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Research Article

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Abstract

Objective
This retrospective study aimed to compare the outcomes of rapid deployment aortic valve replacement (rdAVR) and conventional bioprosthetic sutured AVR (cAVR) in high-risk patients undergoing redo surgery.

Methods
A total of 79 patients who underwent redo AVR between 2014 and 2021 were included in the study. Of these, 27 patients underwent rdAVR and 52 underwent cAVR. Patient characteristics and clinical outcomes were analysed using multivariate regression and Cox-survival analysis.

Results
The groups were similar in terms of age, gender, left ventricular function, and number of previous sternotomies. In cases of isolated AVR, rdAVR had significantly lower cross clamp times than cAVR (71 vs. 86 minutes, p = 0.03). Postoperatively, 4 cAVR patients required pacemaker compared to zero patients in the rdAVR group. There were no significant differences between the two groups in terms of postoperative complications, intrahospital stay (median 9 days, IQR 7–20), or in-hospital mortality (1 rdAVR; 2 cAVR). The long-term survival rate was similar between the rdAVR (90%) and cAVR (92%) groups (log rank p = 0.8). The transvalvular gradients at follow-up were not affected by the type of valve used, regardless of the valve size (coef 2.68, 95%CI -3.14-8.50, p = 0.36).

Conclusion
The study suggests that rdAVR is a feasible and safe alternative to cAVR in high-risk patients undergoing redo surgery. The use of rdAVR offers comparable outcomes to cAVR, with reduced cross clamp times and a lower incidence of postoperative pacemaker requirement in isolated AVR cases. The

Introduction
As the age of recipients of bioprosthetic aortic valve replacements (AVR) continues to decrease, we are witnessing a rise in mid-term and late AVR prosthetic dysfunction cases. The widespread practice of redo-surgical access and replacement of the failed AVR with another sutured valve prosthesis or root replacement is complex and requires careful patient and prosthesis selection (1)(2). Transcatheter technology is also emerging as an alternative to treat cases of bioprosthetic AVR failure, eliminating the need for sternal re-entry and its associated complications (3)(4). However, in younger, fitter patients with early valve failure caused by accelerated leaflet calcification or prosthetic valve endocarditis, surgical explanation of the prosthetic valve and repeat implantation of a new prosthesis remains highly advantageous.
The selection of a suitable prosthesis during complex redo AVR procedures depends on various factors, including the patient's age, comorbidities, and lifestyle, as well as technical aspects such as aortic access, annular size, shape, and whether it can accept a Perceval. The index procedure is also vital to consider implanting a Perceval within a previous root replacement (including homograft) would be different from implanting within a native root, and different still from a previous stented valve.

In this regard, providing patients with technological "upgrades" in the second, third, or even fourth AVR may be necessary, particularly if there are potential technical advantages. The advantages of using RDAVR include the avoidance of extensive tissue damage during explanation of the old valve ring, as well as the prospect of fast and simple implantation, which reduces the risk of cardiac ischemia and cardiopulmonary bypass, particularly in a long and protracted redo case. This has the potential to decrease post-operative complications and improve patient recovery.

As noted, while the use of RDAVR in redo-AVR procedures may have potential advantages over conventional sutured bioprostheses, there are also potential disadvantages to consider (5). One of these is the need for a higher aortotomy, which may not be achievable in a redo-sternotomy(5). Additionally, the long-term outcomes of Perceval valves in redo-AVR procedures are not yet clear, particularly with regard to the incidence of paravalvular leak. However, despite these uncertainties, some published case reports have shown promising outcomes when using sutureless or RDAVRs in complex redo procedures, particularly for replacing degenerated stentless bioprostheses and homografts(5). Nonetheless, further studies are needed to understand the potential benefits and drawbacks of these approaches more fully, particularly compared to conventional sutured bioprostheses(5).

To this end, the current study aims to contribute to the existing body of knowledge on RDAVR by reporting our experience using the Perceval valve for redo-AVR procedures. Our analysis will consider short and mid-term outcomes and compare the performance of the Perceval valve with that of conventional sutured bioprostheses. Ultimately, our findings may help to inform future clinical decision-making regarding the optimal selection of prostheses for patients undergoing redo-AVR procedures.

