Aortic valve replacement with biological prosthesis in patients aged 50–69 years

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Author Comments:	Southampton 01.10.2020 To the attention of Friedhelm Beyersdorf, Editor-in-Chief of European Journal of Cardio-Thoracic Surgery Dear Editor, Thank you for this new opportunity to review our paper “Aortic valve replacement with biological prosthesis in patients aged 50-69 years”. We have focused on the statistical reviewer's remarks and concerns. Our cumulative incidence analysis was correct and met all the previous requests, unfortunately our response was not clear and this caused some confusion. We have hopefully better clarified in this new version. Regarding the survival analysis, we have performed a backward stepwise Cox analysis as suggested by the statistical reviewer, as you can see no significant difference emerged and this was in keeping with our previous results but, as you suggested, a more rigorous and clear model can also enhance the strength of our message. We look forward from hearing from you. Thank you again for your consideration. Best regards Pietro G Malvindi Wessex Cardiothoracic Department University Hospital Southampton
Abstract:	Objectives There is no consensus regarding the adoption of biological or mechanical prostheses in patients 50-69 years of age. Previous studies have reported a survival advantage with mechanical valves. Methods

	We conducted a retrospective analysis of patients in the age groups 50-59 years (n=329) and 60-69 years (n=648) who had first-time isolated aortic valve replacement between 2000 and 2019. Kaplan-Meier and competing risk analysis were performed to compare survival, incidence of aortic valve reoperation, haemorrhagic complications, and thromboembolic events for mechanical versus biological prostheses. Results Patients aged 50-59 with a biological prosthesis had a higher probability of aortic valve re-intervention (26.3%, biological vs 2.6% mechanical, p<0.001 at 15 years). The incidence of haemorrhagic complications or thromboembolic events was similar in the two groups. Patients aged 60-69 years with mechanical prosthesis had a higher risk of haemorrhagic complications (6.9%, biological vs 16.2%, mechanical, p=0.001 at 15 years). Biological prostheses had a higher overall probability of re-intervention for valve dysfunction (20.9%, biological vs 4.8%, mechanical, p=0.024). In both age groups, there was no difference in long-term survival between patients receiving a biological or a mechanical prosthesis. Conclusions There was no difference in long-term survival between mechanical and biological prostheses for both age groups. Mechanical prosthesis had higher bleeding risk in 60-69 years group whereas biological valves had higher overall re-intervention probability without an impact on long term survival. It may be safe to use biological valves based on lifestyle choices for patients in the 50-69 years age groups.
Response to Reviewers:	Dear colleagues, Thank you for the revised version. As you may see, there are still important points to be solved regarding the statistical methods. Since this is a major aspects of your work, I would recommend to improve the analysis. This will for sure also improve the overall quality and power of the paper. Reviewer 1: Authors have answered reviewers' queries. Some considerations: - Authors have reported freedom from valve-re-intervention. Did authors explore incidence of SVD (not requiring reoperation)? Answer 1. We have reported the cumulative incidence of reoperations for any cause and the number of patients reoperated for SVD. We have not explored the incidence of SVD. Changes 1. No changes. - Rate of re-intervention in the bioprosthesis group (pts aged 50-59) is 13/132 pts (10%) at 6-years follow-up!! Which valves were involved? Small-sized prostheses? Answer 2. The rate of reintervention is 10% a median 6-years follow-up time. Details of cumulative incidence of reoperation after biological aortic valve replacement in patients aged 50-59 were reported in Table 3. Ten out of these 13 valves were Carpentier Perimount prostheses, 1 Trifecta, 1 Epic, 1 Mitroflow. They were not small size valves n 21=2, n 23=5, n 25=6. Changes 2. No changes Reviewer 3: This revision is an improvement relative to the earlier version. The information on valve types is appreciated as is the paragraph in the discussion relating to the newer generation mechanical valves. Given that most of the authors' conclusions as to recommendation of valve type relate to the higher risk of hemorrhagic complications in the 60-69 age group and that newer generation mechanical valves (e.g. OnX) have been demonstrated to have much lower hemorrhagic complication, more mention needs to be made of this so that the overall picture is represented in a more transparent, even-handed way.

For instance, in the "limitations" section it should be noted that ~80% of the mechanical valves used were of the older-generation, higher INR requiring type. Some reference to this fact should be made in the "conclusions" section, for instance line 262-3 could be revised to "However, the possibility of increased risk of haemorrahge with aging should be discussed (especially if a conventional mechanical valve with and INR target of 2-3 is planned) ... "
Answer 1. Thank you for your comments. We have underlined the possible benefits of a lower anticoagulation and reported the results coming from the PROACT trial.
Changes 1. No change

Reviewer 4: STATISTICAL REVIEW

Thank you for your revision. I have several follow-up questions / comments.

In the statistical methods section, authors state the following: "A Cox regression analysis was performed to determine cause-specific hazard ratios of long-term survival. Occurrence of re-intervention, haemorrhagic complications and cerebral ischaemic events was studied using Cumulative incidence function and Gray's test was used for comparison between mechanical and biological aortic valve replacement."

This does not align with their answers to reviewers. The Cox model for long-term survival would not be cause specific - it would merely be a Cox proportional hazards model. Re-intervention, haemorrhagic complications and cerebral ischaemic events were analysed in a competing risks context, but from the methods section is still not clear that death was used as the competing risk in each case. Further, authors indicate in the response to reviewers that the HR for biological valve use in the analysis of re-intervention, haemorrhagic complications and cerebral ischaemic events was still determined via sub-distribution hazard models, which is now left out of the methods section entirely.

Lines 153 and 175 in the results should also then still reflect an sHR, rather than an HR, as should Table 3. The caption for Table 3 is also then incorrect, since it indicates the use of a Cox model, not the Fine and Gray model that was used (according the response to reviewers, not the methods section).

ANSWER 1. Our previous answer to two of your questions in the first review process generates some confusion.
Please refer to the table uploaded as a source material, this is the same as reported in the manuscript, showing the cumulative incidence analysis with death as a competing risk
In blue the cumulative incidence for each outcome from competing risk analysis with death as a competing risk. In red the results of Gray’s test for comparison. In yellow the HRs from Cox analysis, the sHR were reported in the first submission and no longer showed in the revised submission.
CHANGES 1. No changes made to Table 3 and Lines 153 and 175. A new sentence was added reporting the use of Cox analysis to determine HR for each outcome (page 6, line 115). As in the first revision, there is no mention about Subdistribution HR as this analysis was no longer reported.
The use of death as a competing risk in the cumulative incidence analysis was reported in the methods (page 4, line 114) and in the results (page 8, line 152, and page 9, line 174).

