Accepted Manuscript

Submission Date: 2023-09-24
Accepted Date: 2024-02-27
Accepted Manuscript online: 2024-03-05

The Thoracic and Cardiovascular Surgeon

Recent outcomes of surgical redo aortic valve replacement in prosthetic valve failure

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DOI: 10.1055/a-2281-1897

Please cite this article as: Kang Y, Soehartono N, Choi J et al. Recent outcomes of surgical redo aortic valve replacement in prosthetic valve failure. The Thoracic and Cardiovascular Surgeon 2024. doi: 10.1055/a-2281-1897

Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Background. As redo surgical aortic valve replacement(AVR) is relatively high risk, valve-in-valve transcatheter AVR has emerged as an alternative for failed prostheses. However, the majority of studies are outdated. This study assessed the current clinical outcomes of redo AVR.
Methods and Results. This study enrolled 324 patients who underwent redo AVR due to prosthetic valve failure from 2010 to 2021 in four tertiary centers. The primary outcome was operative mortality. The secondary outcomes were overall survival, cardiac death, and aortic valve-related events. Logistic regression analysis, clustered Cox proportional hazards models, and competing risk analysis were used to evaluate the independent risk factors.
Redo AVR was performed in 242 patients without endocarditis and 82 patients with endocarditis. Overall operative mortality was 4.6% (15 deaths). Excluding patients with endocarditis, the operative mortality of redo AVR decreased to 2.5%. Multivariate analyses demonstrated that endocarditis (HR 3.990, P=0.014), longer cardiopulmonary bypass time (HR 1.006, P=0.037) and lower left ventricular ejection fraction (LVEF) (HR 0.956, P=0.034) were risk factors of operative mortality. Endocarditis and lower LVEF were independent predictors of overall survival.
Conclusions. The relatively high risk of redo AVR was due to reoperation for prosthetic valve endocarditis. The outcomes of redo AVR for non-endocarditis are excellent. Our findings suggest that patients without endocarditis, especially with acceptable LVEF, can be treated safely with redo AVR.

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Supplemental Table S1 Clustered Cox Proportional Hazards Models for Factors Associated with Overall Survival and Competing Risk Analysis for Factors Associated with Cardiac Death

Factors associated with overall survival				
Variables[a]	Univariate analysis		Multivariable analysis	
	HR [95% CI]	*P* Value	HR [95% CI]	*P* Value
Age (years)	**1.077 [1.042-1.125]**	**<0.001**	**1.069 [1.023-1.118]**	**0.003**
Endocarditis group	**4.009 [2.107-7.630]**	**<0.001**	**2.238 [1.161-4.314]**	**0.016**
LVEF	**0.947 [0.922-0.973]**	**<0.001**	**0.943 [0.919-0.967]**	**<0.001**
Factors associated with cardiac death				
Variables[a]	Univariate analysis		multivariable analysis	
	HR [95% CI]	*P* Value	HR [95% CI]	*P* Value
Age	**1.093 [1.010-1.183]**	**0.028**	**1.119 [1.034-1.211]**	**0.005**
Male Gender	**14.010 [3.395-57.790]**	**<0.001**	**0.381 [0.066-2.205]**	**0.281**
Endocarditis group	**30.500 [5.596-166.200]**	**<0.001**	**31.420 [3.254-300.330]**	**0.003**
LVEF	**0.909 [0.871-0.948]**	**<0.001**	**0.882 [0.848-0.917]**	**<0.001**
AF	**0.243 [0.058-1.017]**	**0.053**	**0.295 [0.076-1.150]**	**0.079**

LVEF= left ventricular ejection fraction, AF = atrial fibrillation

[a]All variables in Table 1 were analyzed and factors that entered into the multivariable analysis were shown.

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Abstract

Background As redo surgical aortic valve replacement(AVR) is relatively high risk, valve-in-valve transcatheter AVR has emerged as an alternative for failed prostheses. However, the majority of studies are outdated. This study assessed the current clinical outcomes of redo AVR.

Methods and Results This study enrolled 324 patients who underwent redo AVR due to prosthetic valve failure from 2010 to 2021 in four tertiary centers. The primary outcome was operative mortality. The secondary outcomes were overall survival, cardiac death, and aortic valve-related events. Logistic regression analysis, clustered Cox proportional hazards models, and competing risk analysis were used to evaluate the independent risk factors.

Redo AVR was performed in 242 patients without endocarditis and 82 patients with endocarditis. Overall operative mortality was 4.6% (15 deaths). Excluding patients with endocarditis, the operative mortality of redo AVR decreased to 2.5%. Multivariate analyses demonstrated that endocarditis (HR 3.990, P=0.014), longer cardiopulmonary bypass time (HR 1.006, P=0.037) and lower left ventricular ejection fraction (LVEF) (HR 0.956, P=0.034) were risk factors of operative mortality. Endocarditis and lower LVEF were independent predictors of overall survival.

Conclusions The relatively high risk of redo AVR was due to reoperation for prosthetic valve

endocarditis. The outcomes of redo AVR for non-endocarditis are excellent. Our findings suggest that patients without endocarditis, especially with acceptable LVEF, can be treated safely with redo AVR.

Keywords
Aortic valve
Aortic valve replacement
Prosthesis

Introduction

Aortic valve replacement (AVR) is one of the most frequently performed open heart surgeries (1). With the increase in patients undergoing AVR, patients who require redo AVR due to structural valve degeneration (SVD), prosthetic valve endocarditis, paravalvular leak or thrombosis/pannus formation are also increasing. With the increase in the number of patients using aortic valve bioprostheses and recent advances in valve-in-valve transcatheter aortic valve implantation, an increase in the number of patients with failing bioprostheses is to be expected.

In previous studies, the in-hospital mortality rate of redo AVR after surgical AVR ranged from 2% to 18%, averaging around 5% (2,3). However, these studies are outdated, and their study populations were heterogeneous with various surgical indications. Therefore, the present study evaluated recent clinical outcomes of redo AVR after surgical AVR for failing prostheses.

Patients and Methods

Patient Enrollment

The study protocol was reviewed by our Institutional Review Board and approved as a minimal risk retrospective study (Approval Number: H-2202-061-1299) that did not require individual consent on February 18, 2022. From January 2010 to December 2021, 392 consecutive patients underwent redo AVR after surgical AVR in four tertiary centers. None of the patients had underwent coronary artery bypass grafting as a primary procedure. Of these patients, 66 who had severe mitral or tricuspid valve disease and two who underwent intended concomitant coronary artery bypass graft were excluded. Thus, this study enrolled 324 patients (62.1±13.8 years;145 males and 179 females).