**Methods**

**Study Design and Ethical Evaluation**

Perioperative data was retrospectively analysed from a prospectively collated database at a single cardiothoracic institution between 2014 and 2021. Due to the retrospective nature of the study, the requirement for ethical approval was waivered by the Research Ethics Office at the Royal Brompton and Harefield Foundation Trust.

**Inclusion criteria**

Patients were included if they fulfilled two important criteria: i) they had previously undergone aortic valve surgery (non-repair) in adulthood more than 6 months prior to their inclusion in the study; and ii) they
were undergoing re-sternotomy and reimplantation of a new aortic valve prosthesis.

Patients who had received both mechanical and biological valves in the prior index procedure were included. Prior aortic root replacements were also included, including homograft procedures.

All indications for redo aortic valve intervention were considered, including structural valve degeneration and endocarditis. Patients were divided into two groups according to the type of AVR prosthesis they were receiving: either i) a rapid deployment (RDAVR) Perceval valve; or ii) a Perimount Magnaease prosthesis as a conventional sutured valve (cAVR).

Patients receiving other types of RDAVR were excluded. To ensure a consistent comparison between the groups, other marketed conventional sutured valves, although used in our institution, were excluded from the study.

**Procedure**

All reoperations were performed via median sternotomy, with the use of an oscillating saw. The strategy of cannulation for cardiopulmonary bypass was patient-specific and subject to the surgeon’s discretion. In general, if vital mediastinal structures were not at risk from sternal re-entry (as assessed from pre-operative cross-sectional imaging, sternal re-entry followed by standard central cannulation was the first-line desirable method. However, femoral cannulation was performed prior to sternotomy i) injury to vital structures was of concern when planning sternotomy on pre-operative cross-sectional imaging; and ii) femoral vessels were of suitable calibre and amenable to cannulation. Once CPB was initiated, systemic normothermia or mild hypothermia (32°C) if a patent mammary artery bypass was present. Once the aorta was cross clamped, and the heart successfully arrested, myocardial protection was achieved with intermittent antegrade blood cardioplegia (including direct ostial infusion), with or without retrograde cardioplegia, if the coronary sinus was accessible during initial myocardial dissection.

The choice of prosthesis or root replacement was at the discretion of the surgeon. If a Perceval valve were to be implanted, the aortotomy was performed usually as a high-transverse incision. Where possible, the failed prosthesis in its entirety along with the sewing ring was removed. Patch repair of the aortic root was used in cases of root endocarditis with neo-sinus/fistulation. Concomitant procedures were performed according to standard techniques.

**Data collection**

The cardiac surgical database is locally managed and centrally overseen at a national level, following national guidelines for minimal perioperative data collection, including pre-operative co-variates, detailed operative characteristics and post-operative care, including the record of short-term complications. Early and mid-term outcomes were assessed based on echocardiographic findings and grading of aortic regurgitation.

**Statistical analysis**
Results were analysed and presented as means and standard deviations. Pre-operative covariates were assessed for normal distribution using the Shapiro-Wilk test. Between group characteristics were assessed for statistical differences using the Student T test or Wilcoxon Rank Test for non-parametric variables. Multivariate logistic regression models were constructed to assess the influence of a variety of covariates on short term outcomes. Linear regression was used to assess the influence of covariates on parametric outcomes, namely hospital stay. Adjusted odds ratio with 95% confidence interval (CI) of binary outcomes were calculated. Statistical analyses were conducted using the Stata 13.0 software (Stata Corp., College Station, TX, USA).

Results

A total of 79 patients who underwent redo AVR between 2014 and 2021 were included in the study. Of these, 27 patients underwent rdAVR and 52 underwent cAVR.

Patient characteristics

Table 1 presents a comprehensive comparison between the rdAVR group and the cAVR group. In terms of demographics, there was no significant difference observed in the mean age between the cAVR (57.6 ± 2.5 years) and rdAVR (59.6 ± 2.4 years) groups (P = 0.607). Similarly, gender distribution displayed no significant difference, with 36 males in the cAVR group and 16 males in the rdAVR group (P = 0.379). The Body Mass Index (BMI) for patients in the cAVR group was 26.6 ± 0.7, while the rdAVR group had a slightly higher BMI of 28.7 ± 1.0 (P = 0.081).