Further, in the "multivariable" Cox models used for overall survival, I worry about the model building process: a backwards stepwise procedure was recommended yes, but the valve type should remain in the model regardless of p-value, since it is the variable of interest. I assume that it was removed, given that authors report HR at steps prior to the final model. This is incorrect.

In addition, it appears that the HR changed direction depending on whether year was included - this indicates to me that the impact of year needs further analysis, not less. If authors are concerned about the format of inclusion, they can include the variable as continuous. I would also look at interactions between year and valve use, given the swap in direction of the HR.

Authors did not include this result in their paper - only reporting on a model for overall survival with valve type, age and sex - I would suggest that at the very least this (the impact of year) should be explored more fully in supplementary material, and otherwise reported in the main text. Also, why did the authors included age in the model that was reported on? Age is already accounted for by having split the subjects into 2 groups based on age.

I think that the authors are a bit confused with the statistical analysis - it would be beneficial to consult a qualified statistician.

ANSWER 2. There were two suggestions coming from the previous review: a backward stepwise procedure or an a priori selection of variables were both proposed as possible alternatives.
In the previous version, we have included the results coming from a model with type of valve, age and gender as covariates and reported the results of a possible model of backward stepwise procedure. Two considerations. The first about the inclusion of age; despite as you correctly said the two groups were already split based on patients' age, patients who had a biological prosthesis were significantly older than patients who underwent mechanical aortic valve replacement. The second about the backward stepwise procedure; we have mentioned the HR for biological valve at step 4 out 6 and this was a mistake.
However, we fully agree with you that a definitive clear model should be provided if we want to go for a backward stepwise analysis. For this reason we have followed this protocol including:
•Type of valve (mech or bio)
•Type of haemodynamic (stenosis or regurgitation)
•LVEF (< or > 30%)
•Diabetes Mellitus (yes or no)
•Gender (M or F)
•NYHA class (I-II or III-IV)
•Hypertension (yes or no)
•Smoking history (yes or no)
•Period of surgery (considering 4 periods of 5 years 2000-2004, 2005-2009, 2010-2014, 2014-2019)

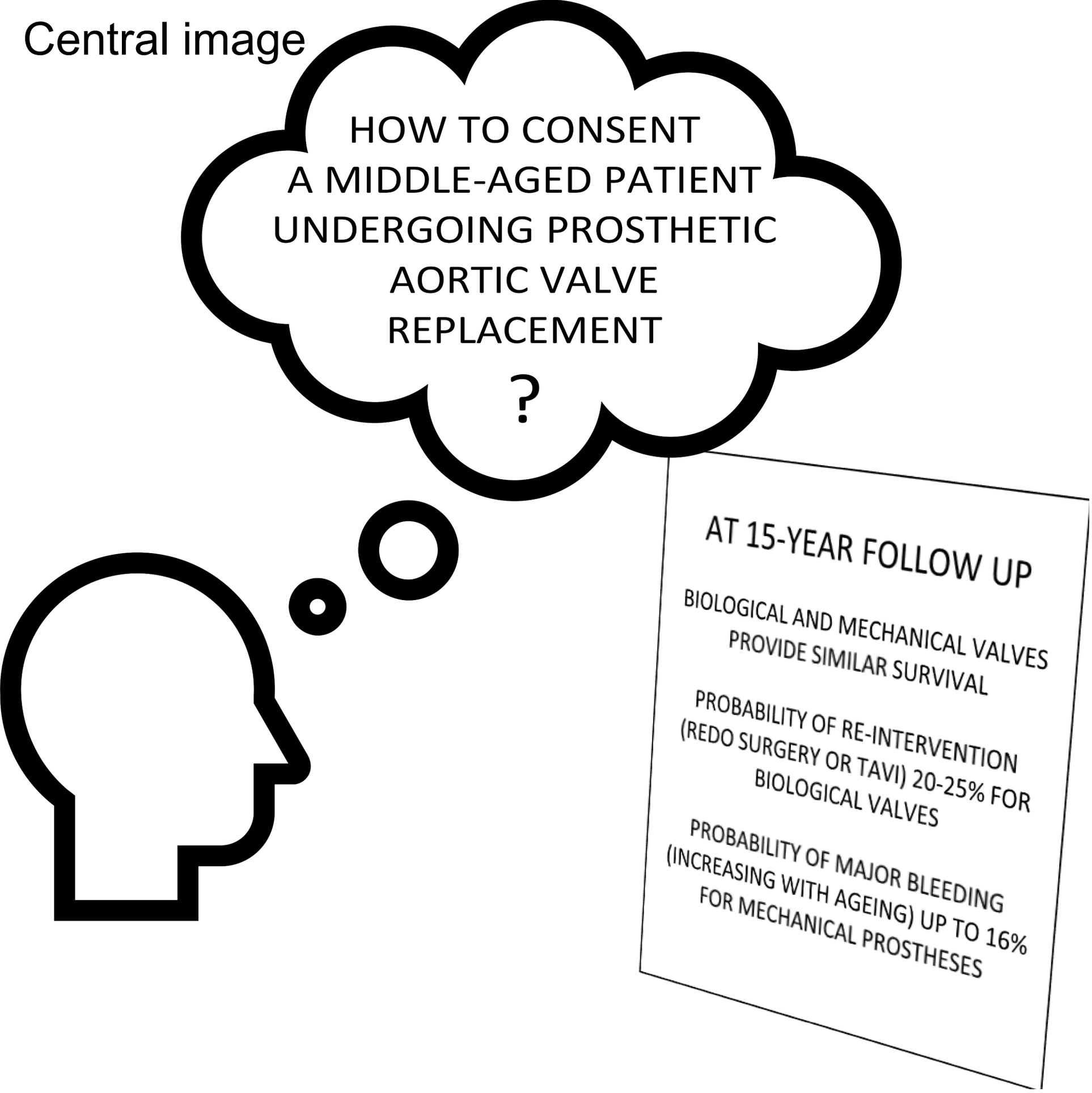
As for your suggestion age and poorly represented preoperative factors (i.e. CKD and PVD) were not included.

