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# Survival Outcomes in Under 65 Years Old Patients Receiving Either Biological or Mechanical Aortic Valve? A Single Centre Study

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***Abstract***

**Objectives:** *Several recent studies of prosthetic aortic valve replacement (AVR) have suggested a poorer long-term survival of tissue valves compared to mechanical valves. For intermediate age group (55- 65 years), the impact of the type of aortic prosthesis on long term survival is still not very well understood. The aim of our study is to examine the impact of prosthesis choice on long term survival following AVR in patients under 65 years of age.*

**Methods:** *A retrospective analysis of patients who underwent surgical aortic valve replacement between January 1998 and September 2018 was performed. Inverse probability weighting (IPW) was used to balance baseline characteristics between valve type groups. Kaplan-Meier estimation was used to assess long-term survival between groups, with log-rank tests to calculate statistical significance (assumed significant p<0.05).*

**Results:** *A total of 1981 patients were included. 1425 patients received the biological and 556 the mechanical prosthesis. Initial analysis of all patients showed survival rates at 15 years post-operatively were reduced in the biological valve recipients compared with mechanical (66.6% and 82% respectively, p<0.001). Subsequently patients were split into sub groups of <55 years of age and 56 to 65 years of age. Using IPW showed no significant difference in survival between the valves at 1, 5, 10 and 15 years post-operatively in both groups.*

**Conclusions:** *Long term survival following AVR is not related to the type of prosthesis.*

**Keywords:** *Aortic valve replacement, Biological, Mechanical, Prosthesis, Long term survival.*

## Abbreviations and Acronyms

AHA/ACC - American Heart Association/American College of Cardiology

AVR - Aortic Valve Replacement

BMI - Body Mass Index

CABG - Coronary Artery Bypass Grafting

EACTS - European Association of Cardiothoracic Surgery

HR - Hazard Ratio

NHS - National Health Service

NICOR - National Institute for Cardiovascular Research Outcomes

PDS - Personal Demographics Service

## Introduction

Aortic valve replacement (AVR) is an established treatment for severely symptomatic aortic valve disease. There are several types of prosthesis available, ranging from mechanical to biological and homograft's [1,2]. Mechanical prostheses require lifelong anticoagulation due to the increased risks of blood clot formation [3]. Biological prostheses are made from bovine, porcine aortic valves or autologous pericardium and are at risk of structural degeneration over time [1,4]. These considerations influence patients and clinicians decision making when choosing a preferred prosthesis [5].

European Association of Cardiothoracic Surgery (EACTS) guidelines suggest that a mechanical prosthesis should be used for aortic valve replacement in patients <60 years of age (level of evidence II) and a biological one in patients >65 years old [6]. Mechanical prostheses are favoured if rapid structural valve degeneration is suspected and are mainly used in young patients or those with increased metabolic activity (hyperthyroidism, hyperparathyroidism and renal failure) [7-9]. There are reasons for re-operation beyond structural valve deterioration, such as pannus growth, endocarditis and valve thrombosis, but the requirement for re-operations is low [10].

Biological prostheses are also recommended if anticoagulation compliance is of concern or for re-operation of thrombosed mechanical prostheses despite therapeutic anticoagulation. Both of these recommendations are class IIa and level C [6].

The American Heart Association/American College of Cardiology (AHA/ACC) have also produced guidance for aortic valve type choice in 2014 and updated these in 2017. These largely mirror the EACTS guidelines, stating that it is the patients informed choice. However they recommend that patients under the age of <50 years receive the mechanical valves and patients over the age of >70 years receive the bio prosthetic option **[**11**]**.

At Blackpool Victoria Hospital we have been implanting both types of valves for 20 years and recently we noted a trend towards using more biological valves across all patients. This correlates with retrospective reports from other centres which show an increased number of patients having biological valves at younger ages **[**12,13**]**. Several retrospective reviews have been performed to try to ascertain which valve has better longevity and prognosis for the patient. There are studies which show conflicting results, some suggest that a mechanical valve shows significantly better survival rates at 15 years post-op, and others show no significant difference in survival between valve types.

Generally, there is a clinical consensus that younger patients have better outcomes with mechanical valves and older patients with biological valves. However for patients between the ages of 55 and 65 the choice of type of implant prosthesis is down to the discretion of patients and recommendation from clinicians. The aim of this study is to evaluate and compare survival outcomes of patients in this age group receiving either a biological or mechanical aortic valve.

## Patients and Methods

### Data Collection

All patients who underwent an isolated surgical aortic valve replacement at Blackpool Victoria Hospital between May 1998 and September 2018 were retrospectively reviewed. Aortic valve replacement is defined as removal of the native valve and replacement with a prosthesis. Patients that had concomitant coronary artery bypass grafting or other valve surgery during the same operation were excluded. Both emergency and elective cases were included. Some patients were excluded from the study due to unknown post-operative outcome and a small number were excluded due to low BMI which would not have allowed for reliable statistical analysis (Figure 1).

Patients were compared across two prosthesis groups (mechanical vs biological) and were further split into sub-populations of patients up to 55 years ("younger" group) and patients 56-65 years ("middle-aged" group).