The indications for redo SVR were (1) non-structural valve dysfunction (non-SVD; n=84), (2) SVD (n=151), (3) prosthetic valve endocarditis (n=82), and (4) thrombosis (n=7).

Operative Strategy

The procedures were performed using various approaches, including median sternotomy (n=303), upper partial sternotomy (n=19) or right anterior thoracotomy (n=2). One-hundred and twenty of the patients underwent redo AVR with a mechanical valve, and the other 204 patients underwent bioprosthetic redo AVR. Two different types of rapid deployment/sutureless valve were used (Sorin Perceval (n=3) and Edwards Intuity (n=5)). The surgical approach and type of prosthesis were selected at the discretion of the attending

surgeon.

Evaluation of Early and Long-Term Clinical Outcomes

Operative mortality was defined as death within 30 days of operation or during the same hospitalization period. Postoperative low cardiac output syndrome was defined as the need for mechanical or inotropic support to maintain systolic blood pressure>90 mmHg after correcting reversible factors.

Regular (3- to 6-month intervals) postoperative follow-up was performed at the outpatient clinic. The patient's condition was checked via telephone if they did not attend the scheduled clinic visit. Cardiac death was defined as any death of a cardiac origin, including sudden death. Aortic valve-related events (AVRE) were defined as following; (1) cardiac death, (2) congestive heart failure, (3) reoperation for aortic valve, (4) thromboembolism, (5) major bleeding that caused death, hospitalization or need for a transfusion, (5) prosthetic aortic valve endocarditis, and (6) permanent pacemaker implantation following AVR.

The clinical follow-up period ended on April 30, 2022. The median follow-up duration was 51 months (interquartile range:16.8-79.0months). The completeness of follow-up was 94.1% (305 out of 324) for overall survival and other long-term clinical outcomes.

Statistical Analysis

Statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical

Computing) and SAS (version 9.4; SAS institute, Cary, NC, USA). The two groups were compared using the Chi square test or Fisher's exact test and Student's t-test for categorical and continuous variables, respectively. Survival rates were estimated using the Kaplan-Meier method.

Logistic regression analysis was performed to evaluate the factors associated with operative mortality. Risk factors for longitudinal data were analyzed using multivariate Cox proportional hazards model.

The patients were divided into subgroups according to the presence of preoperative endocarditis. The cumulative incidences of cardiac death and AVRE were estimated with non-cardiac death as a competing risk for the events. The cumulative incidences of composite of thromboembolism and bleeding (CTEB) were estimated with all-cause death as a competing risk for the events. The cumulative incidences of the two groups for each event were compared using Fine-Gray's test. Variables with a *P* value<0.10 in the univariate analyses were entered into multivariate models. A *P* value<0.05 was considered statistically significant.

To balance the patients for differences in baseline characteristics, inverse probability of treatment weight (IPTW) analysis was used. The following preoperative variables were entered into the logistic regression model: age, sex, body surface area, hypertension, diabetes mellitus, history of stroke, chronic kidney disease, coronary artery disease,

dyslipidemia, atrial fibrillation, and left ventricular ejection fraction (LVEF). A clustered Cox regression analysis of overall survival based on the IPTW analysis was performed.

Results

Patient Characteristics and Operative Data

The baseline patients characteristics are presented in Table 1. Redo AVR was performed in 242 patients for reasons other than prosthetic valve endocarditis (non-endocarditis group) and the other 82 patients underwent redo AVR due to endocarditis (endocarditis group). Patients in the non-endocarditis group were younger, more likely to be male, and have diabetes mellitus, a history of stroke, and atrial fibrillation than the endocarditis group (Table 1). There were no significant differences in preoperative characteristics between the two groups after IPTW adjustment. The aortic cross clamp time was longer and tricuspid valve procedures were performed more frequently in the endocarditis group after IPTW adjustment (Table 1).

Early Results

Operative mortality occurred in 15 patients(4.6%) overall. Excluding the patients with endocarditis, the operative mortality of redo AVR decreased to 2.5%(6 of 242 patients), whereas that of redo AVR in patient with endocarditis increased to 11.0%(9 of 82 patients). In the non-endocarditis group, the operative mortality was 1.3%(2 of 151 patients) for SVD, and

4.8%(4 of 84 patients) for non-SVD. The operative mortality was significantly higher in the endocarditis group (11.0% vs 2.5%, P=0.004).

Table 2 summarizes the postoperative complications. There were significant differences in the operative mortality rate and incidences of postoperative acute kidney injury, stroke, and respiratory complications between the two groups (Table 2). After applying the IPTW procedure, the endocarditis group also had significantly worse clinical outcomes in operative mortality and postoperative acute kidney injury than the non-endocarditis group, whereas the other postoperative outcomes were comparable.

The results of the univariate and multivariate logistic regression analyses for operative mortality are shown in Table 3. Independent risk factors of operative mortality were the presence of preoperative endocarditis (HR 3.990; 95% CI: 1.343-12.580; P=0.014), longer cardiopulmonary bypass time (HR 1.006; 95% CI:1.000-1.011; P=0.037), and lower LVEF (HR 0.956; 95% CI:0.918-0.998; P=0.034).

Long-Term Survival

Late death occurred in 53 patients including 10 cardiac deaths. The 1- and 5-year overall survival rates were 93.4% and 83.5%, respectively (Figure 1A). In the non-endocarditis group, the overall survival at 1- and 5-years was 96.2% and 88.2%, respectively (Figure 1B). Kaplan-Meier curves showed that the overall survival was higher in the non-endocarditis (P<0.001). The freedom from cardiac death at 1- and 5-years was 98.1% and 96.2%, respectively (Figure 2A). In the non-endocarditis group, the freedom from cardiac death at 1-

and 5-years was 100.0% and 98.8%, respectively (Figure 2B). Kaplan-Meier curves showed that the freedom from cardiac death was higher in the non-endocarditis (P=0.010). Multivariate analysis showed that age, the presence of endocarditis and LVEF were significantly associated with overall survival (Table 4). In the competing risk analysis for cardiac death, the endocarditis group was associated with increased risk (HR 10.260, 95% CI: 2.137-49.268; P=0.004, Table 4). After IPTW, the clustered Cox regression also revealed that the endocarditis group had poorer overall survival (HR 2.238; 95% CI:1.161-4.314; P=0.016; Supplemental Table 1 and Supplemental Figure 1).