Group of patients 50-59
When considering 4 different period for the variable time of surgery, the new value of HR for biological valve after this Cox analysis was 1.464 [0.788, 2.724], p=0.23
As in Step: 7
Biological valve: exp 1.464, p=0.2279
LVEF<30%: exp 3.199, p=0.0084

Group of patients 60-69
When considering 4 different period for the variable time of surgery, the new value of HR for biological valve after this Cox analysis was 1.117 [0.809, 1.721], p=0.39
As in Step: 6
Biological valve: exp 1.117, p=0.3911
Diabetes Mellitus: exp 2.267, p=0.0007
Time of surgery (years): p=0.0013
•2000-2004: exp 6.207, p=0.0002
•2005-2009: exp 4.070, p=0.0044
•2010-2014: exp 3.437, p=0.0111

	CHANGES 2. The use of the model with backward stepwise Cox analysis including 4 different period 2000-2004, 2005-2009, 2010-2014, 2015-2019, was clearly stated in the Methods (page 6, lines 107-112 + Supplemental Table 1). HR for biological valve was changed for patients aged 50-59 (page 7, line 142) and for patients aged 60-69 (page 8, line 162). We hope that this model could find your favour. As you stated, the period of surgery seems to be an important determinant, however we were not able to find any significance associated with type of valve and mortality during the follow-up. We do not believe that the introduction of the variable date of surgery with the swap in the HR for biological valve in the group 60-69 years old has a dramatic impact on our conclusions. We are talking about viable options in these two groups of patients. In our conclusions, we did not claim as inappropriate the use of a mechanical valve for people 60-69 because of a crude HR of 0.926 for biological valves and, at the same time, we do not think that our conclusions, based also on secondary outcomes, are less valid because the correction for the period of surgery turned a non statistically significant HR of 1.117 for biological valves. The general improvement in surgical and medical practice could explain the impact of the date of surgery on survival and this is not merely associated with technical factors since timing of surgery, indications and long-term clinical follow-up and the availability of further interventions, treatment of complications, have changed over time. As you can see, we found a better survival across the study period both for mechanical and biological valves (Supplemental Figures 1 – 4)). In people aged 50-59, the inclusion of the period of age reduced the HR value for biological valves as it was very common in the past to reserve in middle-aged people a biological valve to patients with a reduced life-expectancy, maybe due to comorbidities like malignancies, chronic non cardiac and non pulmonary disease or other diseases requiring non cardiac surgical treatment, all factors that are poorly intercepted by risk scores and not well coded in institutional databases. Similarly, the progressive general medical improvement, as said not only technical, could advantage in terms of results biological valves as they gained a larger use over the study period. We believe that it is important to add that the long interval time of our study period can represent a limitation for the reasons stated above (page 12, lines 253-256). Editorial office: Please ask a medical language editing expert to correct the English of the revised version to ensure that the grammar and syntax are correct. Answer 1 + Changes 1. The manuscript has been fully reviewed.
Order of Authors (with Contributor Roles):	Pietro Giorgio Malvindi, MD, PhD (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing)
	Suvitesh Luthra (Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing)
	Carlo Olevano (Data curation; Investigation; Methodology)
	Hamdy Salem (Data curation; Methodology)
	Mariusz Kowalewski (Data curation; Formal analysis; Methodology; Writing – review & editing)
	Sunil Ohri (Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Writing – review & editing)

Central image



Title: Aortic valve replacement with biological prosthesis in patients aged 50-69 years

Running head: biological valves in 50-69 years

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Visual abstract

Key question: is there any survival advantage associated with a biological or a mechanical valve in patients between 50 to 69 years?

Key findings: similar survival at 15-year after tissue and mechanical aortic valve replacement for patients aged 50 to 59 and 60 to 69

Take-home message: a biological valve is a viable option also for patients aged 50 to 59, the risk of a redo procedure is high, but reintervention seems safe

Abstract

Objectives - There is no consensus regarding the adoption of biological or mechanical prostheses in patients 50-69 years of age. Previous studies have reported a survival advantage with mechanical valves.

Methods - We conducted a retrospective analysis of patients in the age groups 50-59 years (n=329) and 60-69 years (n=648) who had first-time isolated aortic valve replacement between 2000 and 2019. Kaplan-Meier and competing risk analysis were performed to compare survival, incidence of aortic valve reoperation, haemorrhagic complications, and thromboembolic events for mechanical versus biological prostheses.

Results - Patients aged 50-59 with a biological prosthesis had a higher probability of aortic valve re-intervention (26.3%, biological vs 2.6% mechanical, $p<0.001$ at 15 years). The incidence of haemorrhagic complications or thromboembolic events was similar in the two groups. Patients aged 60-69 years with mechanical prosthesis had a higher risk of haemorrhagic complications (6.9%, biological vs 16.2%, mechanical, $p=0.001$ at 15 years). Biological prostheses had a higher overall probability of re-intervention for valve dysfunction (20.9%, biological vs 4.8%, mechanical, $p=0.024$).

In both age groups, there was no difference in long-term survival between patients receiving a biological or a mechanical prosthesis.

Conclusions - There was no difference in long-term survival between mechanical and biological prostheses for both age groups. Mechanical prosthesis had higher bleeding risk in 60-69 years group whereas biological valves had higher overall re-intervention probability without an impact on long term survival. It may be safe to use biological valves based on lifestyle choices for patients in the 50-69 years age groups.

Abstract word count: 250

Keywords: aortic valve, aortic valve replacement, reoperation, aortic valve prosthesis

Introduction

Mechanical and biologic prostheses are commonly used to treat aortic valve disease. Biological prostheses are associated with higher rates of reoperation due to structural valve deterioration whereas mechanical prostheses have higher rates of haemorrhagic complications and thromboembolic events related to lifelong anticoagulation (1). Two randomized controlled trials (Veterans Affairs and the Edinburgh trial) have previously reported a survival advantage for mechanical recipients (2,3). However, these results were based on relatively younger patients in trials conducted almost 2 decades ago compared to contemporary population groups (4) and included prostheses with older designs and less efficient hemodynamic. Despite these findings, there has been a significant increase in the adoption of biologic prostheses for aortic valve replacement even in relatively younger patients (1)(4). For patients aged over 70 years, a biologic prosthesis seems the most reasonable choice in terms of expected valve durability and avoidance of anticoagulation (5,6). A grey zone includes patients aged 50-70 years where the evidence for the use of biological prosthesis remains conflicting and guidelines and recommendations remain unclear (6-12).

The aim of this study was to compare long term survival between mechanical and biological prostheses in the intermediate age groups of 50-69 years. A secondary aim was to study the association of haemorrhagic complications, thromboembolic events and re-intervention with mechanical and biological prostheses.

Materials and Methods

Population

The internal database of Wessex Cardiothoracic Centre at UHS was interrogated to identify patients who underwent isolated aortic valve replacement for the period January 2000 – December 2019 using the following criteria.

Inclusion criteria

- Isolated aortic valve replacement;

- Use of a mechanical or a biologic prosthesis;
- Age 50-69 years.

Exclusion criteria

- Redo procedure (any previous cardiac operation);
- Acute infective endocarditis;
- Emergency and salvage procedures;
- Associated procedures including CABG, mitral valve surgery, tricuspid valve surgery, pulmonary valve surgery, aortic surgery;
- Use of Homograft, Ross procedure, use of sutureless valve.

Study design, data collection and outcomes

This is a single centre, retrospective study. Approvals for collection and use of data were obtained in compliance with institutional data protection and confidentiality policies. The data was collected from the hospital databases system, patient records and GPs records.