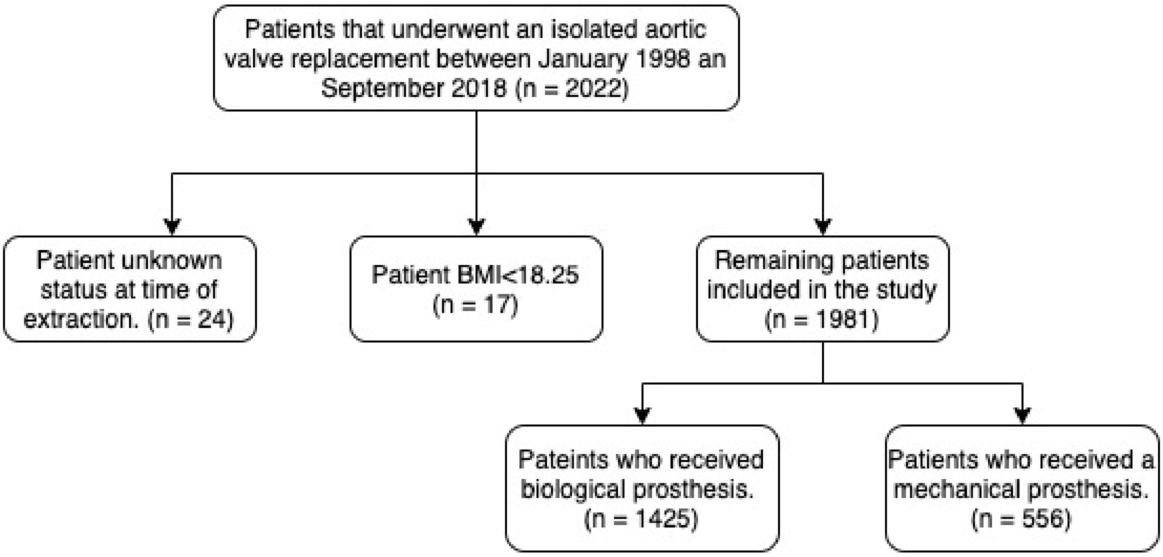


**Figure 1.** Details of selection criteria for patients included in the analysis.

Demographics of the patient, operative data and outcomes were collected using the National Institute for Cardiovascular Research Outcomes (NICOR) database. This database holds national data in the UK for patients undergoing cardiac surgery including those at Blackpool Victoria Hospital. Long term survival was obtained from the Personal Demographics Service (PDS) of the National Health Service (NHS) patients, and data was extracted in December 2018.

**Statistical Analysis**

Pre-operative characteristics were compared across prosthesis groups in both the full cohort (n=1981, Table1) and the sub-populations of the younger and middle-aged groups. Figures are presented as number (%) for categorical variables and median **[**quartile 1, quartile 3**]** for continuous variables; all continuous variables were found to be non-normally distributed (Kolmogorov-Smirnov tests $p<0.05$). Testing of differences between implant groups for categorical variables was performed using Chi-squared tests, or Fisher exact tests where group sizes were small. Testing of differences for continuous variables was performed using unpaired Wilcoxon rank sum tests (Mann-Whitney tests).

Additionally, a standardised mean difference (SMD) is quoted, so that a dimensionless variable difference can be quantified even where differences do not achieve statistical significance. As a rule of thumb, an SMD~0.2 denotes a small difference, SMD~0.5 a moderate difference, and SMD~0.8 a large difference. Here, for addressing covariate imbalance, we desire SMD≤0.1.

Kaplan-Meier estimation was used to assess long-term survival between groups, with log-rank tests to calculate the statistical significance of any observed difference (assumed significant with $p<0.05$).

Univariate Cox Proportional Hazards models were used to explore variables affecting survival outcomes, stepwise regression was used in variable selection for the model (a parameter deemed significant with p<0.05).

| Characteristic | | Biological valve *n=1425* | Mechanical valve *n=556* | Test of difference | |
|---|---|---|---|---|---|
| Age | *raw* | 74 **[68,79]** years | 58 **[49,64]** years | **p<0.001** | |
| | Age ≥ 65 | 1216 (85.3%) | 136 (24.4%) | **p<0.001** | |
| Gender | Female | 661 (46.4%) | 193 (34.7%) | **p<0.001** | |
| BMI | | 27.2 **[**24.2, 31.0**]** | 27.7 **[**24.7, 31.3**]** | p=0.057 | |
| Grouped: | Normal | 451 (31.6%) | 155 (27.9%) | p=0.25 | |
| | Overweight | 548 (38.5%) | 223 (40.1%) | | |
| | Obese | 425 (29.8%) | 178 (32.0%) | | |
| Operative priority | Elective | 1236 (86.7%) | 464 (83.4%) | **p=0.001** | $p_{El}$= 0.07 |
| | Urgent | 13 (0.9%) | 17 (3.1%) | | **$p_{Em}$ <0.001** |
| | Emergency | 176 (12.4%) | 75 (13.5%) | | $p_U$=0.54 |
| Hypertension *(missing = 40)* | Yes | 844 (60.2%) | 229 (42.3%) | **p<0.001** | |
| Diabetes | None | 1194 (83.7%) | 506 (91.1%) | **p<0.001** | **$p_{None}$ <0.001** |
| | Diet | 73 (5.1%) | 12 (2.2%) | | **$p_{Diet}$= 0.005** |
| | Oral medication | 106 (7.4%) | 28 (5.0%) | | $p_{Oral}$= 0.070 |
| | Insulin | 52 (3.6%) | 9 (1.6%) | | $p_{Ins}$= 0.027 |
| Angina | None | 818 (57.4%) | 309 (55.6%) | p=0.15 | |
| | CCS1 | 250 (17.5%) | 92 (16.5%) | | |
| | CCS2 | 246 (17.3%) | 97 (17.4%) | | |
| | CCS3 | 97 (6.8%) | 45 (8.1%) | | |
| | CCS4 | 14 (1.0%) | 13 (2.3%) | | |

| | | | | |
|---|---|---|---|---|
| Dyspnoea | NYHA1 | 249 (17.5%) | 107 (19.2%) | p=0.55 |
| | NYHA2 | 523 (36.7%) | 205 (36.9%) | |
| | NYHA3 | 564 (39.6%) | 204 (36.7%) | |
| | NYHA4 | 89 (6.2%) | 40 (7.2%) | |

