Blood B vs other | 55 (14.6%) | 11 (25%) | 1.79 [0.95-3.39] | 0.072              |
| Blood AB vs other | 27 (7.2%) | 1 (2.8%) | 0.33 [0.05-1.94] | 0.36               |
| Blood O vs other | 162 (42.9%) | 21 (47.7%) | 1.19 [0.68-2.08] | 0.55               |
| Antigen A, n (%) |                       |                                   | 0.56 [0.30-1.05] | 0.071              |
| Positive (A or AB) | 156 (41.4%) | 12 (27.3%) |                     | +                  |
| Negative (B or O) | 221 (58.6%) | 32 (72.7%) |                     |                     |
| Antigen B, n (%) |                       |                                   | 1.79 [0.41-1.43] | 0.41               |
| Positive (B or AB) | 82 (21.8%) | 12 (27.3%) |                     |                     |
| Negative (A or O) | 295 (78.3%) | 32 (72.7%) |                     |                     |
| Rhesus, n (%) |                       |                                   | 1.47 [0.49-4.44] | 0.67               |
| Positive | 339 (89.9%) | 41 (93.2%) |                     |                     |
| Negative | 38 (10.1%) | 3 (6.8%) |                     |                     |
| Bioprosthesi type | CE-3rd | CE-2nd | CE-1st | Other porcine bio. |
|------------------|--------|--------|--------|-------------------|
|                  | 141(33.2%) | 218 (51.3%) | 10 (2.4%) | 56 (13.2%) |
|                  | 20 (38.5%)  | 20 (38.5%)  | 3 (5.8%)   | 9 (17.3%)   |
|                  | 1.0 (reference) | 0.68 [0.38-1.21] | 1.86 [0.61-5.65] | 1.11 [0.53-2.32] |

| Perforations     | Multivariate analysis |
|------------------|-----------------------|
| Blood B vs other | OR (95%CI) | P-value |
|                  | 2.21 [1.83-2.59]      | 0.043   |
| Valve replac.    | 0.70 [0.41-0.99]      | 0.23    |
| Bioprosthesi type| 0.85 [0.70-1.00]      | 0.30    |
| Age at implantation | 0.93 [0.62-1.24] | 0.83 |
| Number of valves | 1.08 [1.01-1.16]       | 0.83    |

The total by factor may be lower than total number of bioprostheses because of missing data.

Since blood type B was the only significant value using univariate analysis, all the factors were included for multivariate analysis.

+ **Additional** Multivariate analysis for blood group A antigen and all other risks, except variables related to ABO blood group, demonstrates that SVD by perforation will decrease in presence of A antigen: OR 0.53 [0.17-0.89] (p=0.076)
Table S5. Multivariate analysis for involvement of AB blood group in porcine and bovine SVD by calcifications (age at implantation $\leq$60yrs).

| Variables                     | Risk of SVD isolated calcification |
|-------------------------------|-----------------------------------|
|                               | 11% [8.4-13.6]                    |
| Bioprostheses n=562 Porcine n=500 + Bovine n=62 | Multivariate Analysis |
|                               | OR (95%CI) | P-value |
| Valves replaced               | 1.92 [1.66-2.14] | 0.0084 |
| Blood group AB vs others      | 2.74 [2.30-3.18] | 0.035  |
| Age at implantation           | 0.82 [0.70-0.94] | 0.10   |
| Number of valves              | 1.49 [1.21-1.77] | 0.17   |
| Bovine vs Porcine             | 1.97 [1.69-2.59] | 0.28   |
| Longevity                     | 0.80 [0.53-1.07] | 0.43   |
| Male sex                      | 0.83 [0.54-1.12] | 0.55   |
| Bioprosthesis type            | 0.92 [0.78-1.06] | 0.58   |
| Rhesus positive               | 1.00 [0.53-1.47] | 1.00   |
Table S6. Multivariate analysis for involvement of AB blood group in porcine and bovine SVD by pannus or tears (age at implantation ≤60yrs).

| Bioprostheses n=562 | Risk of SVD pannus or tears |
|---------------------|-----------------------------|
| Porcine n=500       | 84.4% [81.4-87.4]           |
| + Bovine n=62       |                             |

| Variables                  | Multivariate Analysis |
|----------------------------|-----------------------|
|                            | OR (95%CI)            | P-value   |
| Number of valves           | 0.52 [0.27-0.77]      | 0.014     |
| Blood group AB vs other    | 0.37 [0.07-0.67]      | 0.03      |
| Valves replaced            | 1.54 [1.32-1.76]      | 0.05      |
| Bioprosthesis type         | 1.18 [1.06-1.3]       | 0.17      |
| Bovine vs Porcine          | 0.53 [0.28-0.78]      | 0.28      |
| Age at implantation        | 1.08 [0.98-1.18]      | 0.47      |
| Male sex                   | 0.93 [0.55-1.07]      | 0.81      |
| Rhesus positive            | 0.90 [0.49-1.31]      | 0.82      |
| Longevity                  | 1.02 [0.78-1.26]      | 0.91      |