Regarding cardiac comorbidities, the presence of hypertension was observed in 29 patients from the cAVR group and 18 patients from the rdAVR group, with no significant difference in distribution (P = 0.352). Peripheral Arterial Disease (PAD) was reported in 2 patients in both the cAVR and rdAVR groups, with no significant disparity (P = 0.496). A comparable number of cases of Infective Endocarditis were seen in the cAVR (9 patients) and rdAVR (8 patients) groups (P = 0.252). The New York Heart Association (NYHA) classification demonstrated a median of 3 (range 2–3) in the cAVR group and a median of 2 (range 1–3) in the rdAVR group, showing a statistically significant difference (P = 0.036). The occurrence of more than one previous sternotomy was noted in 4 patients in the cAVR group and 6 patients in the rdAVR group, with no significant distinction (P = 0.250).

In terms of the other comorbidities, the prevalence of Oral Diabetes was recorded in 3 patients from the cAVR group and 4 patients from the rdAVR group (P = 0.542). No cases of Insulin-dependent Diabetes were observed in the rdAVR group, while 2 cases were reported in the cAVR group (P = 0.542). Smoking was found in 22 patients from the cAVR group and 13 patients from the rdAVR group, with no significant discrepancy (P = 0.555). Chronic Obstructive Pulmonary Disease (COPD) was documented in 5 patients in the cAVR group and 6 patients in the rdAVR group, showing no significant difference (P = 0.127). A history of stroke was reported in 3 patients from the cAVR group and 2 patients from the rdAVR group, with no
significant variance ($P = 0.816$). Chronic Kidney Disease (CKD) was observed in 2 patients from both the cAVR and rdAVR groups, displaying no significant difference ($P = 0.514$).

Regarding the preoperative echocardiographic findings, the assessment of left ventricular functions demonstrated no significant difference between the groups. In the Conventional Aortic Valve Replacement (cAVR) group, 46 patients exhibited good left ventricular ejection fraction (EF), while 5 patients had moderate EF, and 1 patient had poor EF. Similarly, the Rapid-deployment Aortic Valve Replacement (rdAVR) group showed 22 patients with good EF, 4 patients with moderate EF, and 1 patient with poor EF. The mean EF percentage was $57.5 \pm 1.3$ in the cAVR group and $58.2 \pm 2.0$ in the rdAVR group, with no statistically significant difference observed between the two groups ($P = 0.742$). In the cAVR group, 12 patients exhibited aortic stenosis, 31 patients had aortic regurgitation, and 6 patients had aortic mixed pathology. In the rdAVR group, 9 patients showed aortic stenosis, 12 patients had aortic regurgitation, and 5 patients had aortic mixed pathology. No significant differences in valvular functions were noted between the two groups ($P = 0.527$).

In terms of the reasons for reoperation, there were no substantial discrepancies between the cAVR and rdAVR groups. In the cAVR group, 19 patients required reoperation due to prosthetic failure, 8 patients due to infection, 4 patients due to paravalvular leak, 1 patient due to thrombosis, 2 patients due to native valve degradation, and 10 patients due to regurgitation. In the rdAVR group, 13 patients underwent reoperation for prosthetic failure, 8 patients for infection, 4 patients for paravalvular leak, 1 patient for thrombosis, 1 patient for native valve degradation, and none for regurgitation. The differences in reasons for reoperation did not reach statistical significance between the two groups ($P = 0.067$).

**Operative parameters**

The table 2 showcases the varying types of explants within each group. In the cAVR group, there were 6 mechanical valve explants, 22 biological valve explants, 19 native valve explants, 2 autograft explants, 1 homograft explant, and 2 freestyle explants. The rdAVR group displayed 5 mechanical valve explants, 17 biological valve explants, 1 native valve explant, 4 homograft explants, and no cases of autograft or freestyle explants.

The table 3 demonstrates intraoperative outcomes. The cAVR group exhibited a CPB time of $168.4 \pm 11.1$ minutes, while the rdAVR group had a CPB time of $165.9 \pm 19.6$ minutes ($P = 0.452$). Regarding XC time, the cAVR group had a mean time of $108.8 \pm 6.3$ minutes, while the rdAVR group demonstrated a mean time of $92.0 \pm 8.6$ minutes ($P = 0.124$). In the cAVR group, 36 cases were elective, 15 were urgent, and 1 was emergency, while in the rdAVR group, 17 cases were elective, 10 were urgent, and none were emergency, displaying no significant difference ($P = 0.622$). The cAVR group included 12 cases with a valve size of 21, 21 cases with size 23, 14 cases with size 25, and 5 cases with size 27. In contrast, the rdAVR group comprised 10 cases with size 21, 13 cases with size 23, 3 cases with size 25, and 1 case with size 27. A statistically significant difference was noted in valve size distribution between the groups ($P = 0.048$).