**Table 1.** Pre-operative characteristics of the 1981 patients.

### Inverse Probability Weighting (IPW)

Logistic regression is used to create propensity scores for the probability of receiving a mechanical valve. Covariates used in this logistic regression are characteristics known to affect the choice of valve and/or mortality: age, sex, BMI, previous myocardial infarction (yes/ no), angina (none/CCS 1-2/CCS 3-4), dyspnoea (NYHA 1-2/NYHA 3-4), renal disease (yes/no), diabetes (yes/ no), smoking status (never/ex/current), ejection fraction category (poor/fair/good), history of neurological disease (yes/no), extracardiac arteriopathy (yes/no), hypertension (yes/no), and haemodynamic pathology (mixed/stenosis/regurgitation). Inverse probability weights are calculated as the inverse of these propensity scores for the mechanical group and as the inverse of one minus the propensity score for the biological group, and are then stabilised by multiplying each by the marginal probability of receiving the treatment that patient did actually receive. To avoid undue bias from extreme weights, stabilised weights are then truncated at the 1st and 99th percentile, with truncated weights set to the value of those percentiles. Balance is then assessed on this weighted population and characteristics are deemed as well-balanced with a standardised mean difference (SMD) of no more than 0.1.

As the question of interest concerns the middle-aged patients, and because this group demonstrate the largest change in valve choice over time, the data is stratified first by age with separate models, propensity scores and survival analyses then carried out for each stratification. The focus is on patients aged 56-65 years old, though some consideration is made of patients aged 55 years and under in view of increasing patient choice for biological valves.

## Results

### Valve Type Trends Over Time

Considering all patients, we see both a large increase in the number of AVRs taking place, and that most of these use biological valves (Figure 2, top).

Breaking down these procedures into age groups shows that the greatest driver for this is the rise in the number of AVR procedures among patients over 65 year old, who most often opt for a biological valve (Figure 2, centre).

However, we know that the youngest patients largely opt for mechanical valves, so splitting the younger patients further into those 55 years old or under, and those aged 56-65 (Figure 2, bottom) gives greater insight: patients under 55 years old still mostly have mechanical valves and this is unchanged over time. Patients in the “middle-aged” (56-65) category are increasingly shifting towards having biological valves rather than mechanical ones; from 2011 we observe that although the number of procedures performed is roughly constant, the proportion of having mechanical implants is declining and biological valves is increasing.

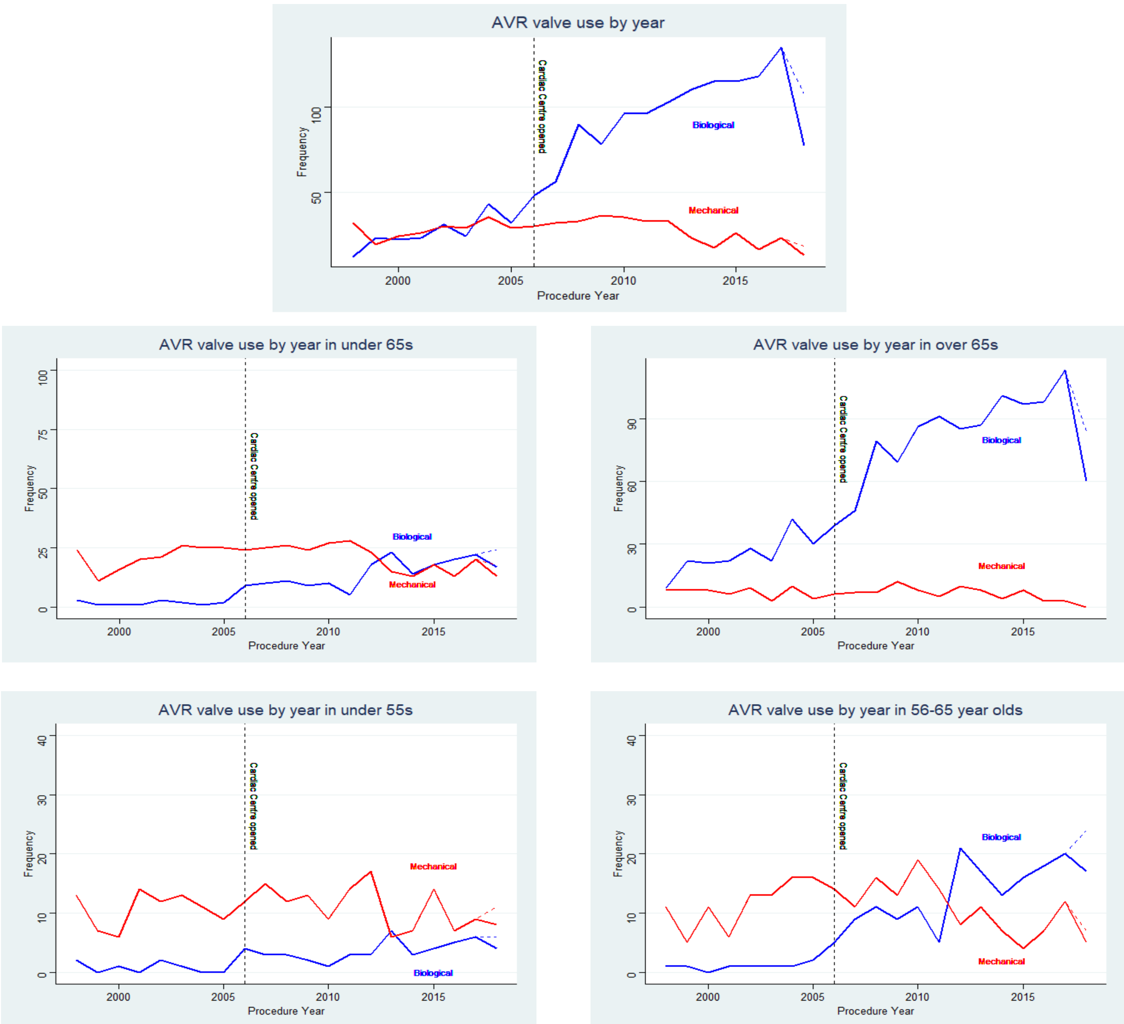


**Figure 2.** AVR valve use over time for particular age groups. Note that around 9 months of data is available for 2018; the dashed lines at the end of each plot forecast the 2018 full year total from the part year total.