The preoperative data collected was as previously defined for EuroSCORE (13). Preoperative, operative and postoperative data collected is summarized in Tables 1 and 2.

Outcome data included 30-day mortality, survival, aortic valve re-intervention, haemorrhagic complications and cerebral ischaemic events.

Definitions

All-cause mortality was considered for survival during the follow-up. Every new procedure for aortic prosthesis dysfunction (14) was included in the count of aortic valve re-intervention. Haemorrhagic complications were coded according to standard definitions of Valve Academic Research Consortium – 2 (VARC-2) criteria for 'Life-threatening or disabling bleeding' or 'Major bleeding', and cerebral ischaemic events according to VARC-2 criteria for 'Stroke and TIA' (15).

Statistical analysis

The cohort was divided into two groups of patients - aged 50 to 59 years and 60 to 69 years for comparison of mechanical and biological prostheses. Univariable comparisons of preoperative and operative variables were performed for the groups using Student's T-test, Mann–Whitney U-test, Chi-squared or Fisher's Exact test as appropriate.

Survival probabilities were calculated using the Kaplan-Meier method and comparisons were performed with the log-rank test. A Cox regression analysis was performed to determine hazard ratios of long-term survival; a backward stepwise model with a significance $p<0.15$ was used, the variables included were type of valve (mechanical and biological), type of haemodynamic dysfunction (stenosis or regurgitation), LVEF<30%, gender, NYHA class I-II, Hypertension, Diabetes Mellitus, Smoking history, time of surgery (years 2000-2004, 2005-2009, 2010-2014, 2015-2019).

Occurrence of re-intervention, haemorrhagic complications and cerebral ischaemic events was studied using Cumulative incidence function with death as a competing risk and Gray's test was used for comparison between mechanical and biological aortic valve replacement. Cox regression was used to determine the hazard ratio of biological valve for each outcome.

A p value ≤ 0.05 was considered statistically significant.

Statistical analyses were performed using the Stata/MP version 13 (StataCorp, College Station, Texas 77845 USA) integrated with stcrreg, stcompet and stcomlist commands.

Results

Nine hundred and seventy-seven (977) patients were included (group [50-59]: 329 patients, 33.7%; group [60-69]: 648 patients, 66.3%). Overall, 359 patients (36.7%) had a mechanical and 618 patients (63.3%) had a biological prosthesis.

Carbomedics mechanical valves were used in 47% of the cases (n=169), St Jude Regent mechanical valves were implanted in 28% of the patients (n=100), On-X prostheses in 19% of the cases (n=67) and Sorin Bicarbon valves in 6% of the patients (n=23).

Edwards bovine tissue valves were implanted in 78% of the cases (482 patients; models 2900, 3300 TFX, 11500A), St Jude Medical/Abbott bovine valves in 13% of the cases (80 patients; models TF and TFGT) and porcine valves in 2% of the cases (15 patients; model E100), Sorin/Livanova tissue prostheses were used in 7% of the patients (41 patients models 12LX, CNA, PN).

Preoperative and operative data for the groups and subgroups is summarized in Tables 1 and 2.

Over the last two decades there was an increasing use of biological prosthesis in this intermediate age group (Figure 1, A and B). The use of mechanical prosthesis declined from 96% in 2000 to 35% in 2019 in patients [50-59], and from 74% in 2000 to 6% in 2019 in patients [60-69].

Group [50-59]

The survival at 1-year, 5-year, 10-year and 15-year was 97% (SD: 1.0) , 93% (SD: 1.6%), 87% (SD: 2.8%), 80% (SD: 3.9%), respectively, after mechanical aortic valve replacement, and 97% (SD: 1.7%), 84% (SD: 4.0%), 81% (SD: 4.5%) and 81% (SD: 4.5%), respectively, after biological aortic valve replacement (log-rank test p=0.16) (Figure 2, Panel A). After Cox analysis, no significant association was found between the type of prosthesis and survival, biological valve HR 1.562 [0.838, 2.906], p=0.16. This finding was confirmed after Cox analysis; biological valve HR 1.464 [0.788, 2.724], p=0.23 (Supplemental Table 1).

Sixteen valve re-interventions were performed at a median time of 6.0 [3.2, 8.0] years after aortic valve replacement. At the time of re-intervention, patients mean age was 61 (SD: 3.6) years, 81% of them were male (13/16 patients). Structural valve failure or dysfunction were the main cause for a reintervention in thirteen cases. These patients received in 12 cases conventional redo surgical aortic valve replacement and in one 1 case transcatheter aortic valve-in-valve procedure; they were all successfully discharged from hospital.

At a median time of 5.0 [0.7, 8.2] years, nine patients suffered a haemorrhagic complication; patients mean age was 62 (SD: 5.8) years and 78% of them were male (7/9). Eight patients suffered intracranial bleeding and in one case a perioperative haemorrhage occurred after the re-induction of anticoagulant therapy.

Table 3 and Figure 3 report the cumulative incidence with death as a competing risk of aortic valve re-intervention, haemorrhagic complications and cerebral stroke for mechanical and for biological valves, and the hazard ratio (HR) for biological prosthesis.

Group 60-69

The survival at 1-year, 5-year, 10-year and 15-year was 96% (SD: 1.6%), 86% (SD: 2.8%), 74% (SD: 3.8%), 64% (SD: 4.7%), respectively, after mechanical aortic valve replacement, and 98% (SD: 0.6%), 88% (SD: 1.7%), 77% (SD: 2.7%) and 55% (SD: 5.3%), respectively, after biological aortic valve replacement (log-rank test p=0.91) (Figure 2, Panel B). No significant association was found after Cox analysis between the type of prosthesis and survival; biological prosthesis HR 0.926 [0.630-1.360] p=0.69. This finding was confirmed after Cox analysis; biological valve HR 1.117 [0.809, 1.721], p=0.39 (Supplemental Table 1).

Thirty aortic valve re-interventions were performed at a median time of 8.1 [3.6, 11.4] years after aortic valve replacement. At the time of re-intervention, patients mean age was 73 (SD: 5.6) years, 47% of them were male (14/30 patients). During the period 2000-2014 there were 8 cases of redo aortic valve replacement for structural valve failure or dysfunction with an early mortality of 12% (thrombosis of a mechanical valve). In

the last 5 years (2015-2019), 16 patients were reoperated and 5 patients underwent trans-catheter aortic valve-in-valve procedures, and they were all successfully discharged from hospital.