Aortic Valve-Related Events

During follow-up, AVRE occurred in 65 patients including cardiac death in 10, congestive heart failure in 20, reoperation for the aortic valve in 11, and prosthetic AV endocarditis in 9 patients.

The 1- and 5-year rates of freedom from AVRE were 91.4% and 76.8%, respectively (Figure 3A). The 5-year rates of freedom from AVRE in the non-endocarditis and endocarditis groups were 93.8% and 79.7%, respectively (Figure 3B). Although there were significant differences in AVRE between the two groups in the log-rank test (P=0.010), there was no significant difference in AVRE after IPTW adjustment. The multivariate analyses showed that the endocarditis was not an independent risk factor for AVRE (HR 1.456; 95% CI: 0.792-2.710; P=0.236). Instead, the presence of chronic kidney disease was associated with AVRE (Table

5)

Comment

This study demonstrated three main findings. First, the clinical outcomes of redo AVR for non-endocarditis were excellent with 2.5% operative mortality. In particular, the mortality of redo AVR for SVD was very low at 1.5%. Second, endocarditis, prolonged cardiopulmonary bypass time, and low LVEF were independent risk factors in redo AVR. Third, redo AVR was associated with better overall survival and lower risk of cardiac death in younger patients with an acceptable LVEF without endocarditis.

As the proportion of patients undergoing bioprosthetic AVR is increasing (4), increasing numbers of patients are expected to require redo AVR (5,6). Based on reports of a relatively high risk of redo surgical AVR with around 5% operative mortality (1), valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) has been increasingly used. Although some previous observational studies found that ViV-TAVI was associated with lower early mortality than redo AV (7,8), those were not randomized controlled trials. In addition, those studies were based on the administrative hospital-discharge database, which has limited information about the existing bioprosthetic valve size. In patients with smaller bioprostheses, surgery may be preferred over intervention due to patient-prosthesis mismatch; however, the reoperation of smaller existing prostheses can be technically more demanding due to the possible need for annular enlargement (9). Moreover, compared to our patients, the patients

in those studies tended to undergo previous coronary artery bypass grafting more frequently (approximately 3% vs. 15-20%), which can confer a relatively higher risk for redo surgery (10,11). In addition, Deharo et al. included patients with previous endocarditis (7).

Recent meta-analyses that directly compared ViV-TAVI and surgery showed that the early (12) and mid-term (13) all-cause mortalities were comparable. There has been concern regarding the mid- and long-term results of ViV-TAVI because of the higher postoperative pressure gradient compared to surgery (14,15). Regarding that ViV-TAVI is challenging in patients with small bioprostheses (<21mm) in terms of hemodynamic performance (16) and Asians are tend to implant smaller bioprostheses at the index procedure. In our study, 290 patients (89.5%) had bioprostheses less than or equal to 21mm. Hawkins et al., (17) has also sized that in patients with life expectancy longer than the duration of TAVI valve and unsuitable anatomy for ViV-TAVI should be considered as a surgical AVR candidate.

Regarding reported mortality rates of 12% and 29-32% at 1- and 3-years after ViV TAVI (18,19), we observed relatively high 1- and 5-year overall survival rates of redo AVR (96.2% and 88.2%) in the non-endocarditis group. In addition, early studies suggested high rates of device malposition, elevated transvalvular gradients, and coronary obstruction (20,21). Consistent with other studies (1,22,23), the operative mortality of redo AVR in our study was 4.6%. Mortality around 5% observed with heterogeneous surgical patients, including reoperation involving aortic surgery (22,23) and various surgical indications (1). Moreover,

most of those studies were published before 2010. After excluding the patients with prosthetic valve endocarditis, the operative mortality in our study fell to 2.5%, and decreased further to 1.5% for the patient with SVD. Our data show that the operative mortality of prosthetic aortic valve endocarditis is up to 11.0%. Prosthetic valve endocarditis is one of the most important indications of redo AVR and, its reported mortality rate is between 5% and 17% (24,25). In numerous previous studies, prosthetic valve endocarditis as an indication for redo AVR was a risk factor for early mortality, which is similar to our findings (1,26,27).

The reported results after redo AVR are associated with the timing and indications of reoperation, cardiac/non-cardiac risk factors, and the type of valve implanted (27-29). In our study, the multivariate analysis showed that preoperative prosthetic valve endocarditis, prolonged cardiopulmonary bypass time and low preoperative LVEF were independent risk factors for operative mortality. In particular, a reduced LVEF is a well-known risk factor for early mortality, which is similar to our results (5,27). These findings show the importance of a comprehensive preoperative evaluation of the candidates for redo cardiac surgery.

As technological advances have led to the introduction of transcatheter valve implantation in selected patients who require redo cardiac surgery, a thorough understanding of the operative outcomes and risk factors of redo AVR is essential. Although redo cardiac surgery is technically demanding, surgical advances and standardized intensive care unit protocols to minimize perioperative complication help reduce the associated morbidity. Minimally invasive

surgical techniques continue to be developed and new surgical devices have been introduced, including sutureless valves, rapid deployment valves, and automated suture fasteners, such as Cor-Knot (1). Minimally invasive surgery can facilitate access to redo surgery, expanding the surgical options to make redo surgery safer. In addition, the introduction of new surgical devices can help reduce aortic cross clamp time, and avoid the dissection of a previous aortotomy site and annulus injury during hand-tying. Moreover, the postoperative cardiac intensive care protocols have been developed and standardized (30). As a re-evaluation of recent clinical outcomes of redo AVR was needed, we conducted this study to re-assess the contemporary results of redo AVR.

Several limitations of this study must be noted. First, it was limited by its retrospective design. As the patients were not randomized to the interventions, there was selection bias. However, we applied IPTW analysis to minimize bias. Second, the indications for valve selection for redo AVR might have affected the clinical outcomes. However, due to the retrospective nature of the study, we could not delineate the precise indications for valve selection. Finally, we did not compare the clinical outcomes of redo AVR and ViV-TAVI.

In conclusion, the early and long-term clinical outcomes of redo AVR for non-endocarditis were excellent. Our findings suggest that patients without endocarditis, especially with an acceptable ejection fraction, can be treated with redo AVR safely. However, the long-term

results of redo AVR and ViV-TAVI are needed to establish the superiority of redo AVR with degenerated bioprosthetic aortic valves.