**Survival**

Survival rates of the 1981 patients from the two groups are calculated at 1 year, 5 years, 10 years and 15 years and shown in Table 2. Mortality from any cause was included. Results suggest that survival is similar in the short term, but that mechanical valves increasingly out-perform biological valves in the longer term. Biological vs mechanical valve survival at 5 years (93.7 and 97.2%), 10-years (76.6% and 91.2%) and 15 years (51.1% and 80.8%) all showed a significant difference. Knowing that patients receiving mechanical valves are on average 16 years younger than biological valve patients (Table 1), further exploration is required to discern whether it is the biological valve itself or the fact that those patients are more elderly that causes this observed difference in survival rates.

The Kaplan-Meier estimate of survival of AVR patients in each group is shown in Figure 3. There is a clear difference in survival for patients receiving biological (red) and mechanical (blue) valves, demonstrated by both the very significant log-rank test ($p<0.001$) and by the distinct separation between confidence bands around the KM estimates.

The relationships between patient characteristics, valve type and survival are further quantified using a Cox model; results shown in Table 3. The interpretation of the two age covariates is that being in the 65-and-over age group is associated with a risk of death 2.8 times that of a patient aged under 65, but that each year a patient is older than 65 confers an additional 4% risk of death as well.

The model shows that gender and diabetes status are not associated with any increase in risk of death, but that patients that were overweight or obese had better survival than those with a healthy BMI (Hazard Ratio (HR) 0.63 and 0.71 respectively.).

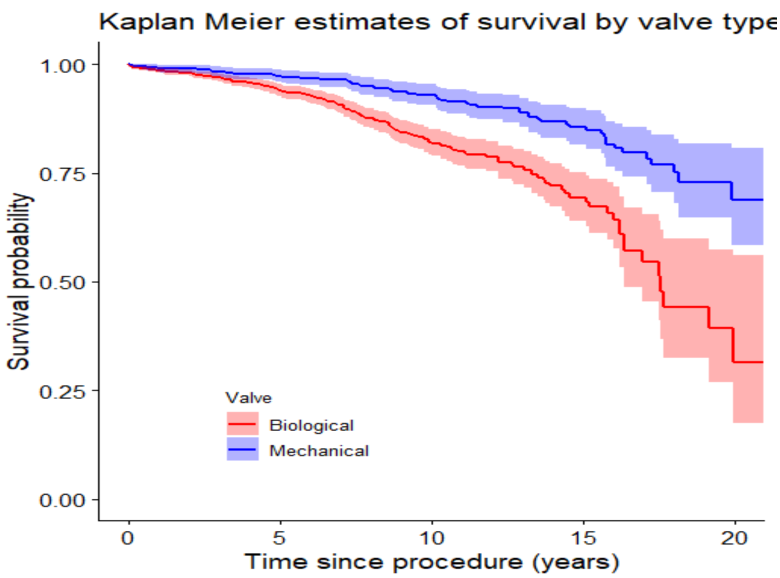


**Figure 3.** Kaplan-Meier survival estimates by valve type (n=1981). Log rank test: $p<0.001$

| | Biological valve | Mechanical valve | Test of difference |
|---|---|---|---|
| **1 year** Op. date < 31/12/2017 $n_B$=1350 , $n_M$=543 | 1330(98.5%) | 538 (99.1%) | p=0.46 |
| **5 years** Op. date < 31/12/2013 $n_B$=869 , $n_M$=469 | 814 (93.7%) | 456 (97.2%) | **p=0.007** |
| **10 years** Op. date < 31/12/2008 $n_B$=389 , $n_M$=317 | 298 (76.6%) | 289 (91.2%) | **p<0.001** |
| **15 years** Op.date < 31/12/2003 $n_B$=131 , $n_M$=156 | 67 (51.1%) | 126 (80.8%) | **p<0.001** |

**Table 2.** Survival estimates of all patients in the study (n=1981).

| | | Hazard Ratio (HR) | | p-value |
|---|---|---|---|---|
| Valve type | *Ref: biological* | | | |
| | Mechanical | 2.029 | (0791, 5.207) | 0.141 |
| Age *(binary)* | *Ref: age < 65* | | | |
| | Age ≥ 65 | 2.833 | (1.071, 7.495) | **0.036** |
| Age *(continuous)* | Years older than 65 | 1.040 | (1.018, 1.063) | **<0.001** |
| Gender | *Ref: female* | | | |
| | Male | 0.979 | (0.753, 1.273) | 0.875 |
| Mechanical AND age ≥ 65 | (interaction term) | 0.372 | (0.131, 1.055) | 0.063 |
| BMI | *Ref: Normal weight* | | | |
| | Overweight | 0.634 | (0.471, 0.854) | **0.003** |
| | Obese | 0.706 | (0.501, 0.995) | **0.046** |
| Priority | *Ref: elective* | | | |
| | Emergency | 1.732 | (0.750, 4.000) | 0.199 |

| | | | | |
|---|---|---|---|---|
| | Urgent | 1.712 | (1.250, 2.344) | **<0.001** |
| Diabetes | *Ref: none* | | | |
| | Diet controlled | 1.186 | (0624, 2.254) | 0.603 |
| | Oral therapy | 0.761 | (0.387, 1.494) | 0.427 |
| | Insulin | 1.777 | (0.131, 1.055) | 0.117 |

**Table 3:** Cox proportional hazards model for time to death, n=1979 with 234 events (2 observations removed due to incomplete data). Independent variable

## Sub-Population Analysis

### Characteristics

Having shown that age is significantly associated with the hazard of death in our dataset, we analysed subgroups of patients under 65 years of age. The two sub-populations analysed consist of 270 patients aged up to 55 years ("younger" group), of whom 53 received a biological and 217 a mechanical valve, and 401 patients aged 56-65 years ("middle-aged" group), of whom 178 received a biological and 223 a mechanical valve. The median length of follow-up for the younger group is 5.4 years for those with a biological valve and 10.6 years for mechanical valves. In the middle-aged group follow-up is 5.4 years and 11.3 years respectively.

