A COMPARISON OF OUTCOMES BETWEEN BOVINE PERICARDIAL AND PORCINE VALVES IN 38,040 PATIENTS IN ENGLAND AND WALES OVER 10 YEARS

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Short title: A comparison of bovine and porcine valves

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ABSTRACT

Aim: Biological valves are the most commonly implanted prostheses for aortic valve replacement (AVR) surgery in the United Kingdom. The aim of this study was to compare performance of porcine and bovine pericardial valves implanted in AVR surgery with respect to survival and intervention-free survival in a retrospective observational study.

Methods: Prospectively collected clinical data for all first-time elective and urgent AVRs with or without concomitant coronary artery bypass graft (CABG) surgery performed in England and Wales between April-2003 and March-2013 were extracted from the National Institute for Cardiovascular Outcomes database. Patient life-status was tracked from the Office for National Statistics. Time-to-event analyses were performed using log-rank tests and Cox proportional hazards regression modelling with grouped frailty for responsible cardiac surgeons.

Results: A total of 38,040 patients were included (64.9% bovine pericardial; 35.1% porcine). Patient and characteristics were similar between the groups. Median follow-up was 3.6 years. There was no statistically significant difference in survival (P=0.767) (10-year survival was 49.0% and 50.3% in the bovine pericardial and porcine groups respectively) or intervention-free survival. The adjusted hazard ratio for porcine valves was 0.98 [95%CI 0.93-1.03]. Sensitivity analysis in small valve sizes showed no difference in intervention-free survival. There was some evidence of a protective effect for porcine valves in relatively younger patients (P=0.074).

Conclusion: There were no differences in intervention free survival between bovine pericardial and porcine valves used in first-time AVR ± CABG up to a maximum of 10 years.

Keywords: aortic valve replacement; porcine; bovine pericardial; outcomes

INTRODUCTION

Biological prosthetic valves are a standard choice of implant for aortic valve replacement (AVR) in older patients, as they do not require the patient to take a lifelong regime of anticoagulation medication, negating the associated complications. There has also been a shift towards biological valve implantation in relatively younger patients reported.[1] Between 2004 and 2008, 21,360 out of 30,443 (70.2%) implanted prostheses were reported as being biological.[2] The most frequently implanted biological valves are either porcine xenograft valves or bovine pericardial tissue valves. These valves have been extensively studied since their first use in the 1960s and 70s because they suffer calcification and structural deterioration, in addition to standard valve replacement complications such as thromboembolic events; endocarditis; and patient-prosthesis mismatch. To date, the evidence base of outcomes for these valves is based on a series of relatively small-randomised studies and some larger non-randomised case series. The data on comparative outcomes is inconclusive with some reported benefits in haemodynamic and complication endpoints, but no differences in survival.[3]

The largest study to date contains fewer than 2000 valves of any one type, which would be unlikely to pick up small but important differences in late outcomes. The aim of this study is to compare the performance of prosthetic porcine xenograft and bovine pericardial valves implanted in aortic valve replacement surgery with respect to in-hospital mortality, mid-term survival and intervention-free survival on a large cohort using 10-years of national registry data collected in hospitals in England and Wales.

MATERIALS AND METHODS

Data extraction and pre-processing

Prospectively collected data were extracted from The National Institute for Cardiovascular Outcomes Research (NICOR) National Adult Cardiac Surgery Audit (NACSA) registry (version 4.1.2) on 14th January 2014 for all adult cardiac surgery procedures performed in the United Kingdom. As described elsewhere, reproducible cleaning algorithms were applied to the database.[4] Briefly, duplicate records and non-adult cardiac surgery entries (including transcatheter aortic valve implantations [TAVIs]) were removed; transcriptional discrepancies harmonised; and clinical and temporal conflicts and extreme values corrected or removed. The data is returned regularly to each unit for local validation as part of the National Adult Cardiac Surgery Audit in the United Kingdom.[2]

For this study, records were included if they corresponded to either an isolated AVR or AVR + CABG operation, with a bio-prosthetic implant performed in England and Wales between 1st April 2003 and 31st March 2013. No other concomitant surgery was included. Exclusion criteria for this study were: 1) evidence of previous cardiac surgery; 2) emergency or salvage operation; 3) missing data for the responsible consultant cardiac surgeon; 4) data on discharge status or postoperative follow-up were missing.

Study and outcome variables

For each operation, data are recorded on patient characteristics, comorbidities, surgical team, intra-operative factors, and post-operative outcomes. For this study we extracted data on patient age at time of operation (years); gender; body mass index (BMI; defined as weight [kg] / height^2 [m^2]); operative urgency; dyspnoea (NYHA grade); history of neurological dysfunction; diabetes (diet or insulin controlled); history of hypertension; pulmonary hypertension (defined as a PA systolic pressure >60 mmHg); recent myocardial infarction (defined as within 90-days of surgery); serum creatinine >200 μmol/l; history of pulmonary disease; extracardiac arteriopathy; left ventricular ejection fraction (classified as <30%, 30-50%, and >50%); critical preoperative state (defined as per

the EuroSCORE group); use of preoperative IV nitrates; concomitant CABG; haemodynamics; active infective endocarditis.

Administrative data was also extracted including: patient admission, procedure and discharge dates, and responsible consultant cardiac surgeon. Valve data extracted from the registry were valve name, model and size (mm). Names and model are recorded in the registry as free-text fields. For each record we also calculated the logistic EuroSCORE. Further details of variable definitions are available at http://www.ucl.ac.uk/nicor/audits/adultcardiacsurgery/datasets.

The outcomes for this study were 1) in-hospital mortality, defined as death due to any cause during admission to the base hospital for cardiac surgery; 2) mid-term survival from all-cause mortality; and 3) intervention-free mid-term survival. Patients who died in-hospital on the day of surgery were recorded as having a nominal survival time of 0.5 days. Follow-up data up until the point of discharge was collected by the NACSA clinical registry system and post-discharge survival data was collected by linking the records via patient NHS numbers to the Office for National Statistics (ONS) death registry, which records all deaths in England and Wales. Data on cause of death was unavailable. An attempt to back-fill missing in-hospital mortality data was made by record linkage to the ONS registry.