**Postoperative Complication outcomes**
In-hospital mortality was found to be similar between the two groups. Specifically, there were 2 deaths out of 52 patients (3.8%) in the cAVR group and 1 out of 27 patients (3.7%) in the rdAVR group. This difference was not statistically significant (P > 0.05). The incidence of stroke was lower in the cAVR group, but this difference was not statistically significant (1 out of 52 patients (1.9%) in the cAVR group vs. 3 out of 27 patients (11.1%) in the rdAVR group, P > 0.05). No cases of gastrointestinal bleeding were observed in either group, which was attributed to the use of biologic prostheses and the absence of anticoagulation. However, the rdAVR group had lower rates of respiratory complications (7.4% vs. 19.2%, P > 0.05), the need for dialysis (0% vs. 7.7%, P > 0.05), and pericardial/pleural effusions (3.7% vs. 15.3%, P > 0.05) compared to the cAVR group. In addition, none of the patients in the rdAVR group required postoperative pacemaker implantation, while this was necessary in 4 out of 52 patients (7.7%) in the cAVR group. However, this difference was not statistically significant (P > 0.05). (table 3).

**Echocardiographic Outcomes**

Table 5 provides a comprehensive analysis of postoperative echocardiographic outcomes between the Conventional Aortic Valve Replacement (cAVR) and Rapid-deployment Aortic Valve Replacement (rdAVR) groups. (table 5, Fig. 1, 2)

**Post Discharge**

Left Ventricular Functions displayed no significant differences between groups. In the cAVR group, 31 patients demonstrated good ejection fraction (EF), 9 patients had moderate EF, and 1 patient had poor EF. Similarly, in the rdAVR group, 19 patients exhibited good EF, 4 had moderate EF, and 1 had poor EF. The mean EF percentages were 56.8 ± 10.0 in the cAVR group and 56.1 ± 11.4 in the rdAVR group (P = 0.537). Prosthesis Functions indicated comparable results. The cAVR group had 34 normally functioning prostheses, 6 with mild aortic regurgitation (AR), 1 with moderate AR, and none with severe AR. Likewise, the rdAVR group had 21 normally functioning prostheses, 2 with mild AR, 1 with moderate AR, and none with severe AR (P = 0.714). Aortic Valve Gradient showed variations. Peak gradients were 23.2 ± 10.6 mm Hg in the cAVR group and 30.5 ± 14.8 mm Hg in the rdAVR group (P = 0.026). Mean gradients were 12.9 ± 6.4 mm Hg in the cAVR group and 16.7 ± 8.4 mm Hg in the rdAVR group (P = 0.045). The distribution of gradients under 20 mm Hg, 20–39 mm Hg, and 40+ mm Hg varied between the groups.

**Late Term Follow-up (median 24 months)**

Late Term Follow-up revealed comparable findings. Left Ventricular Functions showed no significant differences, with 31 patients with good EF in the cAVR group and 18 in the rdAVR group. EF percentages were 60.4 ± 6.8 in the cAVR group and 58.5 ± 9.2 in the rdAVR group (P = 0.391). The cAVR group had 29 normally functioning prostheses, 4 with mild AR, none with moderate AR, and none with severe AR. The rdAVR group had 14 normally functioning prostheses, 4 with mild AR, 2 with moderate AR, and none with severe AR (P = 0.116). Aortic Valve Gradient values were similar. Peak gradients were 12.9 ± 7.1 mm Hg in the cAVR group and 15.6 ± 13.6 mm Hg in the rdAVR group (P = 0.360). Mean gradients were 22.8 ± 12.3
mm Hg in the cAVR group and 22.8 ± 13.6 mm Hg in the rdAVR group (P = 0.997). The distribution of gradients within specified ranges also showed similarities between the groups.