Tables 4A and 4B summaries the baseline characteristics of the younger and middle-aged groups respectively, both before and after weighting. Characteristics that are not balanced between biological and mechanical groups, that is, that have SMD>0.1, are highlighted in bold font. We see that the IPW technique yields balanced pseudo-populations for both age categories, with no SMD greater than 0.1 in the younger group and 0.04 in the middle-aged group.

| Variable | BEFORE WEIGHTING | | | | AFTER WEIGHTING* | | | |
|---|---|---|---|---|---|---|---|---|
| | Biological (n=53) | Mechanical (n=217) | p-value | SMD | Biological (n=51.6) | Mechanical (n=216.8) | p-value | SMD |
| **Age in years** | 45.3 (7.7) | 45.0 (8.2) | 0.74 | 0.05 | 45.2 (7.5) | 45.0 (8.2) | 0.94 | 0.03 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sex** | Male | 37 (69.8%) | 159 (73.3%) | 0.61 | 0.08 | 37.4 (72.5%) | 157.7 (72.7%) | 0.97 | 0.01 |
| **BMI** | | 27.4 (5.6) | 28.3 (5.4) | 0.29 | **0.16** | 28.2 (5.9) | 28.1 (5.4) | 0.95 | 0.01 |
| **Angina** | None<br>CCS 1-2<br>CCS 3-4 | 34 (64.2%)<br>14 (26.4%)<br>5 (9.4%) | 131 (60.4%)<br>66 (30.4%)<br>20 (9.2%) | 0.85 | 0.09 | 34.1 (66.1%)<br>13.4 (26.0%)<br>4.1 (7.9%) | 132.9 (61.3%)<br>64.0 (29.5%)<br>19.9 (9.2%) | 0.81 | 0.10 |
| **Dyspnoea** | NYHA 3-4 | 21 (39.6%) | 84 (38.7%) | 0.903 | 0.02 | 202 (39.1%) | 84.1 (38.8%) | 0.97 | 0.01 |
| **Renal disease** | | 2 (3.8%) | 7 (3.2%) | 0.84 | 0.03 | 1.4 (2.6%) | 6.9 (3.2%) | 0.81 | 0.03 |
| **Previous MI** | | 1 (1.9%) | 7 (3.2%) | 0.61 | 0.09 | 1.1 (2.2%) | 6.4 (3.0%) | 0.79 | 0.05 |
| **Diabetic** | | 4 (7.5%) | 14 (6.5%) | 0.78 | 0.04 | 2.7 (5.3%) | 14.3 (6.6%) | 0.70 | 0.06 |
| **Smoking** | Never<br>Ex<br>Current | 20 (37.7%)<br>25 (47.2%)<br>8 (15.1%) | 88 (40.6%)<br>81 (37.3%)<br>48 (22.1%) | 0.34 | **0.23** | 20.1 (39.0%)<br>21.9 (42.4%)<br>9.6 (18.6%) | 86.9 (40.1%)<br>85.0 (39.2%)<br>44.9 (20.7%) | 0.91 | 0.07 |
| **Ejection Fraction** | Poor<br>Fair<br>Good | 1 (1.9%)<br>13 (24.5%)<br>39 (73.6%) | 12 (5.5%)<br>31 (14.3%)<br>174 (80.2%) | 0.13 | **0.31** | 1.8 (3.4%)<br>8.9 (17.2%)<br>40.9 (79.3%) | 10.5 (4.8%)<br>35.5 (16.4%)<br>170.8 (78.8%) | 0.91 | 0.07 |
| **Neurological disease** | | 2 (3.8%) | 19 (8.8%) | 0.23 | **0.21** | 3.4 (6.6%) | 16.9 (7.8%) | 0.81 | 0.05 |
| **Extracardiac arteriopathy** | | 1 (1.9%) | 3 (1.4%) | 0.79 | 0.04 | 0.5 (0.9%) | 2.9 (1.4%) | 0.74 | 0.04 |
| **Haemodynamic pathology** | Mixed<br>Regurg.<br>Stenosis | 12 (22.6%)<br>21 (39.6%)<br>20 (37.7%) | 48 (22.1%)<br>92 (42.4%)<br>77 (35.5%) | 0.93 | 0.06 | 10.1 (19.6%)<br>22.5 (43.6%)<br>19.0 (36.8%) | 47.8 (22.1%)<br>90.9 (41.9%)<br>78.1 (36.0%) | 0.93 | 0.06 |
| **Hypertension** | | 16 (30.2%) | 68 (31.3%) | 0.87 | 0.025 | 14.9 (28.9%) | 67.3 (31.1%) | 0.77 | 0.05 |

**Table 4A:** Weighted and unweighted comparisons of baseline characteristics for patients aged under or equal to 55 years. Figures are given as “mean (SD)” or as “frequency (%)” for continuous and categorical variables respectively. *weighted frequencies may not be integers. SMD=standardised mean difference.