Acknowledgement

We wish to thank the Medical Research Collaborating Center, Seoul National University Hospital for statistical consultation.

Funding Statement: This article received no specific grant from any funding agency.

Disclosure: No disclosure

Data Availability Statement : Data available on request

Authors' contributions:

This study involved the collaboration of data from four different tertiary institutions, requiring the contributions of nine co-authors.

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Figure 1 Kaplan-Meier curve (unweighted) for overall survival (A) in all patients and (B) according to the presence of preoperative prosthetic valve endocarditis.

Figure 2 Kaplan-Meier curve (unweighted) for cardiac death (A) in all patients and (B) according to the presence of preoperative prosthetic valve endocarditis.

Figure 3 Kaplan-Meier curve (unweighted) for aortic valve-related events (A) in all patients and (B) according to the presence of preoperative prosthetic valve endocarditis.

Supplemental Figure S1 Kaplan-Meier curve after inverse probability of treatment weighting for overall survival. E= Endocarditis group, NE=Non-endocarditis group.

Table 1 Preoperative and Operative data of the Study Patients before and after inverse probability of treatment weighting (IPTW)

		Before IPTW, n (%)			*IPTW*
Variables	All	Non-endocarditis group (n=242)	Endocarditis group (n=82)	*P* Value	Non-endocarditis group (n=242)
Age (years)	62.1±13.8	60.9±14.1	65.8±12.2	0.005	62.1±14.1
Female, n (%)	145(44.8%)	81(33.3%)	64(79.0%)	<0.001	44.2
Body surface area (m^2)	1.8±1.6	1.7±1.2	2.0±2.4	0.268	1.7±1.2
Risk factors, n (%)					
Hypertension	115(35.5%)	81(33.5%)	34(42.0%)	0.203	36.0
Diabetes mellitus	63(19.4%)	37(15.2%)	26(32.1%)	0.002	18.3
History of stroke	50(15.5%)	26(10.7%)	24(29.6%)	<0.001	15.1
Chronic kidney disease	54(16.7%)	37(15.2%)	17(21.0%)	0.302	18.0

Coronary artery disease	20(6.2%)	12(4.9%)	8(9.9%)	0.110	6.9
Dyslipidemia	54(16.7%)	44(18.1%)	10(12.3%)	0.228	42.5
Atrial fibrillation	100(30.9%)	83(34.3%)	17(20.7%)	0.031	31.1
LVEF	60.9±10.4	61.6± 9.8	58.7±11.9	0.055	61.1±9.7
CPB time (minutes)	197.5±91.6	189.5±87.4	221.6±99.6	0.006	177.8±81.7
ACC time (minutes)	133.3±68.0	126.6±62.3	153.3±80.1	0.007	124.0±62.5
Concomitant procedure, n (%)					
Mitral valve procedure	68(21.0%)	50(20.7%)	18(22.0%)	0.095	27.6
Tricuspid valve procedure	56(17.3%)	52(21.5%)	4(4.9%)	0.008	23.8
Aorta procedure[b]	38(11.7%)	30(12.4%)	8(9.8%)	0.728	8.2
Arrhythmia surgery	12(3.7%)	10(4.1%)	2(2.4%)	0.732	1.7
CABG	2(0.6%)	1(0.4%)	1(1.2%)	>0.999	0.0

LVEF = left ventricular ejection fraction; CPB = cardiopulmonary bypass; ACC = aortic cross clamp; CABG = coronary artery bypass grafting.

[a]Chronic kidney disease was defined as the definition of chronic kidney disease by The Kidney Disease: Improving Global Outcomes Work Group.

[b]aorta procedure was defined as ascending aorta replacement or reductionplasty

Table 2. Early clinical outcomes

		Before IPTW, n (%)			*IPT*
Variables	All	Non-endocarditis group (n=242)	Endocarditis group (n=82)	*P* Value	Non-endocarditis group (n=242)
Operative mortality	15(4.6%)	6 (2.5%)	9(11.0%)	0.004	3.0
For Non-structural valve dysfunction (n=84)		4 (4.8%)			

For Structural valve degeneration (n=151)	2 (1.3%)				
For thrombosis(n=7)	0 (0%)				
Complications,n (%)					
Low cardiac output syndrome	28(8.6%)	18(7.4%)	10(12.3%)	0.171	7.6
Bleeding	16(4.9%)	10(4.1%)	7(7.3%)	0.559	4.6
Acute kidney injury	48(14.8%)	26(10.7%)	22(26.8%)	0.001	11.6
New onset AF	44(13.6%)	36(14.9%)	8(9.8%)	0.326	14.9
Mediastinitis	2(0.7%)	1(0.5%)	1(1.4%)	0.438	0.3
Stroke	16(4.9%)	8(3.3%)	8(9.8%)	0.042	2.9
CAVB	9(2.8%)	7(2.9%)	2(2.4%)	0.823	3.9
PPM insertion	13(4.0%)	9(3.7%)	4(4.9%)	0.891	3.8
Respiratory	2(0.6%)	24(9.9%)	16(9.5%)	0.037	10.6
Infective endocarditis	2(0.6%)	2(0.8%)	0(0.0%)	0.992	1.6

IPTW= inverse probability of treatment weighting, AF= atrial fibrillation; CAVB= complete atrioventricular block; PPM= permanent pacemaker

Table 3. Logistic regression analysis for factors associated with operative mortality

Variables[a]	Factors associated with operative mortality			
	Univariate analysis		Multivariable analysis	
	HR [95% CI]	*P* Value	HR [95% CI]	*P* Value
Endocarditis group	**4.849[1.693-14.895]**	**0.004**	**3.990[1.343-12.580]**	**0.014**
CPB time	**1.006[1.001-1.011]**	**0.011**	**1.006[1.000-1.011]**	**0.037**
LVEF	**0.946[0.911-0.987]**	**0.007**	**0.956[0.918-0.998]**	**0.034**

CPB= cardiopulmonary bypass, LVEF= left ventricular ejection fraction

[a]All variables in Table 1 were analyzed and factors that entered into the multivariable analysis were shown.