A re-intervention was defined as any surgery on the aortic valve in a separate subsequent admission spell, regardless of urgency or any concomitant surgery, performed up to the 31st March 2013. As the NACSA registry is a procedural database, i.e. each operation receives its own separate entry; re-intervention was determined by identifying patients in the study according to their unique National Health Service (NHS) number who reappeared in the National Adult Cardiac Surgery Audit registry with evidence of aortic valve surgery. The time between the first and second operation on the aortic valve defines the time-to-event.

Valve classification

Valve type (bovine pericardial or porcine) is not explicitly recorded in the adult cardiac surgery registry. Instead, an algorithm was written that maps each recorded free-text name and model

to a homogenous list of known prosthetic valves. This list was developed from studying manufacturer catalogues; directly contacting valve companies; and using the Society of Thoracic Surgeons definitions file (http://www.sts.org/sites/default/files/documents/ValveDevices20140117.txt; last accessed 13 March 2014). Some hospitals used an internal coding system, and these units were contacted directly for the coding system. For each record, we recorded the valve manufacturer, model, series and (xeno-) type. Not all valves could be classified at the model level, for example "Edwards Lifesciences Perimount" could be one of a number of specific valves. In such a situation we could still identify the valve manufacturer, series and (xeno-) type, which was sufficient for this study. For each record, the number of matches to the list of known valves was recorded.

After running this algorithm, a record was excluded if: 1) the valve name / model was missing or completely unidentifiable to the manufacturer level; 2) it was over-matched to more than one manufacturer, series, model or xenotype; 3) no match to a (xeno-) type could be made. In addition, any implants that were identified to be annuloplasty rings, valved conduits, or designed for use in the mitral position, were excluded from the analysis. As the focus of this study is in comparison of bovine pericardial and porcine valves, any bioprostheses identified as being any different type of xenograft (homografts, autografts or equine pericardium) were also excluded. No exclusion criteria on stented / stentless or sutured / sutureless was imposed as the purpose was only to compare material.

As the UK valve market is dominated by five prosthetic heart valve manufactures (Edwards Lifesciences, Medtronic, St. Jude Medical, Sorin Group and Vascutek), we excluded three manufacturers with very small numbers of implants: Cryolife O'Brien, Shelhigh and Labcor.

Statistical analysis

Multiple imputation using chain equations was used to impute missing patient characteristic data and valve size.[5] A total of 5 imputed data sets were generated. Variables included in the imputation models were all clinical and patient study variables in addition to valve model, valve size, year of operation and responsible consultant cardiac surgeon.

Categorical and dichotomous variables are summarised as absolute number and percentage. Continuous data are summarised as mean ± standard deviation (SD). Means of continuous variables were compared between groups using the independent samples *t*-test. Categorical and dichotomous variables were contrasted using the chi-square test. Due to the large sample size in each valve group, patient characteristics were also compared between bovine pericardial and porcine prostheses by means of standardised (bias) difference. A variable with absolute standardised difference of <10% supports the assumption of 'balance' between the two groups of patients.[6] For each surgeon, the bovine pericardial prosthesis implantation rate is determined and compared to the total case volume.

Time-to-event data are presented as Kaplan-Meier graphs stratified by xenotype, and compared using the log-rank test. To derive adjusted effects for xenotype, for each of the five imputed datasets, a Cox constant proportional hazards models with grouped frailty for the responsible consultant cardiac surgeons was fitted using a Gaussian distribution (with mean zero and standard deviation θ) for the random effects.[7] All extracted patient demographics, comorbidities, and pre-operative variables were included in the regression model. Valve type (bovine pericardial / porcine) was forced into the model. The logistic EuroSCORE was not entered into the model as we included most constituent risk factors separately. BMI was included as a quadratic polynomial term. Patient age was entered as piecewise linear polynomial with a single knot at 65 years; this specific modelling decision and knot selection was determined from examination of the smoothed martingale residual plot.[8] The fixed effects for the five models are pooled according to Rubin's rule and reported as hazard ratios with 95% confidence intervals.[9]

Two supportive subgroup analyses were performed, each exclusively comparing differences in intervention-free survival. First, we estimated the univariable hazard ratio (taking into account the missing data by multiple imputation and combining the separate results, as per above) for valve type in the subset of patients implanted with a valve of size ≤21mm. Surgeon effects were adjusted for as per above. This is to examine whether any mid-term differences in intervention-free survival are detectable in the spectrum of valve sizes with known gradient differences between bovine pericardial and porcine prostheses. Second, we compared the valve types in patients aged <60 years, and

separately in patients aged ≥60 years at time of surgery, using a log-rank test for the first-imputed dataset only. Only 3 patients (<0.01%) had missing age data, therefore multiple imputation techniques were not applied. As a sensitivity analysis to this, an adjusted pooled hazard ratio was calculated.

All analyses and data cleaning were performed in R version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Independent samples *t*-tests were used for comparison of means of continuous data. Multiple imputations were performed using the MICE package (version 2.21). Frailty models were fitted using the R coxme package (version 2.2-3). In all cases, a *P*-value <0.05 was considered significant.

RESULTS

Exploratory analyses

From a total of 49,375 AVR ± CABG operations with bio-prosthetic implants performed in England and Wales over the 10-year study period, 38,040 patients were included in this study after applying the inclusion and exclusion criteria (**Figure 1**). In total 31 different valve classifications were included (**Table 1**): 24,695 bovine pericardial (64.9%) and 13,345 porcine (35.1%). The most frequently implanted bovine pericardial prosthesis was the Edwards Lifesciences Perimount 2900 (24.5%; 6062 / 24,695). The most frequently implanted porcine valve was the Medtronic Mosaic (26.5%; 3534 / 13,345). Edwards Lifesciences made up the largest market share (56.7%).

The numbers of missing data were low, with all patient variables having <2% missing data except for BMI (2.5%), pulmonary hypertension (10.1%), creatinine >200 μmol/l (5.4%), haemodynamics (2.8%), active infective endocarditis (6.9%). The patient characteristics between the bovine pericardial and porcine group were well balanced, as shown for the first imputed dataset (**Table 2**), consistent with a hypothesis that there is no treatment assignment selection bias. However, statistical tests of homogeneity did identify some variables as being significantly different; namely logistic EuroSCORE, age, gender, operative urgency, NYHA class, pulmonary hypertension, history of pulmonary disease, extracardiac arteriopathy, left ventricular function, preoperative IV nitrates, critical preoperative state, and valve haemodynamics.