Thirty patients suffered a haemorrhagic complication during the follow-up at 6.0 [2.9, 11.7] years after aortic valve replacement; patients mean age was 72 (SD: 6.4) years and 73% of them were male (22/30). Five patients suffered intracranial bleeding, 12 gastro-intestinal bleeding, 5 cases of haematuria, 4 required ENT intervention, and in the remaining 4 cases a perioperative haemorrhagic complication occurred after the re-induction of anticoagulant therapy following a surgical procedure.

Table 3 and Figure 4 report the cumulative incidence with death as a competing risk of aortic valve re-intervention, haemorrhagic complications, and cerebral stroke for mechanical and for biological valves, and the hazard ratio (HR) for mechanical prosthesis.

Discussion

In the last decade there was an increased adoption of biological prostheses in middle-aged patients undergoing heart valve surgery (1)(4)(16)(17). Throughout our study period, a progressively higher percentage of patients received a tissue valve. In the last 2 years, biological aortic prostheses were implanted in 65% of patients aged 50-59 and in 94% of patients 60-69. In the biennium 2000-2001, these values were 4% and 24%, respectively. Patients' preferences to avoid anticoagulation and the advances of trans-catheter techniques for bioprosthetic degeneration may have promoted this shift to a preference towards biologic implants.

Recent guidelines suggest an individualised approach in patients aged 50-70 years. Life-expectancy, associated comorbidities, anticoagulation related compliance problems, lifestyle, occupation and difficult reoperations are factors that should be evaluated and should guide the choice of either a mechanical or biological prosthesis (6)(12). Both observational and propensity matched studies have reported a survival advantage with mechanical prosthesis for patients 50 to 70 years of age, which seems to be greater for the younger subgroups. A number of these studies included patients requiring revascularization procedures

192 without adequate compensation for the confounding effects of ischemic heart disease on long term survival
193 after aortic valve replacement. The crude survival analysis also failed to study the impact of competing risks
194 for long term survival like haemorrhagic complications and thromboembolic events related to
195 anticoagulation for mechanical and reoperation for biological prostheses.

196 As with other studies, our incidence of aortic valve re-intervention was significantly higher for patients who
197 received a biologic prosthesis in both age groups. This is a common finding in patients younger than 70 years
198 of age and this is notoriously due to structural valve deterioration of biologic prosthesis (1)(2)(3)(8)(9)(11).

199 Previous studies showing a survival advantage for mechanical valves did not consistently report perioperative
200 mortality after reoperations for structural deterioration of biological prostheses (5)(18). Kyto et al recently
201 reported a perioperative mortality of 23.1% for reoperation for SVD, albeit in a much older age group (8).
202 They reported a significant long-term survival advantage in favour of mechanical prosthesis (81.4%,
203 mechanical vs 72.4%, biological at 10 years, p = 0.028). Their reoperation rates for this period were almost 7
204 times higher for biological prosthesis (mechanical 1.4% vs biological 9.5%, p=0.0009). Similarly, Goldstone et
205 al had a re-operative mortality of 7.1% for re-operation for aortic valve replacement. In their series, a
206 biological prosthesis was associated with significantly higher 15-year mortality than a mechanical prosthesis
207 among patients 45 to 54 years of age (30.6% vs. 26.4% at 15 years; hazard ratio, 1.23; 95% confidence interval
208 [CI], 1.02 to 1.48; P = 0.03) but not among patients 55 to 64 years of age.

209 In our experience aortic valve re-intervention for structural valve deterioration or valve dysfunction was
210 associated with an in-hospital mortality rate of 2.8%. In the last 5 years, all patients treated for structural
211 valve deterioration were successfully discharged after redo sternotomy surgical aortic valve replacement or
212 TAVI. Transcatheter valve-in-valve procedure is now a consolidated option for the treatment of bioprosthetic
213 aortic valve failure and represents a safe alternative to redo-surgical aortic valve replacement with
214 acceptable early mortality (1-3%) and midterm results (19)(20)(21). Three-year clinical and echocardiographic
215 follow-up data from PARTNER 2 Registry for Valve-in-Valve TAVI for degenerated surgical bioprostheses
216 similarly showed favourable survival, sustained improved hemodynamic status, and excellent functional and

quality-of-life outcomes (21). A careful patients' selection is mandatory and includes the evaluation of the type and size of the failing surgical prosthesis and the aortic root anatomy in order to avoid malposition of the transcatheter valve, residual high gradients or coronary obstruction (22). Newer tissue surgical aortic prostheses are now designed to facilitate a transcatheter valve-in-valve implantation procedures, by providing a lower valve profile and an adequate internal diameter also for smaller valve sizes (19 mm, 21 mm). Most of our patients (75%) received a biological valve with a size≥23 mm and represent good candidates for valve-in-valve procedures. The multidisciplinary discussion within the heart valve team enhances the possibility of proposing a safe therapeutic option according to patients' characteristics, anatomy and technical factors, thus providing an individualised solution for each patient. The availability of conventional redo surgery and transcatheter procedures as complimentary tools can reduce the interventional risk and improve outcomes in patients with aortic bioprosthesis failure. Our data provided a first glance of the importance of evaluating outcomes for mechanical and biological prostheses by considering the actual practice in aortic valve intervention, which incorporates multidisciplinary evaluations, shared clinical decisions and the possibility of tailored treatments.

Risk of haemorrhagic complications and thromboembolic events is strictly associated with anticoagulant therapy that is mandatory in patients with mechanical prosthesis. Elderly people are more prone to develop haemorrhagic complication (23)(24) as we found a significantly higher risk of major bleeding episodes in patients with a mechanical prosthesis in the group 60 to 69 years of age. Bleeding events could be serious and life-threatening complications as Goldstone et al. (1) found that the occurrence of haemorrhagic episodes after mechanical aortic valve replacement were associated with a significantly increased risk of death both in patients 45 to 54 years of age and in patients 55-64 years of age. Improvement in mechanical valve design and function can reduce the risk of valve related thromboembolic events and allow a lower anticoagulation than recommended for other mechanical valves (6). The PROACT trial tested the safety of different anticoagulation and antiplatelets protocol in patients who underwent mechanical aortic valve replacement with an On-X prosthesis. Lower INR ranges (1.5 to 2.0 with the association of acetylsalicylic acid 81 md/day, after the first 3 months) was shown to be safe with similar freedom from thromboembolic events

and a significantly lower rate of total and major bleeding complications when compared with the standard INR target [2 – 3]. In this setting, a lower anticoagulation protocol has been associated with a 60% reduction of haemorrhagic complications at 5-year (25).

Our study has the limitations associated with a retrospective analysis. We acknowledge that reoperation represents a clinical decision and may underestimate the true impact of valve failure especially for biological prostheses. However, we believe we have provided a realistic estimation of the risk of aortic valve re-intervention which was nevertheless higher than the rate of reoperations reported by several previous studies with similar design and follow-up (7)(8)(26). Similar limitations apply to estimation of the risk of bleeding events. Our analysis was limited to life-threatening and major haemorrhagic events that can be monitored by the review of hospital admissions, surgical charts and A&E records.

The study period included a 20-years interval time and the results could be affected by the general and progressive improvement in surgical outcomes across this long interval time (Supplemental Figures 1-4). However, date of surgery was included in our multivariable model of Cox analysis and no significant association was found between type of valve and mortality during the follow-up.

Conclusion

Based on our results, we believe that a biologic valve can be considered a viable option also for patients between 50 and 59 by providing the information that one in four cases might need a further intervention in 15 years. Patients should be informed that the actual availability of alternative techniques for the treatment of valve failure, a punctual imaging follow-up and a well consolidated multidisciplinary approach are increasing the safety and effectiveness of aortic valve reinterventions. On the other hand, the choice of a mechanical prosthesis in patients 50-59 is associated with a long-term low risk of reoperation and a low risk of bleeding complications and represents a valuable option in case of good compliance to anticoagulant therapy. However, the possibility of an increased risk of haemorrhage with aging should be discussed as we found a significantly higher probability of bleeding in patients aged 60-69 who received a mechanical valve.

For patients 60 to 69 years of age, we favour a biologic prosthesis for isolated aortic valve replacement. The avoidance of life-long anticoagulant therapy is a major advantage for these patients who are at higher risk of haemorrhagic complications, receive often pharmacological treatment for other diseases and are more prone to undergo non-cardiac invasive procedures. The occurrence of structural valve deterioration or dysfunction increases significantly during the second decade after biological aortic valve replacement and the risk of a reoperation is non-negligible. However, the expanding field of less invasive procedures and a solid experience in redo procedures could provide a safe re-interventional option.

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1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
2. Drafting the work or revising it critically for important intellectual content;
3. Final approval of the version to be published;
4. Agreement to be accountable for his/her contributions of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

PGM: 1-2-3-4

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MK: 1-2-3-4

SKO: 1-2-3-4

295 **Figures**

296 **Figure 1.** Trend in mechanical and biological prostheses implantation in patients aged 50-59 years old (Panel
297 A) and in patients aged 60-69 (Panel B). Lines (blue for biological and red for mechanical valves) show the
298 number of procedures, bars show the percentage of mechanical prostheses on total procedures.

299 **Figure 2**. Panel A. Kaplan-Meier survival curves for patients aged 50-59; log-rank test proved no difference
300 between mechanical (red line) or biological (blue line) aortic valve replacement (p=0.16). Panel B. Kaplan-
301 Meier survival curves for patients aged 60-69; log-rank test proved no difference between mechanical (red
302 line) or biological (blue line) aortic valve replacement (p=0.91).

303 **Figure 3.** Reoperation, bleeding and cerebral stroke in patients aged 50-59: cumulative incidence according
304 to mechanical (red line) or biological (blue line) aortic valve replacement (values and Gray's test in Table 3).

305 **Figure 4.** Reoperation, bleeding and cerebral stroke in patients aged 60-69: cumulative incidence according
306 to mechanical (red line) or biological (blue line) aortic valve replacement (values and Gray's test in Table 3).

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Tables

Table 1. Preoperative characteristics of the overall population and the two subgroups of patients aged 50-59 and 60-69 according to type of valve mechanical and biological

	Overall population (n=977)			50-59 (n=329)			60-69 (n=648)		
Variables	Mechanical prosthesis	Biological prosthesis	p	Mechanical prosthesis	Biological prosthesis	p	Mechanical prosthesis	Biological prosthesis	p
	N (%) or mean ± SD	N (%) or mean ± SD		N (%) or mean ± SD	N (%) or mean ± SD		N (%) or mean ± SD	N (%) or mean ± SD	
Number of patients	359	618		197	132		162	486	
Age (years)	59 (SD: 6)	63 (SD: 5)	<0.001	55 (SD: 3)	56 (SD: 3)	0.12	64 (SD: 3)	66 (SD: 3)	<0.001
Gender M/F	227/132	379/239	0.55	124/73	90/42	0.33	103/59	289/197	0.35
Hypertension	170 (47%)	337 (54%)	0.030	86 (43%)	59 (45%)	0.85	84 (52%)	278 (57%)	0.23
Diabetes Mellitus	27 (7%)	71 (11%)	0.046	11 (5%)	11 (8%)	0.33	16 (10%)	60 (12%)	0.40
COPD	56 (16%)	104 (17%)	0.61	36 (18%)	15 (11%)	0.089	20 (12%)	89 (18%)	0.078
Smoking history	231 (64%)	377 (61%)	0.29	121 (61%)	85 (64%)	0.58	110 (68%)	292 (60%)	0.075
NYHA III-IV	132 (37%)	200 (32%)	0.16	70 (36%)	44 (33%)	0.68	62 (38%)	156 (32%)	0.15
Previous AMI	8 (2%)	12 (2%)	0.94	4 (2%)	4 (3%)	0.82	4 (2%)	8 (2%)	0.73
Haemodialysis	3 (1%)	6 (1%)	0.89	1 (1%)	3 (2%)	0.35	2 (1%)	3 (1%)	0.79
Previous cerebral stroke	7 (2%)	12 (2%)	0.99	6 (3%)	4 (3%)	0.74	1 (1%)	8 (2%)	0.56
Extracardiac arteriopathy	14 (4%)	22 (4%)	0.78	8 (4%)	4 (3%)	0.85	6 (4%)	18 (4%)	0.99
LVEF<30%	17 (5%)	35 (6%)	0.53	8 (4%)	9 (7%)	0.27	9 (5%)	26 (5%)	0.92
Aortic stenosis	208 (58%)	418 (68%)	0.002	110 (56%)	85 (64%)	0.12	98 (60%)	333 (68%)	0.061
Elective/Urgent	255/104	455/163	0.38	141/56	93/39	0.82	114/48	362/124	0.30

AMI – acute myocardial infarction; COPD – chronic obstructive pulmonary disease; NYHA – New York Heart Association class; LVEF – left ventricular ejection fraction. P value ≤ 0.05 was considered statistically significant

Table 2. Operative and postoperative data of the overall population and the two subgroups of patients aged 50-59 and 60-69 according to type of valve mechanical and biological