Table 4 Cox Proportional Hazards Models for Factors Associated with Overall Survival and Competing Risk Analysis for Factors Associated with Cardiac Death

Factors associated with overall survival				
Variables[a]	Univariate analysis		Multivariable analysis	
	HR [95% CI]	*P* Value	HR [95% CI]	*P* Value
Age (years)	**1.069[1.039-1.099]**	**<0.001**	**1.065[1.035-1.095]**	**<0.001**
Endocarditis group	**2.654[1.539-4.577]**	**<0.001**	**2.107[1.198-3.709]**	**0.010**
LVEF	**0.967[0.946-0.989]**	**<0.001**	**0.961[0.940-0.984]**	**<0.001**
Factors associated with cardiac death				
Variables[a]	Univariate analysis		multivariable analysis	
	HR [95% CI]	*P* Value	HR [95% CI]	*P* Value
Age	**1.078[1.010-1.151]**	**0.024**	**1.087[1.012-1.167]**	**0.023**
Endocarditis group	**12.800[2.717-60.310]**	**0.001**	**10.260[2.137-49.268]**	**0.004**
LVEF	**0.927[0.890-0.967]**	**<0.001**	**0.918[0.874-0.964]**	**<0.001**

LVEF= left ventricular ejection fraction, AF = atrial fibrillation

[a]All variables in Table 1 were analyzed and factors that entered into the multivariable analysis were shown.

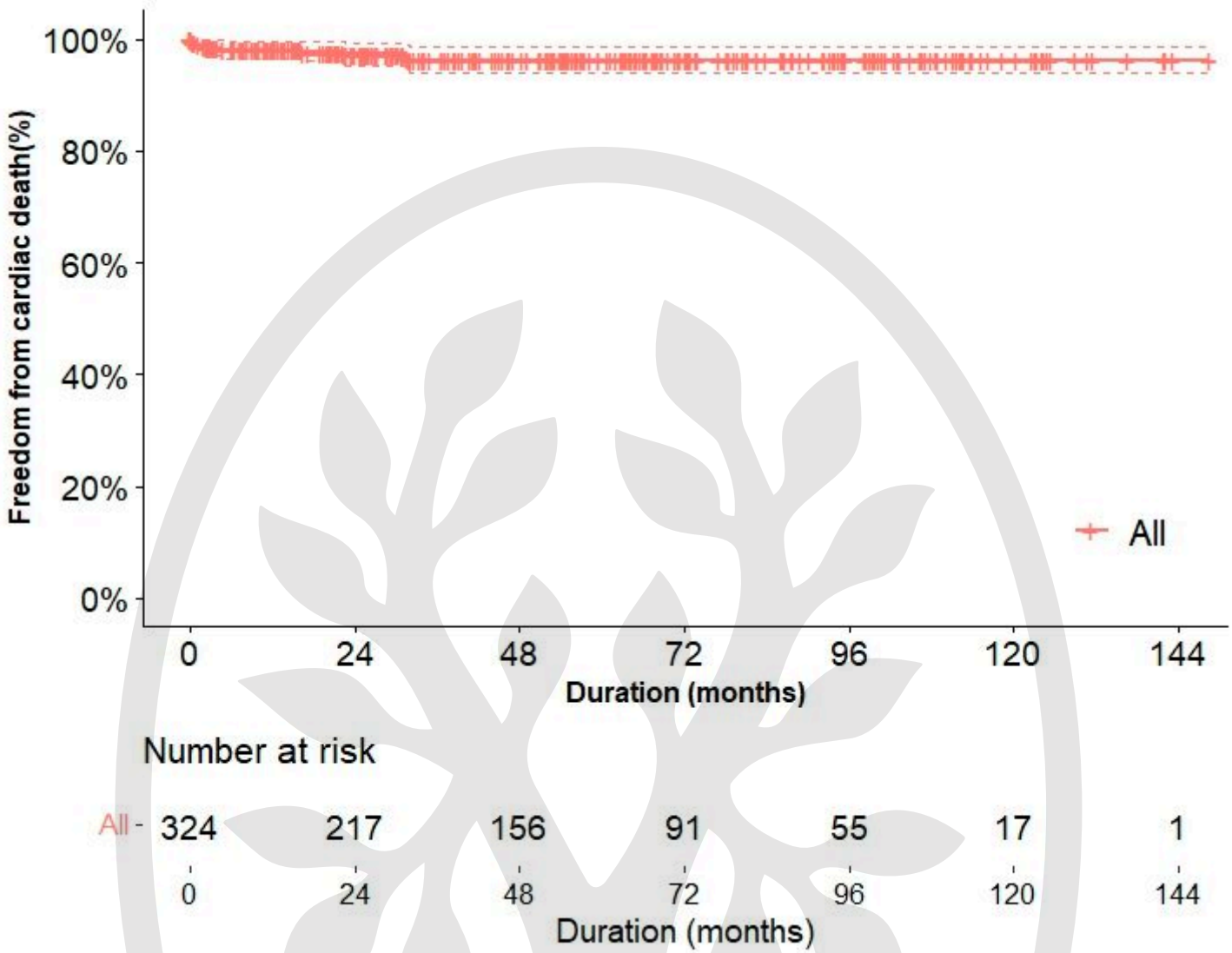
Table 5. Competing risk analysis for Factors Associated with Aortic Valve Related Event (AVRE)

Factors associated with AVRE				
Variables[a]	Univariate analysis		multivariable analysis	
	HR [95% CI]	*P* Value	HR [95% CI]	*P* Value
CKD	**2.050[1.220-3.450]**	**0.007**	**2.030[1.183-3.480]**	**0.010**
LVEF	**0.977[0.955-0.998]**	**0.035**	**0.978[0.956-1.000]**	**0.067**
Endocarditis group	**1.790[1.080-2.990]**	**0.024**	**1.456[0.782-2.710]**	**0.236**

Male gender	**1.690[1.030-2.750]**	**0.036**	**1.280[0.713-2.300]**	**0.408**
History of stroke	**1.670[0.934-2.970]**	**0.084**	**1.291[0.698-2.390]**	**0.415**