There was considerable scatter between total AVR ± CABG volume and the bovine pericardial implantation rate (**Figure 2**). However, there are clusters of surgeons who predominantly use bovine pericardial or porcine valves. Interestingly, low- and moderate-volume surgeons have a greater propensity to use bovine pericardial valves. The decision about whether to implant a bovine pericardial or porcine valve might be explained by a surgeon's propensity to use one particular manufacturer, rather than a particular valve type. There were a large number of surgeons who predominantly implanted an Edwards Lifesciences valve. Edwards Lifesciences predominantly supply bovine pericardial valves.

The bovine pericardial implantation rate forms a distinctive u-shape: dipping in 2007-08 (57.3%) before increasing again (73.2% at 2012-13; **Figure 3**). Conversely, the porcine implantation rate forms an n-shape, peaking in 2007-8. Volume has generally been increasing annually.

In-hospital mortality

There were 764 (3.1%) and 406 (3.0%) in-hospital deaths in the bovine pericardial and porcine groups respectively, which was not statistically significantly different ($P = 0.806$).

Survival

Follow-up data was tracked up until 30th July 2013. A total of 666 patients (1.8% records; 511 bovine pericardial, 155 porcine) did not have post-discharge follow-up; however, they are included in the analysis by censoring them at the point of discharge. The median follow-up time was 3.6 years (ranging from 0.5 days to 10.3 years). There were a total of 8731 deaths during follow-up (5652 bovine pericardial, 3079 porcine), but no statistically significant difference in survival ($P = 0.767$; **Figure 4; top panel**). Survival at 1-, 5- and 8-years was 92.2%, 77.0% and 61.3% respectively in the bovine pericardial group, and 92.1%, 77.0% and 61.8% respectively in the porcine group. Survival at 10-years was 49.0% in the bovine pericardial group and 50.3% in the porcine group, however there were only 354 patients (<1%) at risk at this time point.

For regression model development, pulmonary hypertension was removed as it yielded a counterintuitive coefficient and was highly non-significant. NYHA grades I and II were combined into a single reference group for dyspnoea, and stenosis and mixed lesions were combined into a single reference group for haemodynamics. The adjusted hazard ratio for porcine valve implantation was 0.98 [95% CI 0.93 – 1.03] ($P = 0.41$; **Table 3**).

Intervention-free survival

Of the 38,040 first-time cardiac surgery patients who had an AVR ± CABG, 387 (1.0%) had a re-intervention during the follow-up. Of the 387 patients, 376 (97.1%) had a single re-intervention and 11 (2.8%) had two re-interventions. For the composite endpoint of mortality or re-intervention, there

were a total of 9002 events during follow-up (5817 bovine pericardial, 3185 porcine), but no statistically significant difference in survival ($P = 0.97$; **Figure 4; bottom panel**). Intervention-free survival at 1-, 5- and 8-years was 92.0%, 76.4% and 60.2% respectively in the bovine pericardial group, and 91.8%, 76.2% and 60.6% respectively in the porcine group. At 10-years the intervention-free survival was 47.4% and 49.4% in the bovine pericardial and porcine groups respectively. The adjusted hazard ratio for porcine valve implantation was 0.98 [95% CI 0.94 – 1.03] ($P = 0.50$).

Subgroup analyses

Data on valve size was missing in 0.9% (329 / 38,040) of records and were imputed as part of the data imputation algorithm. The mean valve size in the bovine pericardial and porcine groups was 22.6 ± 2.2 mm and 23.1 ± 2.2 mm respectively for the first imputed dataset (standardised difference -21.8%; *t*-test $P < 0.001$). There were 14,189 valves (9937 [70.0%] bovine pericardial, 4252 [30.0%] porcine) in the first imputed dataset with a valve size ≤21 mm. Note that this number will slightly change with each imputed dataset. There was a statistically significant difference in mid-term intervention-free survival when comparing the 4 groups: bovine pericardial ≤21 mm; bovine pericardial >21 mm; porcine ≤21 mm; and porcine > 21 mm ($P < 0.001$; **Figure 5; top panel**). When comparing bovine pericardial to porcine valves in only the subset of valve sizes of ≤21 mm, there was no significant difference ($P = 0.52$). The pooled hazard ratio in favour of porcine valve implantation was 0.97 [95% CI 0.90 – 1.05] ($P = 0.43$), rejecting the null hypothesis of a difference in intervention-free survival as a result of active selection of a higher gradient.

There were 2084 patients aged <60 years at time of surgery (68.4% bovine pericardial; 31.6% porcine) and 35,956 patients aged ≥60 years (64.7% bovine pericardial; 35.3% porcine), giving a standardised difference of 3.7%. There was a statistically significant difference in mid-term intervention-free survival when comparing the 4 groups: bovine pericardial <60 years; bovine pericardial ≥60 years; porcine <60 years; and porcine ≥60 years ($P < 0.001$; **Figure 5; bottom panel**). Although no difference between valves in the ≥60 years old group ($P = 0.87$), there was some indication of a protective effect in the porcine valves for the <60 years old group ($P = 0.055$). It was

found that in this relatively younger group of patients, the bovine group was on average 1-year older (51.7 vs. 50.6; standardised difference 11.7%); had a higher prevalence of diabetes (13.5% vs. 9.9%; standardised difference 11.2%); and had a higher prevalence of pulmonary hypertension (1.3% vs. 0.3%; standardised difference 10.9%). Adjusting for these potential confounding variables, in addition to selected other variables (gender, operative urgency, NYHA class, creatinine >200μmol/l, left ventricular ejection fraction; concomitant CABG and active infective endocarditis) and surgeon effects, the adjusted hazard ratio pooled over all imputed datasets was 0.78 [95% CI 0.60 – 1.02] (P = 0.075)

DISCUSSION

Principal findings

This study shows no difference in survival or intervention free-survival between a large group of patients who had either a bovine pericardial or porcine tissue valve implanted in the aortic position between 2003 and 2013. Despite previously published evidence on the haemodynamic benefits of bovine pericardial valves as well as biological properties, these do not translate into better survival.[3,10,11] There is no difference in survival between valve types in patients with a small prosthesis (≤21 mm), in whom difference in gradient between the valve types would be most marked. There was some evidence of better long-term intervention-free survival for the porcine valve in the relatively younger patient group (<60 years old), however this did not attain statistical significance.