	Overall population (n=977)			50-59 (n=329)			60-69 (n=648)		
Variables	Mechanical prosthesis	Biological prosthesis	p	Mechanical prosthesis	Biological prosthesis	p	Mechanical prosthesis	Biological prosthesis	p
	N (%), mean (SD) or median [range]	N (%), mean (SD) or median [range]		N (%), mean (SD) or median [range]	N (%), mean (SD) or median [range]		N (%), mean (SD) or median [range]	N (%), mean (SD) or median [range]	
Number of patients	359	618		197	132		162	486	
Size(s)			0.79			0.47			0.27
• 19	10 (3%)	19 (3%)		8 (4%)	4 (3%)		2 (1%)	15 (3%)	
• 21	85 (24%)	136 (22%)		38 (19%)	25 (19%)		47 (29%)	111 (23%)	
• 23	127 (35%)	217 (35%)		70 (36%)	49 (37%)		57 (35%)	168 (35%)	
• 25	77 (21%)	154 (25%)		44 (22%)	37 (28%)		33 (20%)	117 (24%)	
• 27	46 (135)	68 (11%)		25 (13%)	10 (8%)		21 (13%)	58 (12%)	
• >27	14 (4%)	22 (3%)		12 (6%)	5 (4%)		2 (1%)	17 (3%)	
CPB time (minutes)	84 (SD: 34)	82 (SD: 25)	0.52	86 (SD: 40)	83 (SD: 32)	0.46	80 (SD: 25)	81 (SD: 23)	0.15
Crossclamp time (minutes)	62 (SD: 20)	62 (SD: 20)	0.19	63 (SD: 23)	63 (SD: 23)	0.79	60 (SD: 18)	62 (SD: 18)	0.061
Log EuroSCORE	2.8 (SD: 2.3)	3.4 (SD: 2.8)	<0.001	2.4 (SD: 2.2)	2.4 (SD: 2.8)	0.51	3.3 (SD: 2.5)	3.6 (SD: 2.8)	0.16
30-day mortality	3 (0.8%)	4 (0.6%)	0.95	2 (1%)	0	0.66	1 (0.6%)	4 (0.8%)	0.79
Follow-up (years)	9.8 (5.3, 16.5)	5.2 (2.3, 9.2)	<0.001	9.3 (4.8, 15.9)	4.7 (1.8, 8.9)	<0.001	10.7 (6.8, 17.3)	5.4 (2.8, 9.5)	<0.001

CPB – cardiopulmonary bypass time; EuroSCORE – European System for Cardiac Operative Risk Evaluation.

P value ≤ 0.05 was considered statistically significant

Table 3. Competing risk analysis: cumulative incidence of reoperation, major bleeding, and cerebral stroke for biological and mechanical valves; Fine-Gray algorithm p value; Cox regression Hazard ratio.

	Population aged 50-59					Population aged 60-69			
	Mechanical prosthesis	Biological prosthesis	Competing risk p value	HR biological [95% CI]		Mechanical prosthesis	Biological prosthesis	Competing risk p value	HR biological [95% CI]
Reoperation									
• 5-year	0.6%	6.3%	<0.001	12.500		1.2%	2.1%	0.024	3.745
• 10-year	1.4%	16.0%		[3.484, 45.45]		2.1%	5.6%		[1.402, 10]
• 15-year	2.6%	26.3%				4.8%	20.9%		
Bleeding									
• 5-year	1.1%	0.7%	0.28	0.673		5.2%	1.2%	0.001	0.283
• 10-year	3.5%	1.0%		[0.134, 3.367]		9.5%	1.7%		[0.130, 0.617]
• 15-year	6.8%	1.7%				16.2%	6.9%		
Cerebral stroke									
• 5-year	1.8%	0.8%	0.19	0.297		1.4%	1.8%	0.67	1.326
• 10-year	4.3%	1.6%		[0.037, 2.386]		3.2%	3.2%		[0.496, 3.533]
• 15-year	6.6%	1.9%				6.3%	7.8%		

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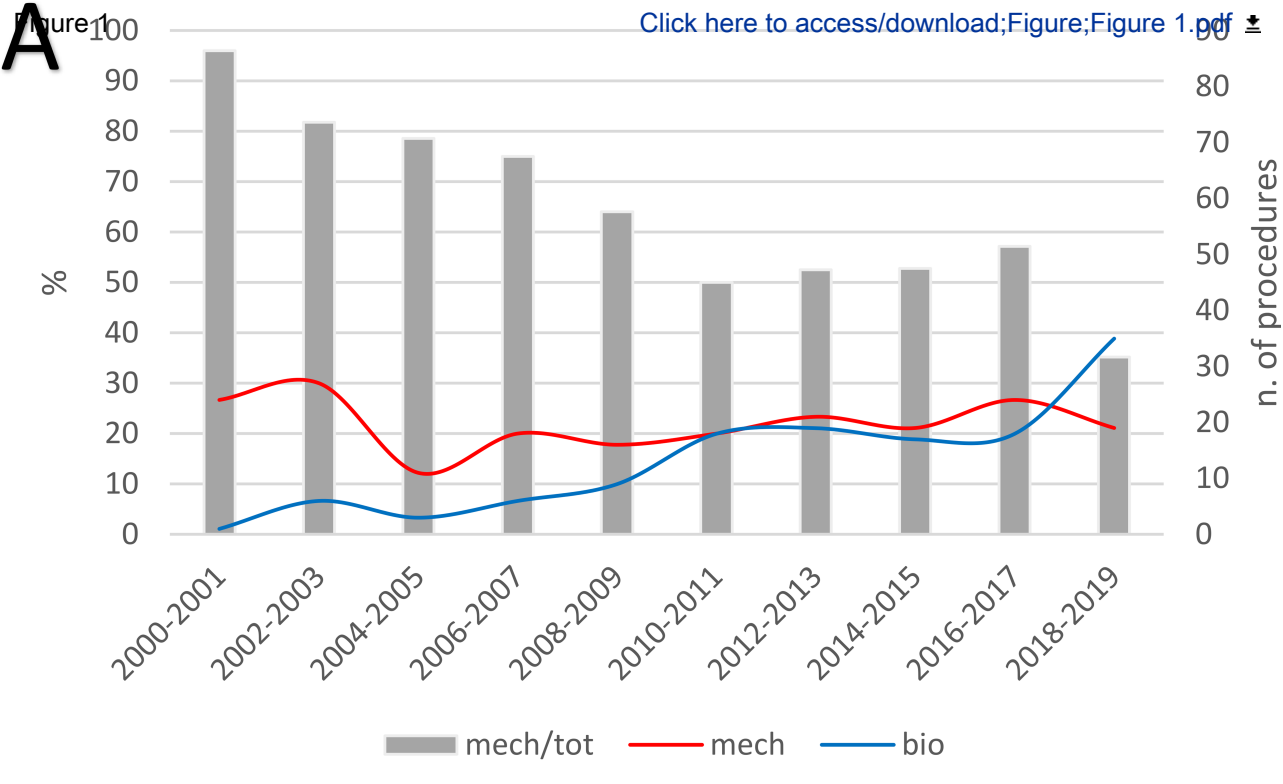