LVEF= left ventricular ejection fraction; CKD=chronic kidney disease

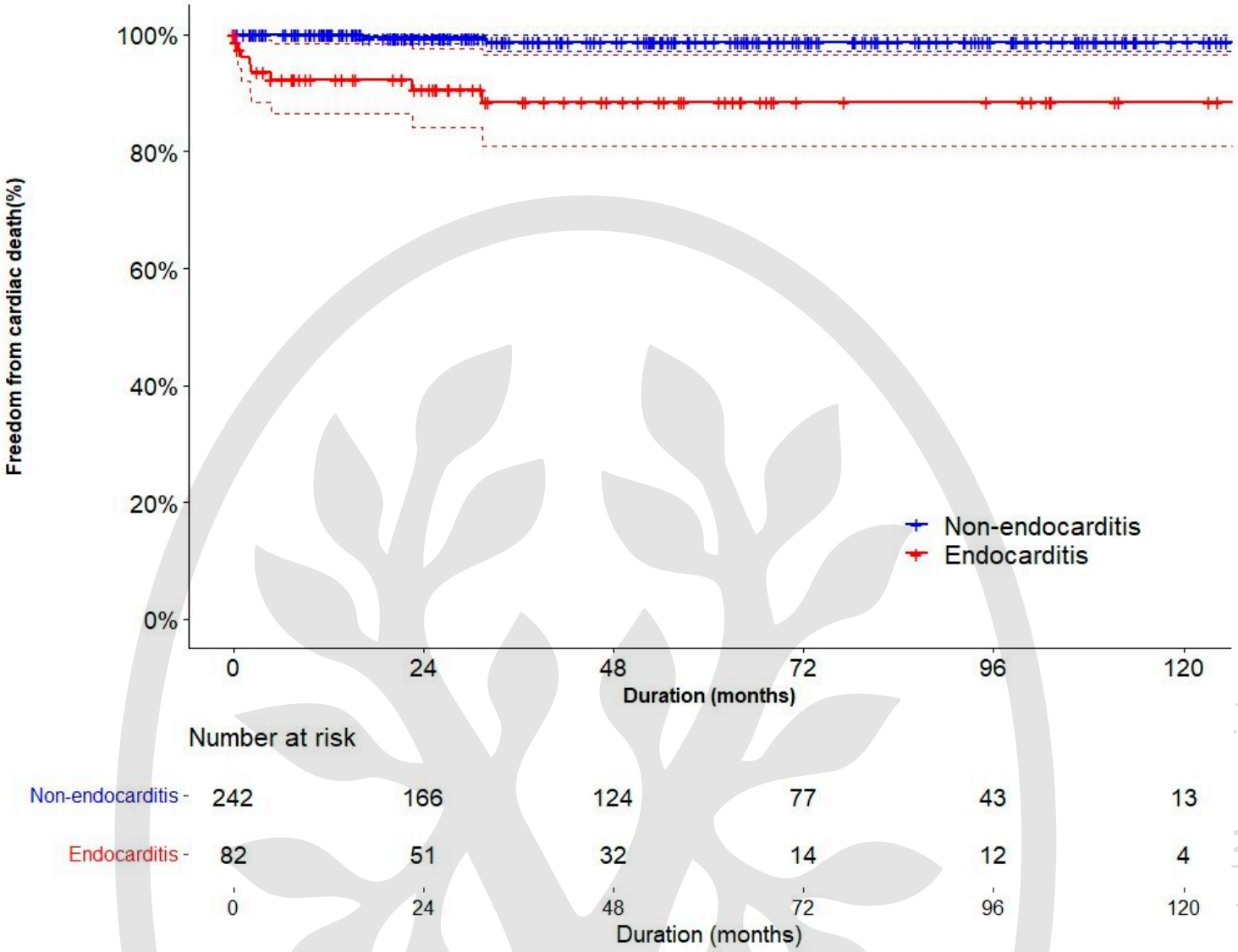
[a]All variables in Table 1 were analyzed and factors that entered into the multivariable analysis were shown.



Number at risk

	0	24	48	72	96	120	144
All	324	217	156	91	55	17	1

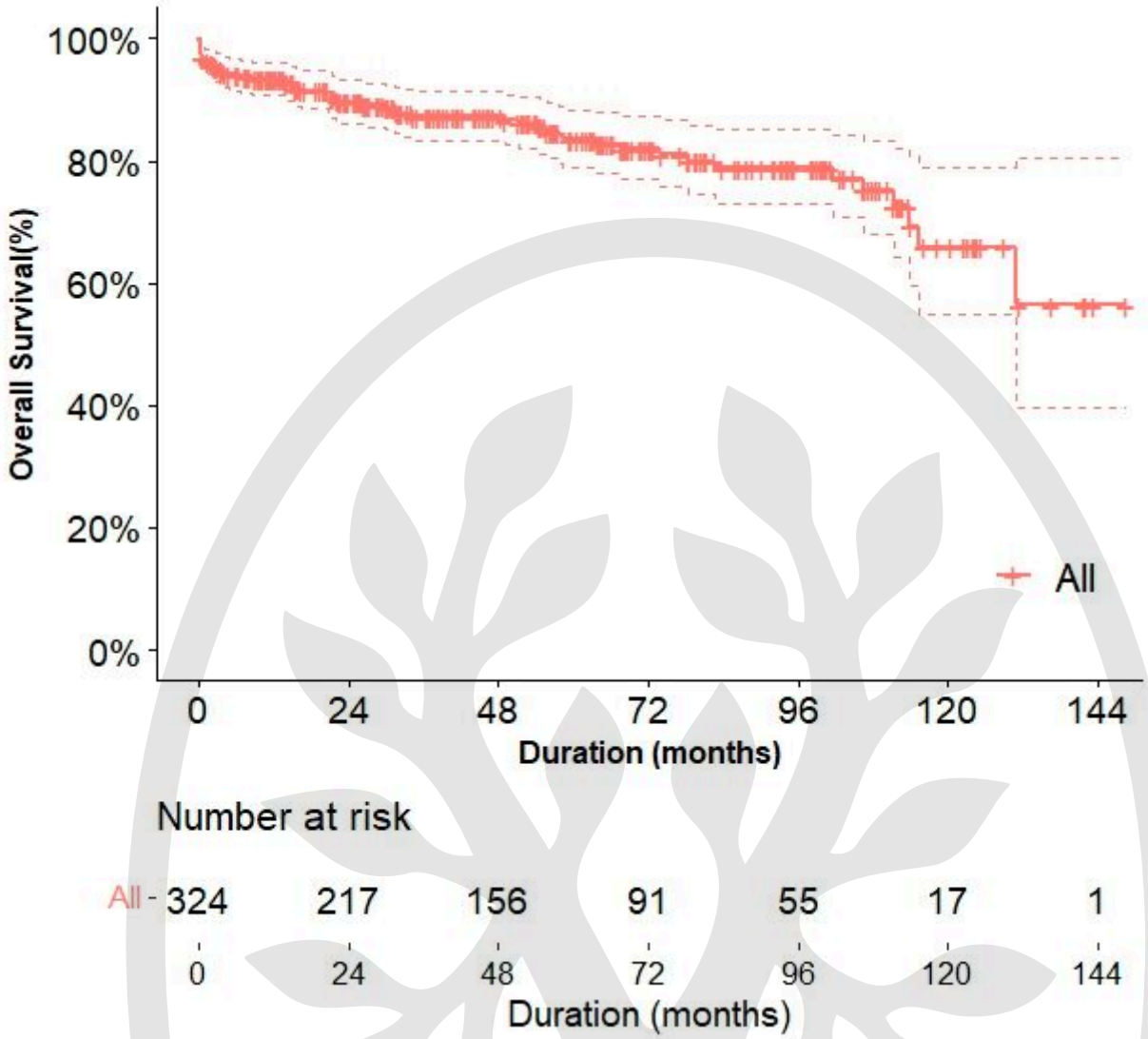
Duration (months)