Comparison to other studies

Reichenspurner et al. examined 1123 bioprostheses (4 bovine pericardial models and 4 porcine models) over a 12-year study window in the aortic (67% of implants), mitral and tricuspid position.[12] They reported a statistically significant ($P < 0.05$) difference in mid-term survival; at 10-years survival was 61.0% (bovine pericardial) and 67.8% (porcine). However, this study represented operations between 1978 and 1990, including a number of first generation valves no longer in commercial use. Dalmau et al. randomised 108 patients undergoing AVR between 2004 and 2006 to receive either Edwards Lifesciences Perimount Magna (bovine pericardial) or Medtronic Mosaic (porcine) implants.[13] They reported survival at 5 years to be 94.4% (bovine pericardial) and 79.6% (porcine), which was statistically significant ($P = 0.039$). They postulated that this difference might be attributable to favourable haemodynamics and improved left ventricular hypertrophy regression. This contrasts with our study where we have seen no difference in survival between porcine and bovine pericardial valves at 10-years of follow-up. Our study includes a heterogeneous group of both bovine pericardial and porcine valves, and whilst it does not preclude adverse or indeed superior outcomes in specific model types, it does show the 'class' of tissue valve, *per se*, does not affect survival.

We found no evidence of selection bias, as measured by the standardised difference. Therefore, the clinical hypothesis that bovine pericardial valves might be selected for females, who are more likely to have small aortic roots, is not irrefutably supported (standardised difference 5.6%), despite being significantly different ($P < 0.001$). Interestingly though, this was one of largest standardised differences, with a increase of 2.7 percentage points in female prevalence for bovine pericardial valves. Of interest there was no difference in the incidence of poor left ventricular function between the groups, indicating that surgeons are not in general using this, and the need for better haemodynamics in these patients, as a decision criterion for bovine pericardial valves. After adjusting for other patient characteristics and surgeon effects, choice of valve type was not associated with a difference in survival or intervention-free survival.

Limitations

This study was based on a national registry that has been collected over many years. Observational 'real world' data routinely has inaccuracies and this registry is no exception. However, there has been extensive validation of the data undertaken after submission and analysis by the units and surgeons submitting data as part of the UK cardiac surgery governance programme. Extensive on-going data cleaning algorithms were applied to the registry before analysis. Another common limitation of large clinical registries is missing data. The numbers of missing data were relatively small in this study; however a few variables did have a large number of missing data. To overcome this we incorporated multiple imputation, which is a robust method for imputation that also takes into account the additional element of uncertainty.

The National Adult Cardiac Surgery Audit registry does not feature predefined valves for selection in completing valve surgery data. Many hospitals have used a specific coding system or homogenous set of models and some allow free-text by the individual surgeons. This has inevitably led to an increase in data inconsistencies and missing data. A total of 5295 (12.0%) records were excluded due to missing data, unidentified coding, conflicts or unknown xenograft type. This situation is expected to improve in the future due to increased scrutiny on healthcare device monitoring.

Our definition of re-intervention was any surgery on the aortic valve performed up to 31st March 2013 in a separate subsequent admission spell. A limitation of this is that re-interventions performed between 1st April 2013 and 30th July 2013 (the date of census for mortality tracking) were not included; hence it is possible that the intervention-free survival rates have been slightly underestimated. Re-intervention was determined by identifying patients in the study according to their NHS number who reappeared in the NACSA registry. The NHS number was missing for 1524 patients (4.0%), which required us to track these patients using their patient-hospital number. If these patients have a re-intervention elsewhere, it might not have been properly counted. Finally, a re-intervention only included surgical aortic valve procedures. Transcatheter aortic valve implantation has been increasingly used in the United Kingdom in the latter half of this study window; however they are recorded in a separate registry and are therefore not included in the re-intervention rate.[14] We do not believe that any of these limitations could significantly affect the overall findings.

The classification of valves into bovine pericardial and porcine valves masks intra-class variation between models. Numerous studies have compared specific valve types, both within and between xenograft types.[11–13,15] Specific valve properties such as stented or stentless mounting might also be associated differently within each xenograft type.[16] The focus of this study is purely on the xenograft type. Although the focus of this study was on xenograft type, future work may involve assessing differences between different valve models.

Although this study recorded results out to a maximum of 10.3 years, the median follow-up time was only 3.6 years. It would be expected that differences would manifest beyond this time interval, thus requiring longer follow-up. Moreover, we do not have data on cause of death, which would be beneficial for learning whether death was due to SVD.

Meaning of study

A number of studies have shown better haemodynamic performance in the bovine pericardial valves than compared to porcine valves.[3,13,17–19] It might be extrapolated that better haemodynamics will translate into more rapid and complete regression of left ventricular modelling with better

survival. On the other hand, some studies have shown either superior haemodynamic performance or no-difference in the porcine group compared to the bovine pericardial group.[20,21]

The differential haemodynamics are most marked in small prosthesis size, and as a sensitivity analysis we have repeated our study including only valves with recorded sizes of ≤21 mm and found no change in conclusions. On the basis of these findings there would seem to be clinical equipoise between porcine and bovine pericardial valves. It was previously believed that porcine valves should not be used in younger patients.[22,23] However, more recent studies have shown that at 20-years, the performance in the Hancock II porcine valve is excellent and superior to that of the Edwards Lifesciences Perimount valve in younger patients.[24,25] We found that there was a trend towards increased intervention-free survival in the porcine valve group compared to the bovine pericardial group; however, this did not reach statistical significance.

Conclusion

Over 10-years follow-up (with a median follow-up time of 3.6 years), there is no statistically significant difference in the performance of bovine pericardial and porcine bioprostheses implanted into first-time cardiac patients undergoing AVR ± CABG. Follow-up beyond 10-years is required as part of continuous monitoring and other endpoints should be monitored post-operatively including non-surgical re-intervention, functional class and haemodynamics.[3] We have not analysed the data for specific model type within the general bovine pericardial / porcine classes, and it remains possible that specific valve models may be associated with different survival characteristics.

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DISCLOSURES

None

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Figure 1. Flowchart describing patient numbers.