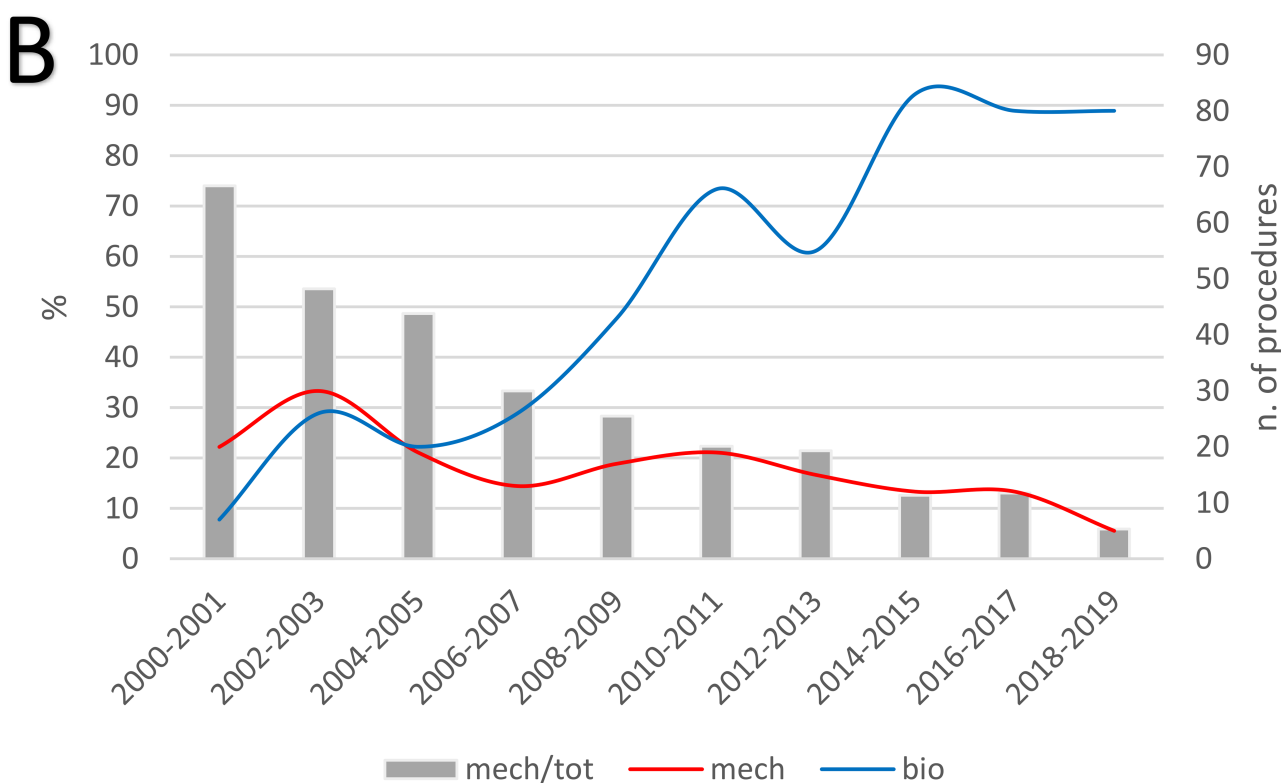

Figure 2

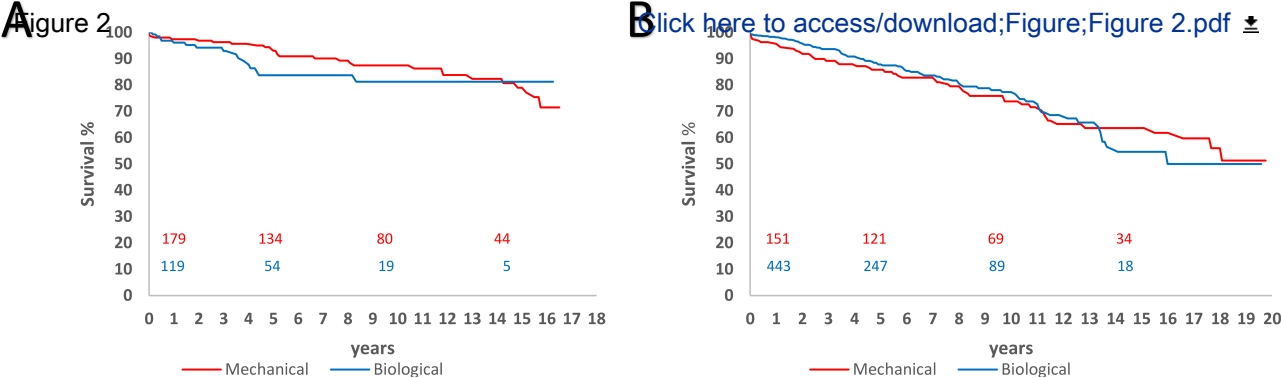

Figure 3

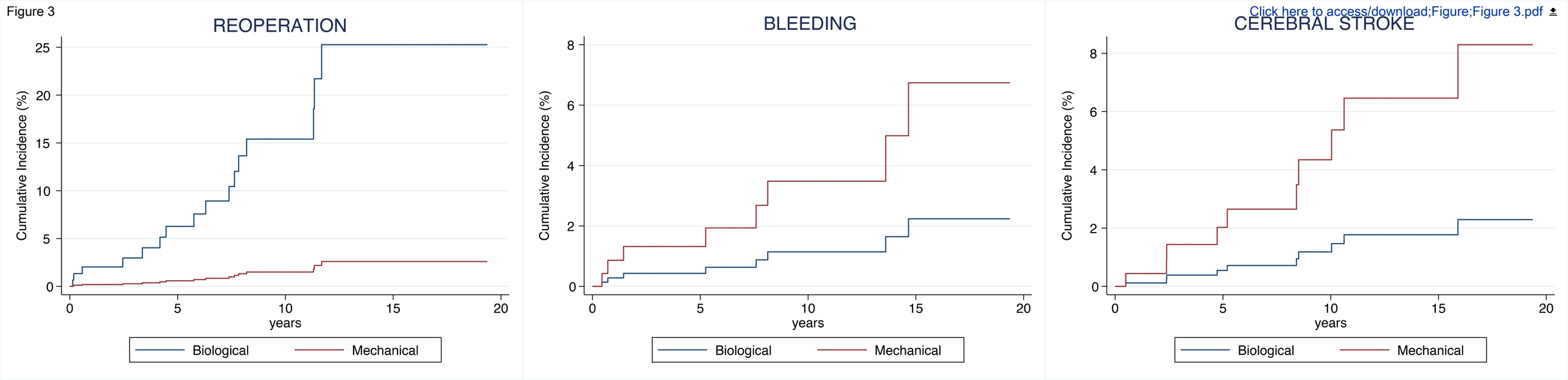

Figure 4