Number at risk

	0	24	48	72	96	120
Non-endocarditis	242	166	124	77	43	13
Endocarditis	82	51	32	14	12	4

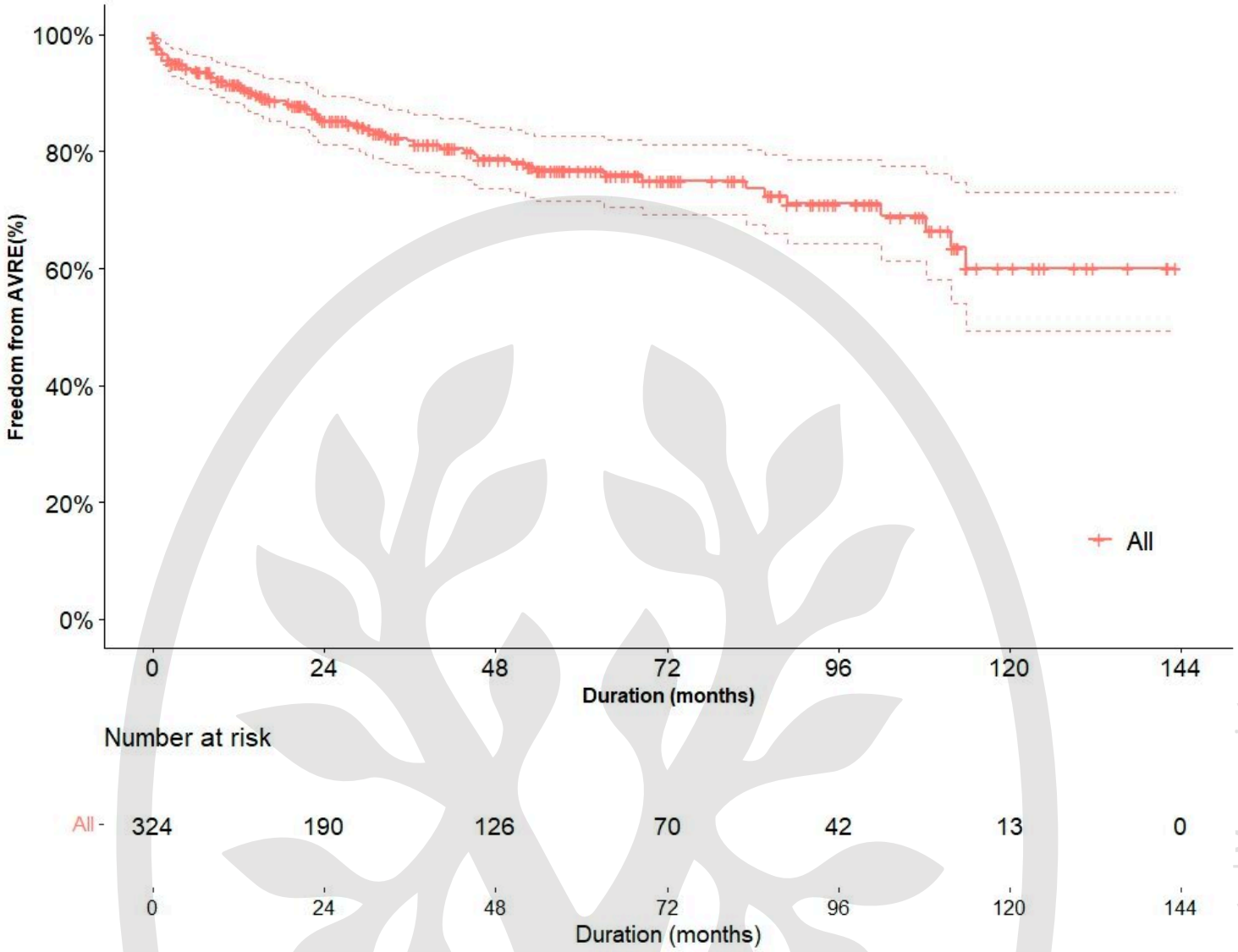
Duration (months)