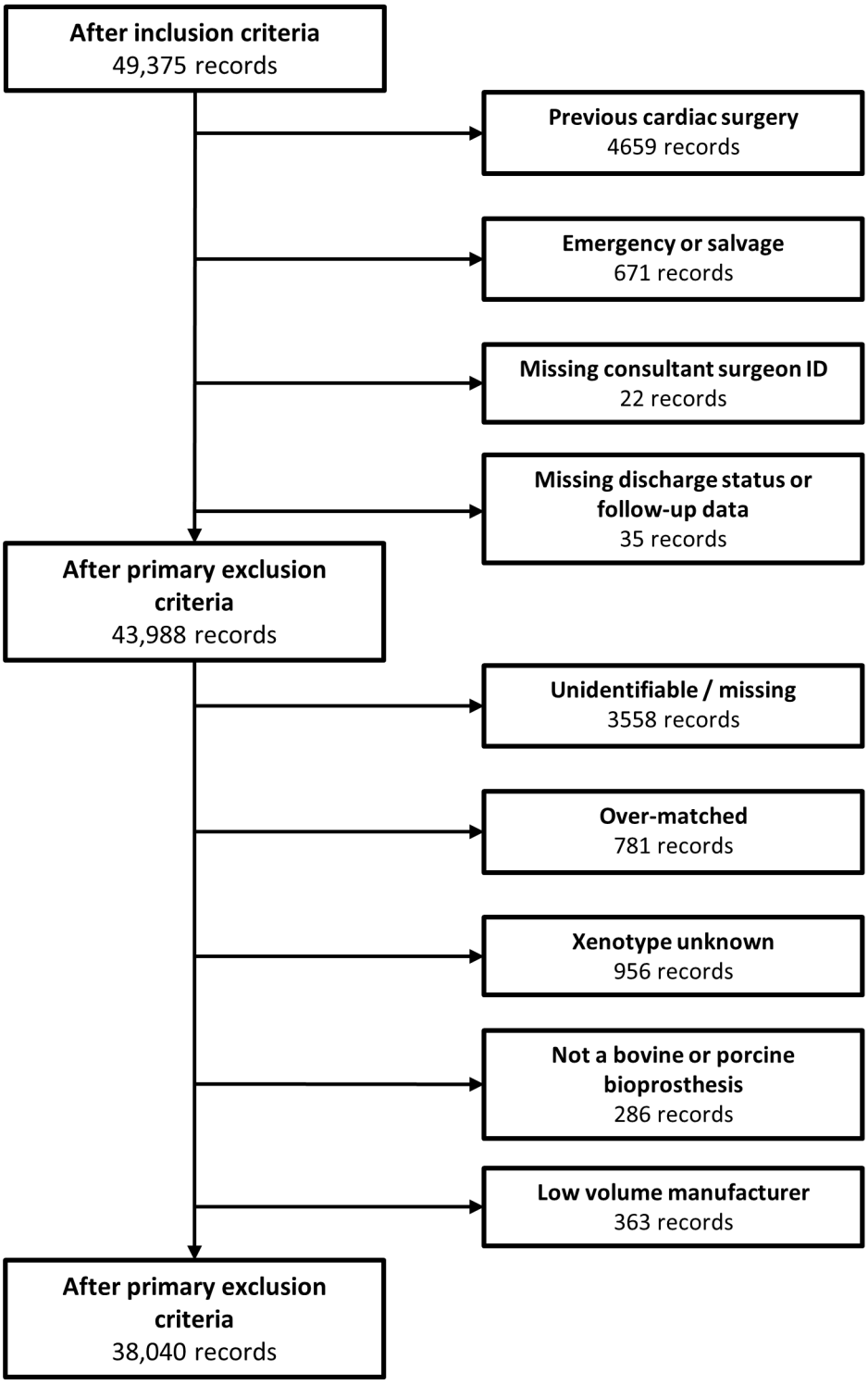


Figure 2. Total AVR ± CABG volume against bovine pericardial prosthesis implantation rate over the 10-years. Each point represents a distinct cardiac surgeon.

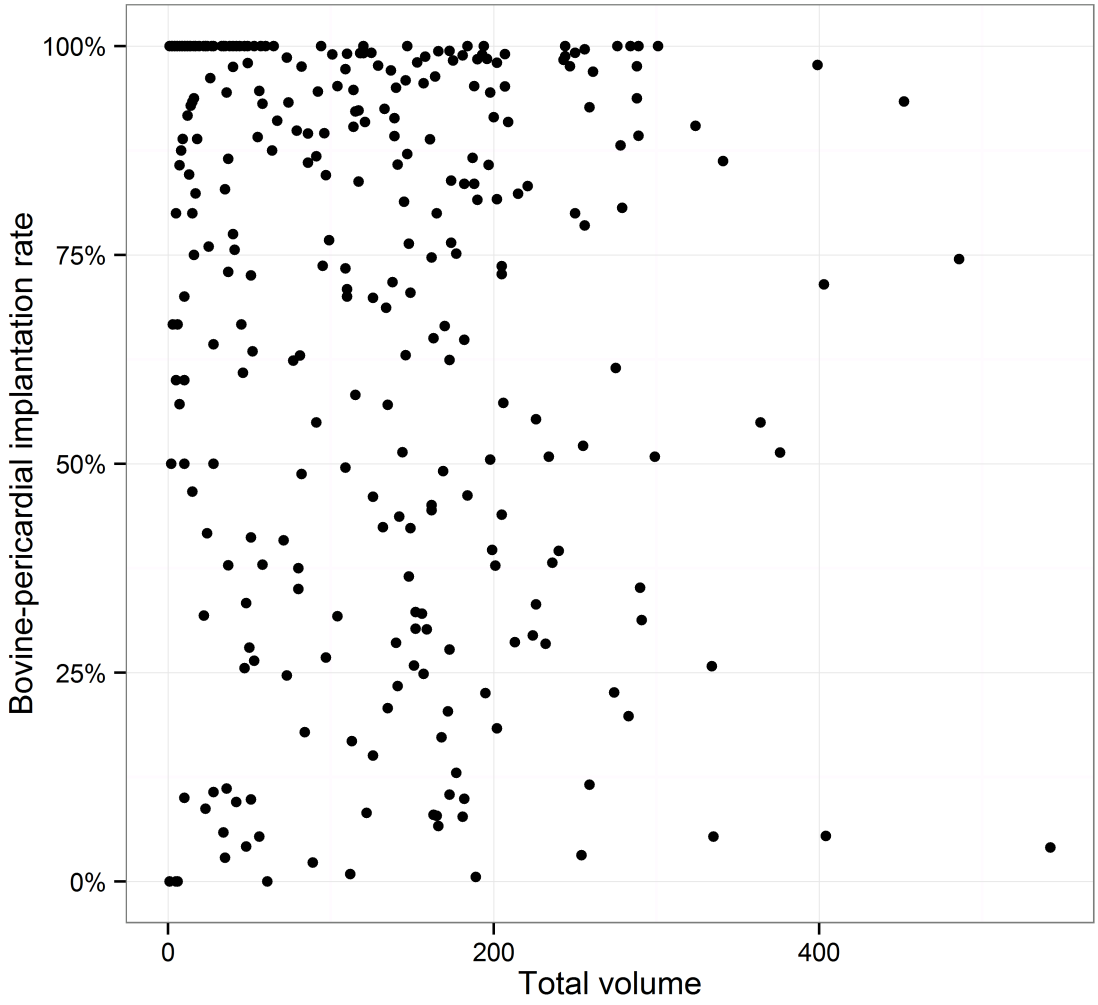


Figure 3. Time trend of bovine pericardial valve implantation rate. The size of the points is proportional to the total number of AVR ± CABG procedures included in the study each year.

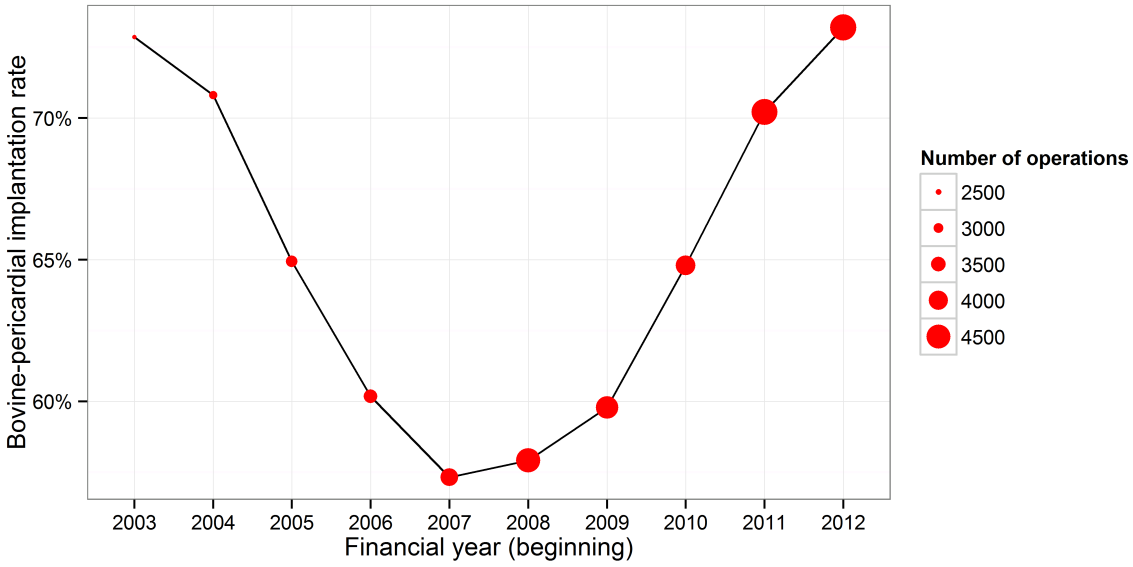


Figure 4. Kaplan-Meier curves stratified by valve type for survival (top panel) and intervention-free survival (bottom panel).

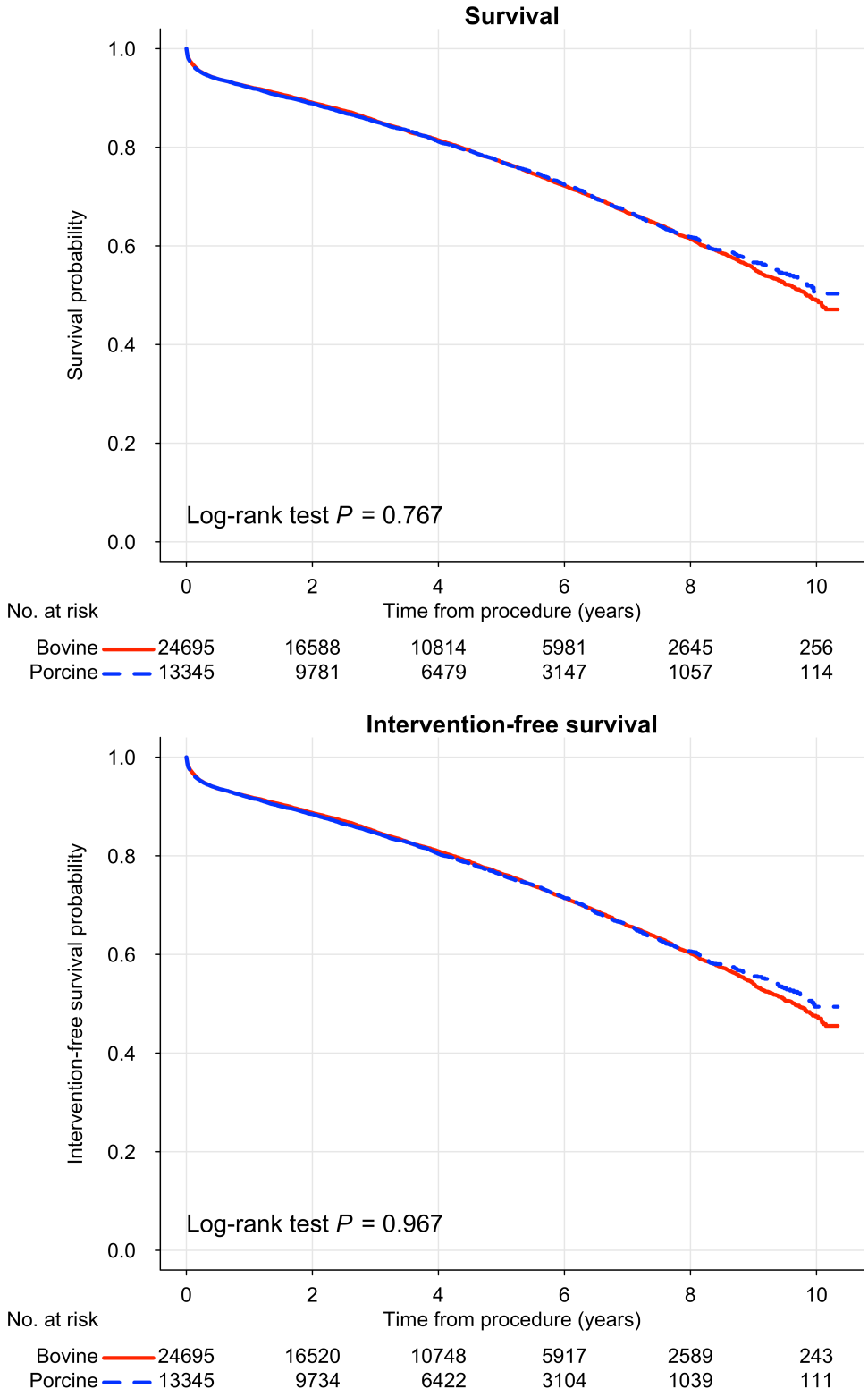
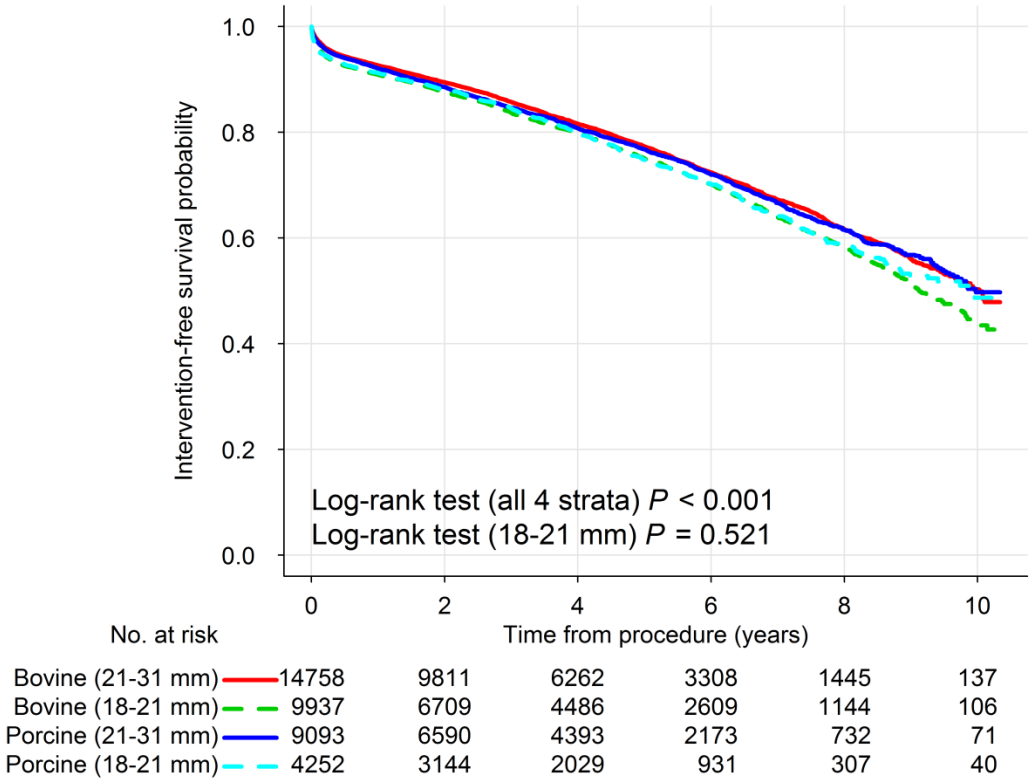


Figure 5. Kaplan-Meier curves stratified by valve type and (i) dichotomised valve size (top panel); (ii) dichotomised age at operation (bottom panel).



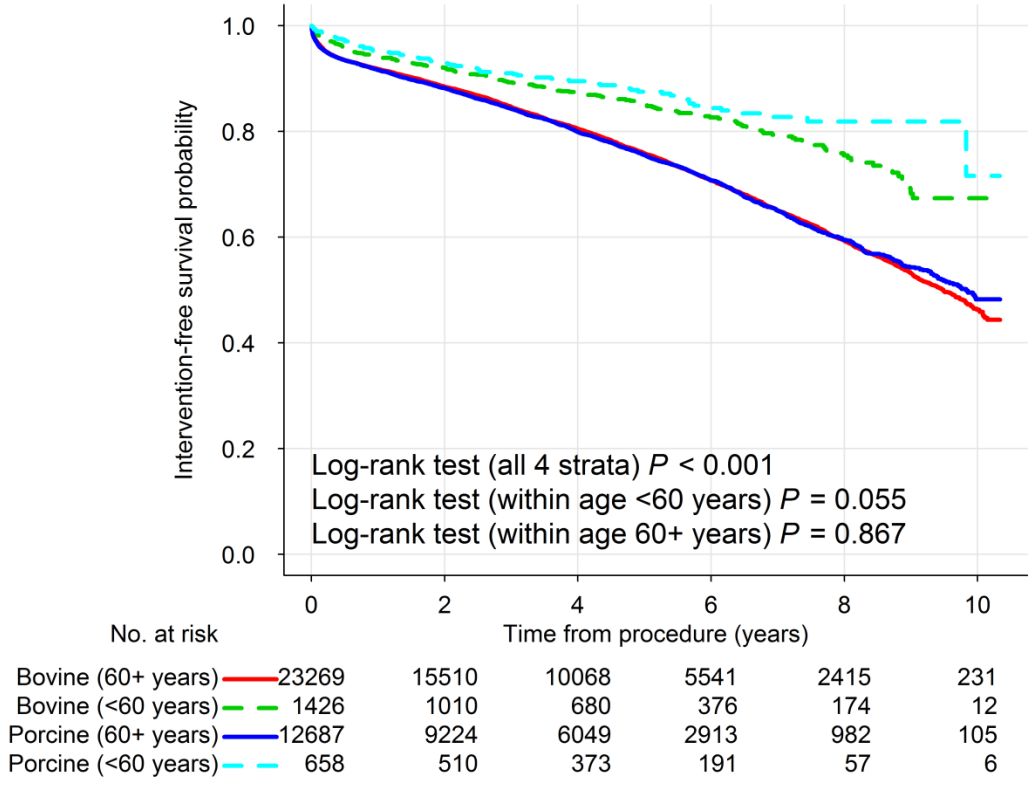


Table 1. Number of bioprostheses implanted over the study period.