**Survival**

Kaplan Meier analysis revealed similar survival rates between the rdAVR and cAVR groups, (crude log rank test p = 0.315) (Fig. 3). Furthermore, a cox-proportional hazard regression analysis was conducted to assess for predictors of long-term survival, including the choice of valve, age, gender, and pre-operative LV function. The results identified no significant predictors of long-term survival (p > 0.05). Specifically, the choice of valve did not influence survival (hazard ratio 1.22, 95% CI 0.14–10.25, p = 0.855). These findings are summarized in Tables 4, 5 and 6.

**Discussion**

This study is the first to directly compare the outcomes of redo-AVR procedures between the Perceval valve and an established sutured bioprosthesis. The results of the study indicate that there were very similar short- and long-term outcomes between the two valve choices, suggesting that the Perceval valve may be a viable option for high-risk patients who require redo-AVR.

The utilization of rdAVR continues to provide the well-established advantage it offers in initial cardiac surgeries, resulting in reduced cardiopulmonary bypass and aortic cross-clamp durations. This has been consistently linked with decreased short-term mortality and a shorter duration of hospitalization in extensive databases (6) (7), making it an attractive option for high-risk operations such as redo AVRs.

**Pacemaker implantation after the procedure**

Our study highlights a crucial finding regarding the lower rate of pacemaker implantation in the rdAVR group. Prior reports have indicated that rdAVR, particularly with the Perceval valve, is associated with a higher incidence of postoperative pacemaker implantation in first-time AVR surgery (8, 9). Although this has been attributed to the initial part of the learning curve, where over-sizing may be more common, this complication is significant and cannot be overlooked (8, 9). However, our research suggests that precise suture placement during cAVR is more challenging in cases where the annulus is already distressed and fibrosed, and the use of rdAVR may help circumvent this issue. Interestingly, our study found that a larger proportion of small-sized valves were used in the rdAVR group compared to cAVR, which may account for the disparity in PPM outcomes (10). Overall, our findings suggest that rdAVR may offer benefits in reducing the incidence of pacemaker implantation, especially in patients with a fibrosed annulus.

**A higher risk patient cohort**

Redo AVR has traditionally been associated with a higher rate of complications compared to first-time SAVR in the literature, with reported operative mortality rates ranging between 4% and 9% (1) (11). The formation of adhesions and loss of tissue planes between the heart, mediastinal structures, and sternum after the index SAVR increases the risk of complications during sternal re-entry and dissection,
particularly in patients who are older or have comorbidities (2). These risks are further compounded by the proximity to critical thoracic structures. The sequelae of redo surgical AVR may include stroke, myocardial infarction, new atrial fibrillation, and permanent pacemaker implantation.

In a meta-analysis by Formica et al., valve-in-valve transcatheter replacement was found to be advantageous in terms of complications compared to redo aortic valve surgery but redo aortic valve replacement surgery had advantages in medium and long-term survival (12). In our study, there was no significant difference in perioperative complications between the rdAVR and cAVR groups. However, there was a reduced frequency of effusion and in-hospital mortality in the rdAVR group. Furthermore, none of the patients in the rdAVR group required dialysis, whereas dialysis was needed in four patients in the cAVR group. This suggests that the reduced operative time afforded by rdAVR may have benefits for reducing post-operative coagulopathy, metabolic disturbance, and ICU complications in redo AVR procedures. Much of this may be attributed to the shorter cross-clamp and CPB times.

**Long-term benefit**

In the absence of long-term data on valve durability, the use of rdAVR in patients undergoing redo cardiac surgery is not typically indicated, due to the complexity of the procedure and the associated risk of perioperative complications and mortality.

The choice of bioprosthetic AVR variant has not been found to offer a significant survival advantage, but rdAVR has demonstrated some advantages in high-risk patient groups. Hanedan et al. found that rdAVR was three times more advantageous than cAVR in terms of short-term survival in high-risk patients, although the difference was statistically insignificant (94.7% vs 84.6%) (13). Similarly, Salmasi et al.'s meta-analysis on rdAVR vs cAVR did not find a significant difference in bleeding and short-term survival, but rdAVR’s shorter operative time was advantageous with a shorter ICU stay (14). Coti et al.’s rdAVR study of 700 cases reported a three-year and five-year survival rate of 91% and 76%, respectively, demonstrating that rdAVR was feasible for mid-term survival, even in redo cardiac surgery patients (15). Our study supports these findings, showing that rdAVR is comparable to cAVR in terms of short/mid/long-term survival in redo surgeries. While the choice of bioprosthetic AVR variant may not significantly affect survival rates, rdAVR's shorter operative time may lead to fewer complications and improved outcomes.