Number at risk

All	324	217	156	91	55	17	1
	0	24	48	72	96	120	144

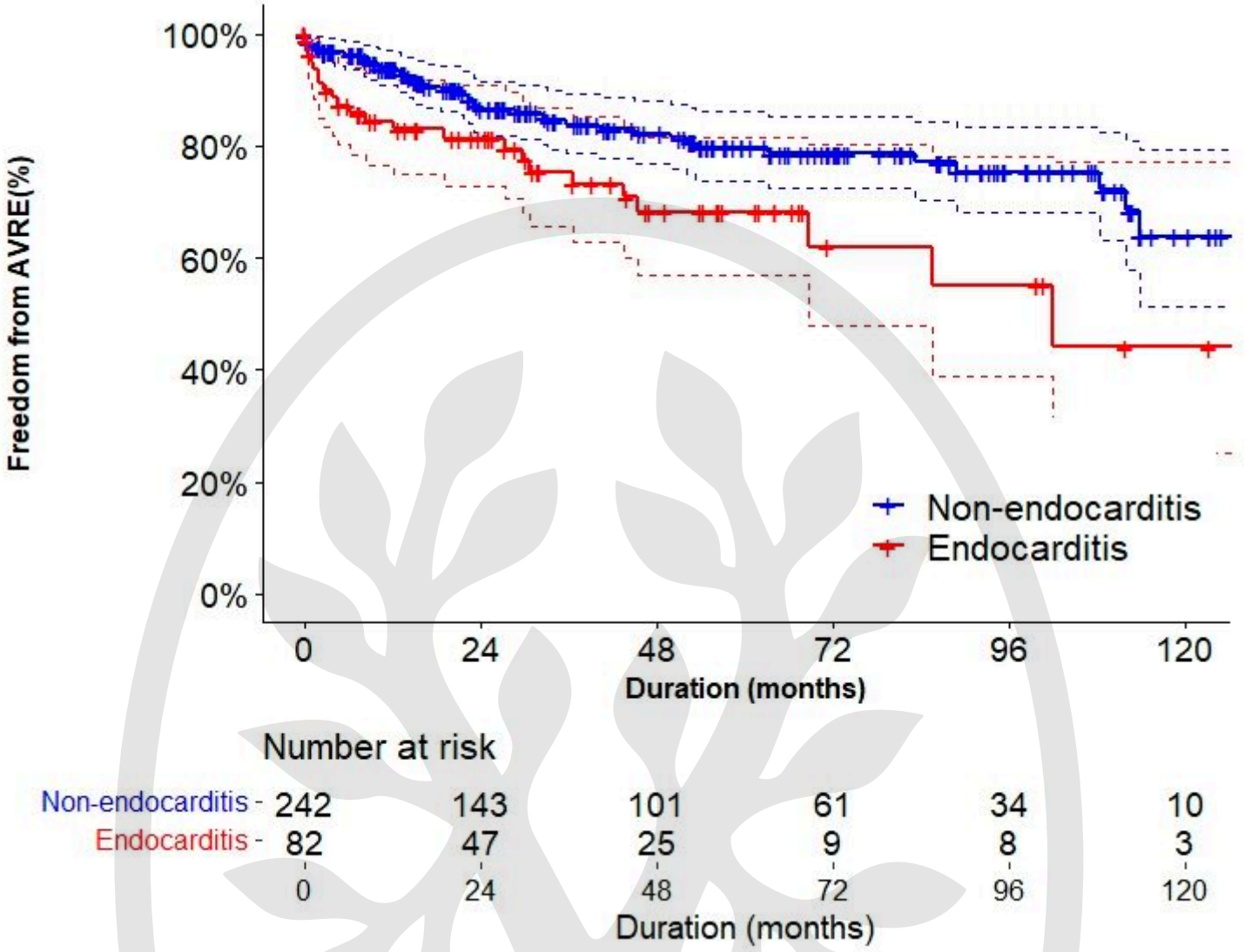
Duration (months)

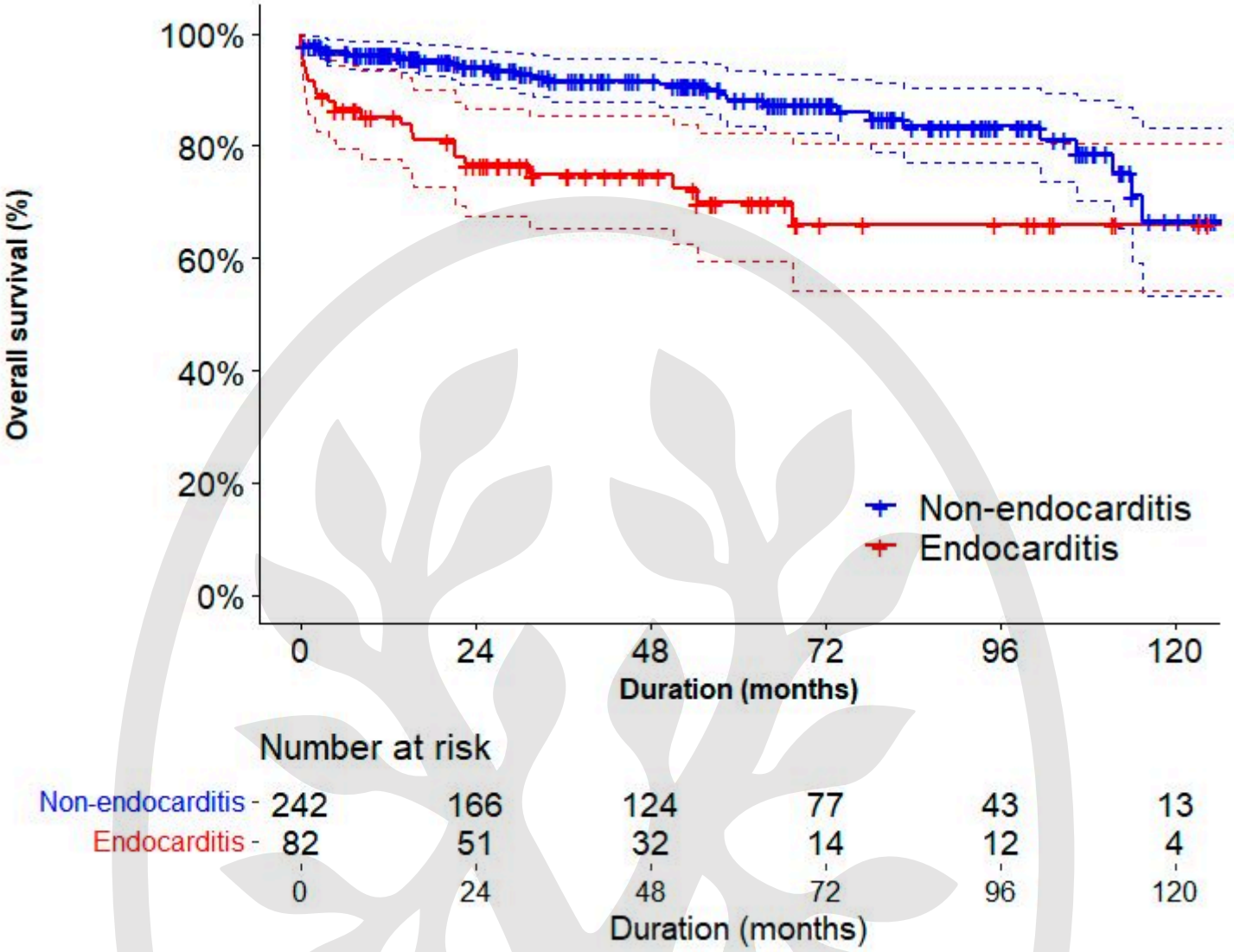


Number at risk

	0	24	48	72	96	120	144
All	324	190	126	70	42	13	0

Duration (months)





Number at risk

	0	24	48	72	96	120
Non-endocarditis	242	166	124	77	43	13
Endocarditis	82	51	32	14	12	4

Duration (months)