Bovine pericardial		(*N* = 24,695)
Edwards Lifesciences	Perimount 2700	31
	Perimount 2900	6062
	Perimount (unidentified sub-model)	3193
	Perimount Magna 3000	3496
	Perimount Magna with Thermafix 3000TFX	617
	Perimount Magna Ease 3300TFX	5509
	Perimount Magna (unidentified sub-model)	1110
	Intuity 8300	1
	Unknown	1
Sorin Group	Freedom Solo	158
	Pericarbon Freedom	284
	Soprano Armonia	353
	Perceval S	11
	Mitroflow #	2973
	Unknown	4
St Jude Medical	Trifecta	892
Porcine		(*N* = 13,345)
Edwards Lifesciences	Aortic Valve 2625	875
	Supra-annular Aortic Valve 2650	588
	Prima Plus Stentless 2500P	52
St Jude Medical	Epic Valve	2445
	Epic Supra Valve	1918
	Toronto Stentless Porcine Valve	14
	Biocor valve	67

Medtronic	Freestyle Stentless	127
	Hancock II	2531
	Mosaic	3534
Vascutek*	Elan	109
	Aspire	1085

* Includes the same valves under the holdings of Tissuemed, Kohler and Aortech.

Includes different generations (12A, LXA and DLA)

Table 2. Patient characteristics for the first imputed dataset stratified by aortic valve type.

	Bovine pericardial (*N* = 24,695)		**Porcine** (*N* = 13,345)		**Standardised difference**	***P***
	Mean	**SD**	**Mean**	**SD**		
Logistic EuroSCORE (%)	8.5	7.7	8.2	7.1	3.7	0.003
Age (years)	73.2	8.6	73.7	8.5	-5.8	<0.001
BMI	28.0	5.0	28.0	4.9	1.0	0.342
	N	**%**	***N***	**%**		
Female	9687	39.2	4870	36.5	5.6	<0.001
Urgent	5777	23.4	2950	22.1	3.1	0.005
Dyspnoea						0.003
NYHA I	3620	14.7	1970	14.8	-0.3	
NYHA II	9738	39.4	5500	41.2	-3.6	
NYHA III	9742	39.4	5039	37.8	3.5	
NYHA IV	1595	6.5	836	6.3	0.8	
History of neurological dysfunction	684	2.8	337	2.5	1.5	0.169
Diabetes	4600	18.6	2444	18.3	0.8	0.461
History of hypertension	16,378	66.3	8853	66.3	0.0	0.980
Pulmonary hypertension	427	1.7	172	1.3	3.6	0.001
Recent MI	1647	6.7	848	6.4	1.3	0.245
Creatinine >200 µmol/l	517	2.1	276	2.1	0.2	0.899
History of pulmonary disease	4038	16.4	2031	15.2	3.1	0.004
Extracardiac arteriopathy	2588	10.5	1242	9.3	3.9	<0.001
Left ventricular function						0.044
LVEF >50%	17,926	72.6	9843	73.8	-2.6	
LVEF 30-50%	5327	21.6	2741	20.5	2.5	

LVEF < 30%	1442	5.8	761	5.7	0.6	
Preoperative IV nitrates or heparin for treatment of unstable angina	490	2.0	192	1.4	4.2	<0.001
Critical preoperative state	488	2.0	189	1.4	4.3	<0.001
Concomitant CABG	11,481	46.5	6189	46.4	0.2	0.840
Haemodynamics						0.049
Stenosis	18,689	75.7	10,018	75.1	1.4	
Regurgitation	1845	7.5	954	7.1	1.2	
Mixed	4161	16.8	2373	17.8	-2.5	
Active infective endocarditis	230	0.9	116	0.9	0.7	0.581

Abbreviations: BMI – body mass index; MI – myocardial infraction; LVEF – left ventricular ejection fraction; IV – intravenous; CABG – coronary artery bypass graft.

Table 3. Pooled results of Cox proportional hazards frailty regression models for mid-term survival fitted separately to each of five multiple imputed datasets.

	HR	95% CI			*P*-value
Porcine valve	0.980	0.933	-	1.029	0.414
Age (years)	1.006	0.997	-	1.015	0.207
$(Age - 65)_+$ (years)	1.066	1.055	-	1.078	<0.001
BMI (kg / m^2)	0.863	0.840	-	0.888	<0.001
BMI^2 $(kg / m^2)^2$	1.002	1.002	-	1.003	<0.001
Female	0.896	0.856	-	0.938	<0.001
Urgent	1.175	1.115	-	1.238	<0.001
NYHA III	1.241	1.184	-	1.301	<0.001
NYHA IV	1.422	1.312	-	1.540	<0.001
History of neurological dysfunction	1.153	1.023	-	1.300	0.020
Diabetes	1.322	1.251	-	1.396	<0.001
History of hypertension	1.047	0.998	-	1.097	0.060
Recent MI	1.035	0.954	-	1.123	0.406
Creatinine >200 µmol/l	2.136	1.929	-	2.365	<0.001
History of pulmonary disease	1.364	1.293	-	1.440	<0.001
Extracardiac arteriopathy	1.293	1.214	-	1.377	<0.001
LVEF 30-50%	1.293	1.230	-	1.361	<0.001
LVEF <30%	1.662	1.534	-	1.801	<0.001
Critical preoperative state	1.232	1.073	-	1.415	0.003
Preoperative IV nitrates	1.135	0.987	-	1.306	0.077
Concomitant CABG	1.201	1.148	-	1.257	<0.001
Regurgitation	1.092	0.995	-	1.199	0.062
Active infective endocarditis	1.303	1.043	-	1.628	0.020

Abbreviations: HR – hazard ratio; CI – confidence interval; BMI – body mass index; MI – myocardial infraction; LVEF – left ventricular ejection fraction; IV – intravenous; CABG – coronary artery bypass graft. $(\text{Age} - 65)_+$ denotes 1 year for every year aged above 65 years; e.g. if age was 75, then $(75 - 65)_+ = 10$; if age = 55, then $(55 - 65)_+ = 0$. Mean value of θ was 0.12 (2 d.p.).