| Variable | | BEFORE WEIGHTING | | | | AFTER WEIGHTING* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Biological (n=178)** | **Mechanical (n=223)** | **p-value** | **SMD** | **Biological (n=176.4)** | **Mechanical (n=222.2)** | **p-value** | **SMD** |
| **Age in years** | | 61.6(2.8) | 60.6 (2.9) | **<0.001** | **0.38** | 61.1 (2.9) | 61.1 (2.9) | 0.91 | 0.01 |
| **Sex** | Male | 110 (61.8%) | 159 (73.3%) | 0.80 | 0.03 | 105(59.6%) | 133.8 (60.2%) | 0.91 | 0.01 |
| **BMI** | | 29.2 (5.8) | 28.3 (5.4) | 0.51 | 0.07 | 29.0 (5.7) | 29.0 (5.9) | 0.97 | 0.01 |
| **Angina** | None<br>CCS1-2<br>CCS3-4 | 78 (43.8%)<br>86 (48.3%)<br>14 (7.9%) | 110 (49.3%)<br>84 (37.7%)<br>29 13.0%) | 0.06 | **0.24** | 83.2 (47.2%)<br>76.0 (43.1%)<br>17.2 (9.7%) | 104.9 (47.2%)<br>93.9 (42.3%)<br>23.3 (10.5%) | 0.97 | 0.03 |
| **Dyspnoea** | NYHA 3-4 | 67 (37.6%) | 104 (46.6%) | 0.07 | **0.18** | 73.4 (41.6%) | 93.5 (42.1%) | 0.93 | 0.01 |
| **Renal disease** | | 7 (3.9%) | 4 (1.8%) | 0.19 | **0.13** | 4.4 (2.5%) | 4.3 (1.9%) | 0.69 | 0.04 |
| **Previous MI** | | 11 (6.2%) | 14 (6.3%) | 0.97 | 0.004 | 10.2 (5.8%) | 13.7 (6.2%) | 0.87 | 0.02 |
| **Diabetic** | | 30 (16.9%) | 25 (11.2%) | 0.10 | **0.16** | 23.6 (13.4%) | 28.6 (12.9%) | 0.89 | 0.01 |
| **Smoking** | Never<br>Ex<br>Current | 73 (41.0%)<br>86 (48.3%)<br>19 (10.7%) | 91 (40.8%)<br>109 (48.9%)<br>23 (10.3%) | 0.99 | 0.01 | 71.9 (40.8%)<br>84.8 (48.1%)<br>19.7 (11.1%) | 89.1 (40.1%)<br>107.7 (48.5%)<br>25.3 (11.4%) | 0.99 | 0.01 |
| **Ejection Fraction** | Poor<br>Fair<br>Good | 8 (4.5%)<br>12 (6.7%)<br>158 (88.8%) | 11 (4.9%)<br>20 (9.0%)<br>192 (86.1%) | 0.69 | 0.09 | 6.7 (3.8%)<br>14.6 (8.3%)<br>155 (87.9%) | 9.7 (4.3%)<br>17.8 (8.0%)<br>194.7 (87.6%) | 0.96 | 0.03 |
| **Neurological disease** | | 5 (2.8%) | 14 (6.3%) | 0.10 | **0.17** | 6.5 (3.7%) | 10.2 (4.6%) | 0.69 | 0.04 |
| **Extracardiac arteriopathy** | | 11 (6.2%) | 13 (5.8%) | 0.88 | 0.02 | 10.2 (5.8 %) | 13.4 (6.0%) | 0.91 | 0.01 |
| **Haemodynamic pathology** | Mixed<br>Regurg.<br>Stenosis | 38 (21.3%)<br>17 (9.6%)<br>123 (69.1%) | 50 (22.4%)<br>48 (21.5%)<br>125 (56.1%) | **0.003** | **0.35** | 41.9 (23.8%)<br>27.7 (15.7%)<br>107 (60.6%) | 50.3 (22.6%)<br>36.4 (16.4%)<br>135.5 (61.0%) | 0.96 | 0.03 |
| **Hypertension** | | 95 (53.4%) | 107 (48.0%) | 0.29 | **0.11** | 88.6 (50.2%) | 112.2 (50.5%) | 0.96 | 0.01 |

**Table 4B:** Weighted and unweighted comparisons of baseline characteristics for patients aged 56-65 years. Figures are given as "mean (SD)" or as "frequency (%)" for continuous and categorical variables respectively. *weighted frequencies may not be integers. SMD=standardised mean difference.

## Inverse Probability Weighting (IPW)

The positivity assumption – that all patients have a non-zero probability of treatment - is met; the minimum propensity score is 0.47 in the younger group and 0.087 in the middle-aged group. In the younger group, weights ranged from 0.27 to 2.62, with mean 0.999 and standard deviation 0.22, and were truncated at the 1st and 99th percentiles (0.475 and 1.78 respectively). In the middle-aged group, weights ranged from 0.49 to 3.15 and were truncated at 0.58 and 2.38 respectively and had mean 0.998 and standard deviation 0.36.

Figure 4 shows the standardised mean differences for each variable before and after inverse probability weighting; the balance for both is excellent, though it is slightly better for the middle-aged group. Possibly the very small number of biological valves implanted into the under 55's group gives this group greater bias.

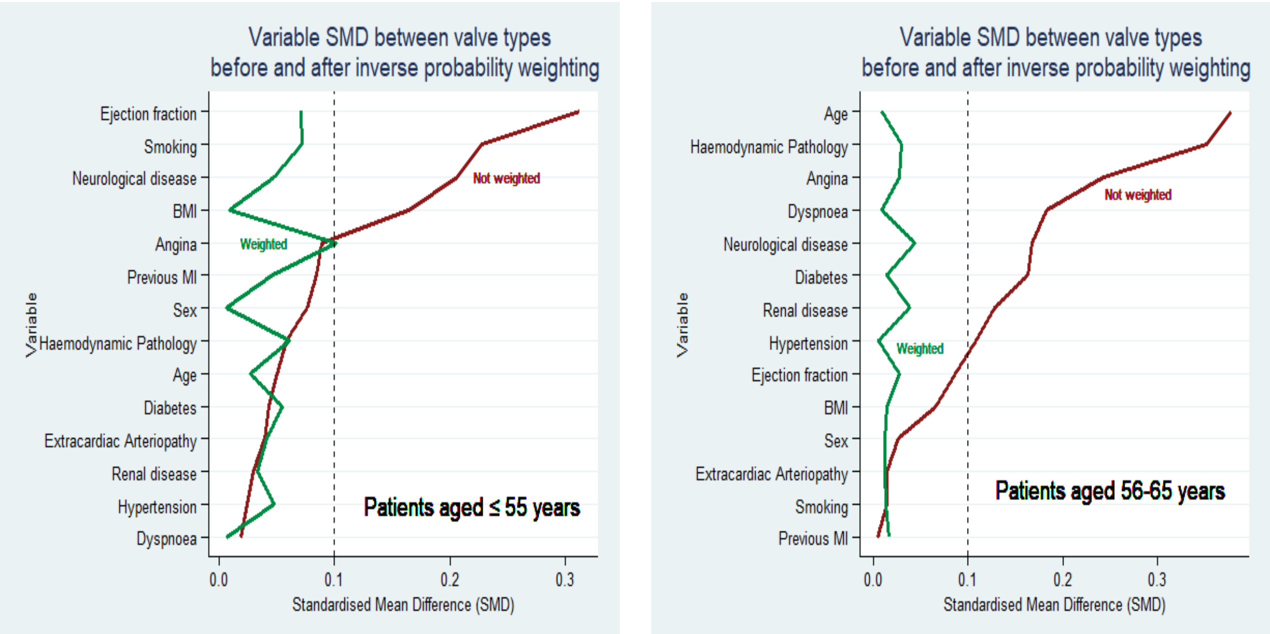


**Figure 4.** Standardized mean differences (SMD) for each variable before and after inverse probability weighting in both subgroups.

## Survival

Crude survival rates for the two weighted pseudo-populations are given in Table 5. There is no evidence of any difference in survival between biological and mechanical valves either for the younger (≤55 years) or middle-aged (56-65 years) groups at hospital discharge, one year post procedure or 5 years post procedure. Small numbers of patients with at least 10-year follow-up make inference on 10- and 15-year survival rates unreliable, though these also show no significant difference.

Kaplan-Meier estimates of survival are visualized in figure 5 (left, younger and right, middle-aged). Log-rank tests of survival difference between patients receiving biological or mechanical valves are non-significant with p=0.89 and p=0.31 for the two age stratifications respectively. Both age stratifications: for younger patients, HR for mechanical valve is 1.44 (CI (0.32-6.46), p=0.63, global test of proportional hazards p=0.75) and for middle-aged patients, HR for mechanical valve is 1.48 (CI (0.43, 5.11), p=0.54, global test of proportional hazards p=0.95).

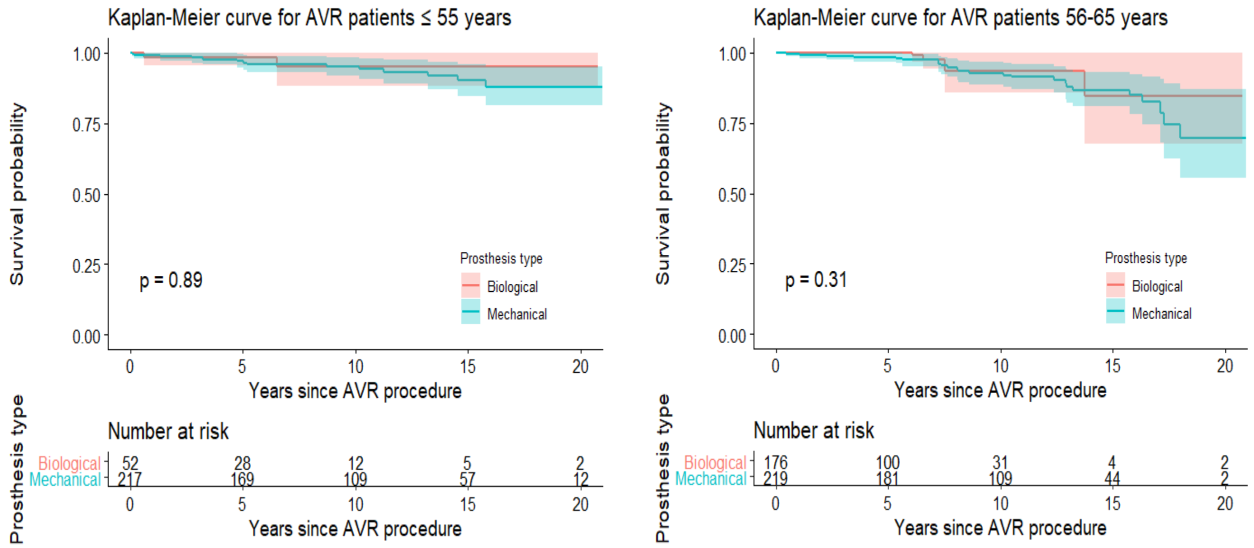


**Figure 5.** Kaplan-Meier curves for patients aged ≤55 years (left) and 56-65 years (right).

| **Survival** | **≤55 years old** | | | **56-65 years old** | | |
|---|---|---|---|---|---|---|
| | Biological | Mechanical | | Biological | Mechanical | |
| **Discharged alive** | n=51.6 98.3% | n=216.8 99.0% | p>0.99 | n=176.4 100% | n=222.2 98.8% | p=0.39 |
| **≥ 1 year** | n=47.6 98.4% | n=210.1 98.4% | p>0.99 | n=162.8 100% | n=220.1 98.4% | p=0.28 |
| **≥ 5 years** | n=28.7 97.4% | n=172.5 97.7% | p>0.99 | n=99.6 100% | n=187.2 96.7% | p=0.18 |
| **≥ 10 years** | n=13.6 89.0% | n=114.3 95.6% | p=0.70 | n=35.1 88.0% | n=123.7 88.9% | p>0.99 |
| **≥ 15 years** | n=6.3 76.3% | n=64.6 88.6% | p=0.80 | n= 5.98 74.6% | n=54.8 79.9% | p>0.99 |

**Table 5:** Weighted survival rates. The given "n" is the total eligible patient weights at each time point.

## Discussion

long term survival following aortic valve replacement is unrelated to prosthesis type. Initial analysis of our data showed better survival for patients with mechanical valves, however the two prosthesis groups were different in terms of patients age and characteristics. We looked at age as a hazard of death using a Cox model and identified that being over the age of 65 increased the risk of death rather than the type of valve that the patient received.

This data set contains significant confounding by indication, whereby the factors determining outcome also influence the choice of treatment. Here, age is the main confounder, as most older patients receive a biological valve and most younger patients a mechanical valve, thus making it difficult to distinguish the effect on mortality due to valve type from that due to age. To address this, we used IPW to create a pseudo-population of patients whose probability of treatment is independent of the measured baseline covariates, so that further analysis of outcomes is unbiased. Our analysis showed that in patients <65 years of age the type of valve did not affect long term survival.

The current guidelines for choice of valve have clear cut-offs for type of valve choice: >70 years for biological valve, and for mechanical <50 years in the United States **[**11**]** and <60 years in Europe **[**6**]**. This leaves the 50 to 70 year old patients in an in-between group where guidance is lacking. Emphasis on patient choice when it comes to choosing the type of prosthesis means that we as clinicians should aim to help patients make the most informed choice possible **[**14**]**. This is difficult when there is limited clear guidance for younger patients requiring an aortic valve replacement.

At this stage studies that concentrate on younger patients are limited and most reflect on long term survival of patients at any age. Few retrospective analyses in the last few years have attempted to assess which type of valve is best for patients between 50 and 70 years of age (and younger). Several different studies support our findings, to show that there is no significant advantage to survival in either valve. Schnittman et al **[**15**]** produced 1175 matched pairs of patients under the age of 50 and showed no significant difference in their survival at 15 years post operatively between the valves. Hirji at al **[**16**]** looked also at patients less than 50 years of age and in their matched analysis showed no significant difference at 10 year survival. Iribarne et al **[**17**]** studied 1449 patients between 50 and 65 years of age, without matched analysis and found no difference in 15-year survival.

Kyto et al **[**18**]** looked at 576 matched pairs of mechanical and biological prostheses in patients aged 50 to 70 years. They showed significantly lower mortality 18.6% vs 27.6% at 10 year-survival in the mechanical vs biological prostheses respectively (P<0.002). They included patients with concomitant coronary artery bypass grafting (CABG) in their analysis and suggested that other analyses with AVR

+/- CABG showed similar results with lower mortality in the mechanical valve groups. Whilst analyses that excluded patients that underwent CABG at the same time, as we have, showed no significant difference in mortality and valve type [15,17]. Patients that require CABG have severe coronary artery disease and this can be accompanied by high blood pressure and hypercholesterolemia [19]. Therefore a hypothesis for Kyto et al findings could be increased incidence of these co-morbidities could contribute to structural degeneration of the bioprosthetic valve, requiring re-operation and therefore increasing risk of mortality, compared to the mechanical valve. Our study only included patients that had isolated AVRs, perhaps including patients that had concomitant surgery would give different results.

Randomised control trials are scarce in this topic area. So far three have been performed to assess differences in long term survival and type of valve. These have shown conflicting results. Hammermeister et al [20] published the Veterans Affairs Trial of Prosthetic Valves and this showed that in 394 patients of all ages, a biological valve showed statistically significant improvement in mortality rates at 15-years compared to the mechanical counterpart. This study enrolled only male patients, therefore other variables and co-morbidities may have influenced the results. Oxenham et al [21] in Edinburgh, showed a survival advantage for the mechanical valve group at 15 years post op vs the porcine prosthesis, but this became statistically insignificant at 20 years post op in 211 patients of all ages. These trials began recruiting patients as early as 1977, since then operative techniques and the valves themselves have changed greatly, which can effect long term survival and account for the discrepancies in the above trials [22]. Stassano et al [23] showed that in 310 patients aged 55 to 70 there was no significant difference in survival at 13 years post-operatively which supports our findings. They attribute this to the narrow age range of patients in their trial compared to the others.

In 2019 Diaz et al [24] produced a systematic review and meta-analysis which had identified a total 4 propensity matched analyses and 1 randomised control trial which looked at patients between 50 and 70 years of age. This allowed for an analysis of 4686 patients. The pooled data was reconstructed and showed that mechanical valves had statistically significant longer survival at 5, 10 and 15 years post-operatively (P=0.012), with a small advantage to survival. At 15 years post-operatively the survival rate for patients with mechanical valves was 61.58% vs 58.04% for those with a biological valve. Diaz et al [24] did not separate the patients into sub-groups of <60 and >60 years of age, and results for these subgroups may have shown no difference to survival advantage.

The most difficult consideration when choosing a mechanical valve is thromboembolic risk vs bleeding complication with anticoagulation [25,26]. Post-operative adverse bleeding events were not analysed in this study. Also we did not consider younger patients that required a re-do surgery following initial biological valve replacement and the effect on mortality following re-operation. The need to have surgical or trans catheter aortic valve replacement is not analysed in this study. Lastly this study does not take into consideration the different valves used within the mechanical and biological prostheses and how a certain manufacturer or valve type may affect survival.

## Conclusion

Our results have shown that valve type is not a predictor of survival once accounted for patient's age at time of valve replacement. This could be due to improving treatments of co-morbidities, such as diabetes and vascular disease, improved surgical technique and developments in valve construction. This would go in support of other studies and to allow younger patients to choose a biological valve that does not require lifelong anticoagulation due to their life style or for their convenience. In conclusion, there is no survival advantage to either type of valve in the long term and randomised controlled trials and matched analyses are needed as the guidelines and surgical techniques and valves evolve.

In the future using the UK database of all aortic valve replacements could provide further answers to which valve is better for the patient.

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