**Endocarditis**

Prosthetic valve endocarditis is a highly morbid condition and compounds the risk of redo surgery according to most risk-scoring systems. The incidence can be as high as 16% in patients with prior AVR (16) and patients who require redo-surgery have exceptionally high morbidity and mortality rates (17) (18). Complex procedures, such as prolonged cardiopulmonary bypass time and cross-clamp time, are often required, and these are associated with increased mortality and severe perioperative complications (19).

In a recent study, 29.6% of the rdAVR group and 17.3% of the cAVR group had infective endocarditis. Despite this, in-hospital mortality was observed in only one out of the eight patients with prosthetic valve
endocarditis in the rdAVR group, while in-hospital mortality was not observed in any of the nine endocarditis patients in the cAVR group. These findings suggest that the use of rdAVR for redo cases with prosthesis infective endocarditis is effective in achieving acceptable short- and medium-term survival, as reported in recent literature.

**Echocardiographic Outcomes**

Evidence on the status of late hemodynamic in rapid-opening aortic valve replacement is still needed in the literature(20, 21). Recent studies have suggested no significant hemodynamic differences early period after surgery between rapid deployment valves and conventional bioprostheses(20–21). This observation extends, although with limited evidence, to redo aortic valve surgeries(22).

Our study aimed to address this gap through a meticulous echocardiographic assessment, evaluating rapid deployment aortic valve prostheses in redo cases. With a median 24-month follow-up, our findings indicate no notable differences between conventional AVR (cAVR) and rapid deployment AVR (rdAVR) regarding aortic valve median gradient and peak gradient. These measurements remain well within acceptable clinical ranges for both groups.

**Strengths and limitations**

The present study provides important insights to the off-label use of an important prosthetic technology in a high-risk patient group. As such, the sample size is considerably smaller than most studies reporting outcomes of aortic valve surgery, and the results should therefore be taken with caution. Additionally, there is some heterogeneity in the patient cohort, namely through the variable comorbid conditions, including prosthetic valve endocarditis, as well as variable prior index procedures. The sample population was not large enough to perform adequate subgroup analysis. As such, larger future studies may provide more detailed analyses and ascertain potential differences in outcome between the two treatment options with more accuracy.

**Conclusion**

The findings of this study suggest that Perceval aortic valve replacement can be safely used in patients undergoing redo cardiac surgery, with equivalent outcomes to conventional sutured valves. This is particularly relevant in the context of prosthetic valve endocarditis, a severe and life-threatening form of endocarditis that affects patients with prosthetic heart valves. The compounded effect of both redo surgery and an infected prosthesis can seriously hamper patient survival in the acute setting, making this an area of significant clinical need. There are several potential benefits of using sutureless aortic valves in high-risk patient populations, and the present study suggests that the use of Perceval valves may be an attractive option for patients undergoing redo cardiac surgery. Further research is needed to confirm these findings and to identify the optimal patient selection criteria for the use of sutureless aortic valves in this context.
Declarations

-Ethics approval and consent to participate.

Due to the retrospective nature of the study, the requirement for ethical approval was waived by the Research Ethics Office at the Royal Brompton and Harefield Foundation Trust.

-Informed Consent

Due to the retrospective nature of the study, the requirement for informed consent was waived by the Research Ethics Office at the Royal Brompton and Harefield Foundation Trust.

-Consent for publication

For this type of study consent for publication is not required.

-Availability of data and material

The data that supports the findings of this study are available upon request. Due to the sensitive nature of the data and the confidentiality agreements in place, we are unable to publicly share the data directly. However, we are committed to promoting transparency in scientific research, and we encourage interested researchers to contact Corresponding Author to request access to the data.

-Competing interests

The authors declare that they have no conflict of interest.

-Funding

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-Acknowledgement

Not Applicable

References


19.


Tables

Tables 1 to 6 are available in the Supplementary Files section.

Figures
Figure 1

LVEF
Figure 2

Aortic Valve Gradient after Redo AVR
Figure 3

Kaplan-Meier survival curve

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx