Surgical solutions for complex aortic root pathology

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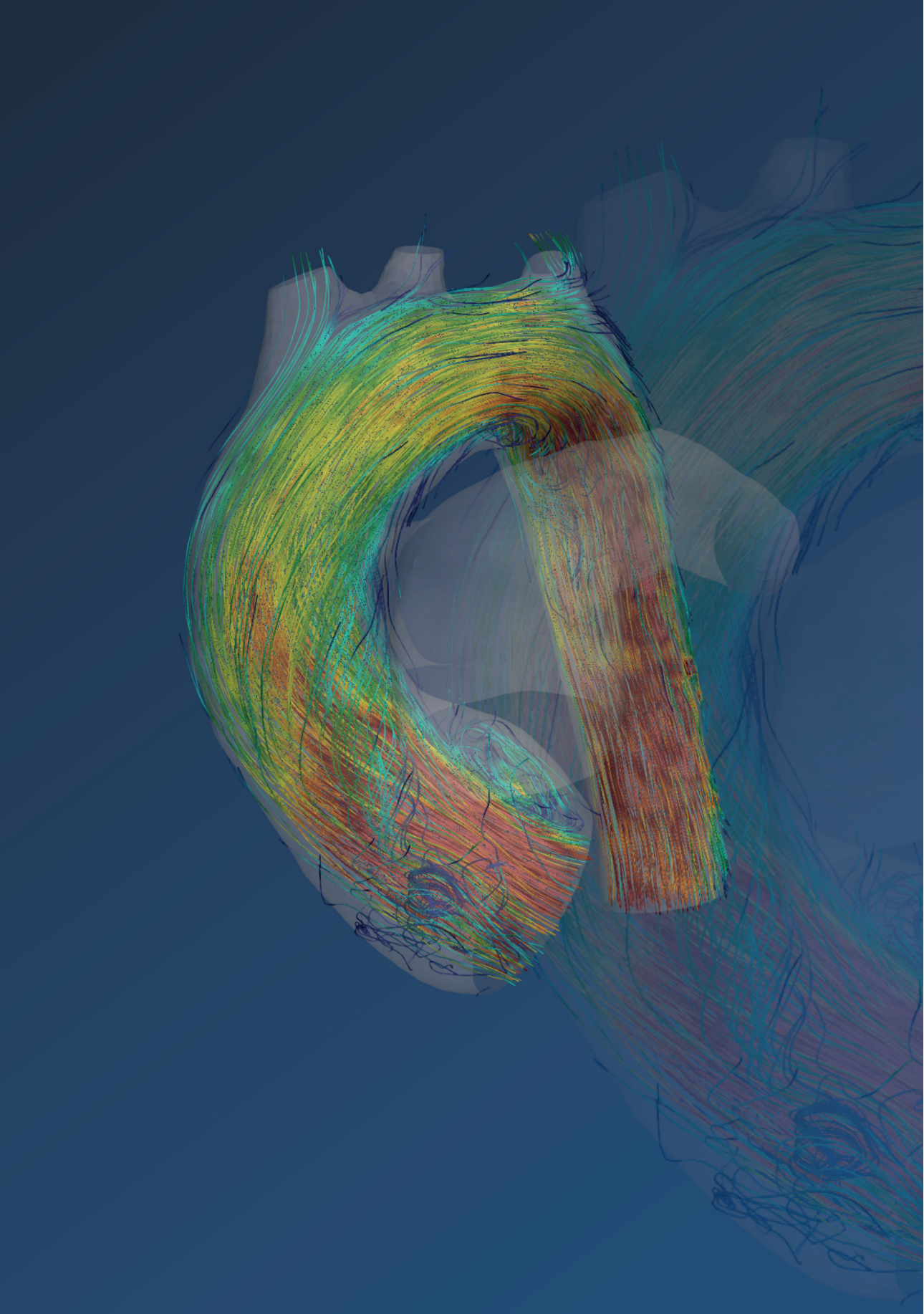
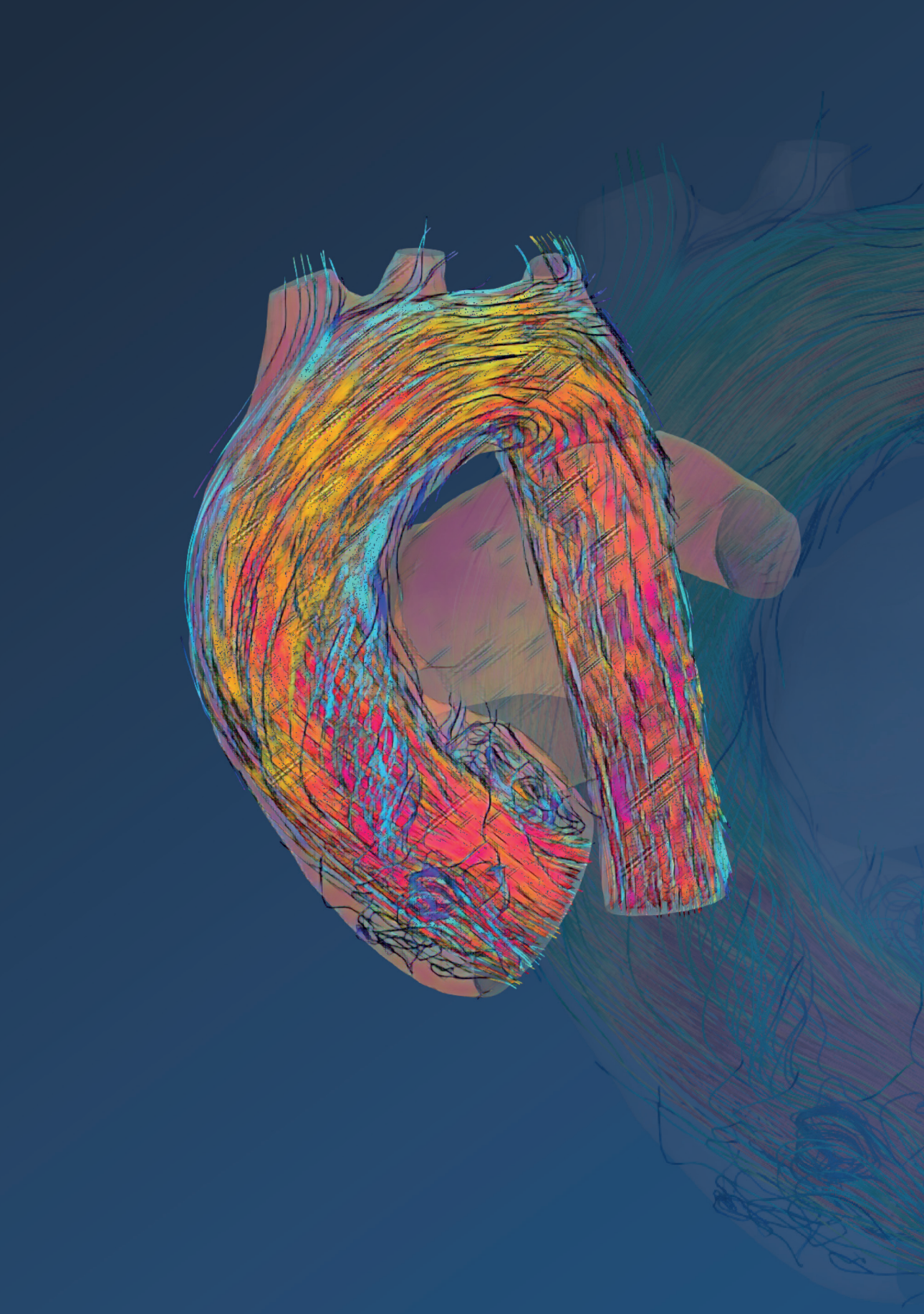


PART 2

THE STENTLESS BIOPROSTHESIS



TWENTY-YEAR EXPERIENCE WITH STENTLESS BIOLOGICAL AORTIC VALVE AND ROOT REPLACEMENT:

Informing patients of risks and benefits

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CHAPTER 5

ABSTRACT

OBJECTIVES

The aim of this study was to provide predictive data on the performance of the Freestyle stentless bioprosthesis that can be used to support and improve the shared decision-making process of prosthetic valve choice for aortic valve replacement.

METHODS

Between 1993 and 2014, 604 patients received the Freestyle stentless bioprosthesis (143 subcoronary, 58 root inclusion and 403 full-root replacement). Perioperative data were collected retrospectively, and follow-up data were collected prospectively from 2015. Follow-up was 96% complete (median 4.3 years), with 114 (19%) patients having a follow-up period exceeding 10 years. A competing risks regression model was developed to predict the probability of mortality, structural valve deterioration (SVD) and reoperation for other causes than SVD.

RESULTS

The median age of patients was 64 years, 91 (15%) patients had undergone previous aortic valve replacement and 351 (58%) underwent concomitant procedures. The 15-year probability of SVD, reoperation for other causes and death were 16.9%, 8.1% and 47.7%, respectively. Linearized occurrence rates for prosthesis endocarditis, thromboembolic events and bleeding were 0.5%, 0.9% and 0.1% per patient-year, respectively. The constructed predictive model, including age, renal function and implantation technique as significant covariates, had good to fair predictive performance up to 19 years.

CONCLUSIONS

The Freestyle stentless bioprosthesis is an efficient prosthesis for aortic valve replacement or root replacement, with low incidences of SVD and valve-related events at long-term follow-up. The predictive model designed in this study can be used to fully inform patients about their expected individual trajectory after implantation of this prosthesis. This improves the shared decision-making process between patients and clinicians.

INTRODUCTION

In recent years, prosthesis selection for valve replacement has become more complex because of the availability of an increasing number of cardiac valve prostheses. Both the American [1] and the European [2] guidelines on the management of patients with valvular heart disease recommend that prosthesis selection should be a shared decision-making process that takes into account the desires of the fully informed patient (Class 1, level of evidence C). Advantages and limitations of the different prostheses should therefore be discussed with the patient.

The choice of an appropriate valve prosthesis requires considering factors such as durability and short- and long-term risks of adverse events. The obvious advantage of biological prostheses is the absence of the need for anticoagulation, which might especially be beneficial in younger and more active patients. Despite the disadvantage of structural valve deterioration (SVD), the use of bioprostheses in younger patients has increased in recent years [3]. This might partly be due to advances in percutaneous valve-in-valve procedures, offering a less invasive reintervention option in case of SVD.

The Freestyle stentless porcine bioprosthesis (Medtronic Inc., Minneapolis, MN, USA) can be used for aortic valve replacement (AVR) and/or root replacement. Since its introduction in 1993, several studies have shown good haemodynamic function up to 18 years after implantation [4–6]. Its stentless design offers a relatively large effective orifice area, which might facilitate future valve-in-valve procedures.

The Freestyle prosthesis has been used since June 1993 in our institution for a variety of indications [7]. This is a single-centre study, with more than 20 years of experience with the Freestyle bioprosthesis. The objective of this study was to provide predictive information to guide patients, cardiologists and surgeons in their shared process of choosing a prosthesis.

METHODS

This is a single-centre observational study. Details of patients who received the Freestyle stentless bioprosthesis in the aortic position between June 1993 and December 2014 at the Leiden University Medical Center, Netherlands, were

identified from the department's database and all patients were included in this study. Preoperative, operative and discharge data were retrospectively obtained from medical records. Surviving patients were prospectively followed up from January 2015. The study end-points were the development of SVD, the occurrence of valve-related events and mortality. SVD and valve-related events were defined according to the 2008 guidelines for reporting mortality and morbidity after cardiac valve interventions [8]. The Ethics Committee of the institution approved the study design and granted permission to conduct the study.

Indications, prosthesis choice, surgical technique and anticoagulation management

Indications for aortic valve and/or root replacement have changed over time, but procedures were always performed according to the recommendations or guidelines that were pertinent at that time. Prosthesis choice was a result of comprehensively weighing several factors, with the wishes of the well-informed patient as a cornerstone. Patient information always included insight into the risks of anticoagulation and thrombosis in mechanical prostheses, and the possible need for reintervention in bioprostheses, with their associated risks. Generally, a stentless valve was preferred over a stented bioprosthesis in younger patients because of the larger effective orifice area and presumably longer durability.

The different techniques used for implantation of the Freestyle prosthesis have been described previously [9]. Until 2005, most prostheses were implanted using subcoronary (SC) or root inclusion (RI) techniques based on the surgeon's preference. Thereafter, the full root replacement (FR) technique was used exclusively to fully maintain prosthesis geometry with the intention of maintaining better durability.

Anticoagulation management after the Freestyle implantation also changed. Initially, patients typically received no anticoagulants. Since the year 2000, patients without indication for vitamin K antagonists receive low-dose aspirin for 3 months after the implantation.

Follow-up

For deceased patients, information on the cause of death, SVD and valve-related events was obtained from hospital and/or general practitioners' databases.

Surviving patients were sent questionnaires regarding their health status and were invited to visit the outpatient clinic to undergo transthoracic echocardiography. When patients declined this invitation, clinical and echocardiographic follow-up data were obtained from the patients' cardiologists after signed informed consent. Patients were mostly followed up annually or biannually after the implantation. Patients who received a second Freestyle prosthesis were censored for SVD and valve-related events. Vital status of the patients were checked on 25 May 2016 and follow-up ended the same day.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (normally distributed) or as median and interquartile range (IQR) (non-normally distributed). Categorical variables were reported as numbers and percentages. Group differences were tested using a 1-way analysis of variance (ANOVA) (normally distributed), the Kruskal–Wallis test (non-normally distributed) and the χ^2 test (categorical data). Early mortality was defined as death within 30 days after surgery or during the same hospital admission. Univariable risk factor analysis (data complete for all 604 patients) for early mortality was performed using the Student's *t*-test or the χ^2 test. Factors with a *P*-value of <0.10 or clinically relevant variables were tested in a multivariable logistic regression model using the backwards stepwise conditional entry method (entry and removal probabilities of 0.05 and 0.10, respectively). Overall survival was estimated using the Kaplan–Meier method. Difference in overall survival between groups was tested using the log-rank test. To avoid informative censoring in the analysis of freedom from SVD, a competing risks analysis was performed considering death and explant for other causes (e.g. endocarditis) as competing risks of SVD occurrence. Excluding the early mortality cases to provide more reliable information on SVD occurrence during the long-term follow-up, the cumulative incidences of mortality, SVD occurrence and prosthesis explant for other causes than SVD were estimated for the remaining 556 patients using the mstate package version 0.2.8 [10] in R (version 3.1.2, R foundation for statistical computing, Vienna, Austria). Cumulative incidences were reported as estimate (95% confidence interval). Deceased patients with signs of SVD in their medical or echocardiographic reports were classified as having SVD. A predictive model for SVD incidence was constructed using a competing risks regression model (cmprsk package version 2.2-7 [11]),

using known risk factors for SVD and death (age, renal function and implantation technique [4, 12]) as covariates. Internal validation of the model was done using 1000 bootstrap samples ['cindex' function in the 'pec' package (version 2.4.9)]. Except for the competing risks analyses, all analyses were performed using IBM SPSS statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). A *P*-value of <0.05 (2-sided) was considered statistically significant.

RESULTS

A total of 604 consecutive patients who received the Freestyle prosthesis were identified from the department database. At the start of the study (January 2015), 385 (64%) patients were alive. Implantation technique was SC in 143 patients, RI in 58 patients and FR in 403 patients. Preoperative patient characteristics for the total study population and for the subgroups based on the implantation technique are listed in Table 1. Patients were younger in the FR group; as this implantation technique has been exclusively used since 2005, this coincides with the global trend of implanting bioprostheses in younger patients in the past decade. Operative details are listed in Table 2.

Table 1: Patient characteristics

Variables	SC	RI	FR	Total
Number of patients	143	58	403	604
Male gender, *n* (%)	83 (58.0)	40 (69.0)	254 (63.0)	377 (62.4)
Age at operation (years), median (IQR)*	69.9 (56.4–74.6)	68.0 (56.4–74.6)	61.8 (51.0–69.9)	64.3 (52.2–72.9)
Preoperative NYHA functional class, *n* (%)*				
I	17 (11.9)	2 (3.4)	172 (42.7)	191 (31.6)
II	57 (39.9)	22 (37.9)	122 (30.3)	201 (33.3)
III	56 (39.2)	32 (55.2)	98 (24.3)	186 (30.8)
IV	13 (9.1)	2 (3.4)	11 (2.7)	26 (4.3)
Atrial fibrillation, *n* (%)	11 (7.7)	5 (8.6)	33 (8.2)	49 (8.1)
Previous cardiac surgery, *n* (%)*	18 (12.6)	5 (8.6)	108 (26.8)	131 (21.7)
Coronary artery bypass grafting	2 (1.4)	1 (1.7)	15 (3.7)	18 (13.7)
Aortic valve repair	3 (2.1)	1 (1.7)	4 (0.9)	8 (6.1)
Aortic valve replacement*	9 (6.3)	3 (5.2)	79 (19.6)	91 (69.5)

Variables	SC	RI	FR	Total
History of cerebrovascular accident, *n* (%)	11 (7.7)	6 (10.3)	48 (11.9)	65 (10.8)
Diabetes, *n* (%)*	20 (13.9)	0	43 (10.7)	63 (10.4)
Hypertension, *n* (%)*	75 (52.4)	22 (37.9)	224 (55.6)	321 (53.1)
History of malignancy, *n* (%)	13 (9.1)	7 (12.1)	29 (7.2)	49 (8.1)
Chronic obstructive pulmonary disease, *n* (%)	17 (11.9)	4 (6.9)	33 (8.1)	54 (8.9)
Renal function, *n* (%)*				
eGFR >85 ml/kg/min	35 (24.5)	17 (29.3)	227 (56.3)	279 (46.2)
eGFR 50–85 ml/kg/min	81 (56.6)	32 (55.5)	139 (34.5)	252 (41.7)
eGFR <50 ml/kg/min	26 (18.2)	9 (15.5)	33 (8.2)	68 (11.3)
Dialysis	1 (0.7)	0	4 (1.0)	5 (0.8)
Coronary artery disease, *n* (%)*	39 (27.3)	16 (27.6)	69 (17.1)	124 (20.5)
LVEF function (*n* = 546), *n* (%)				
>50%	91 (84.3)	29 (74.4)	315 (78.9)	435 (79.7)
31–50%	11 (10.2)	8 (20.5)	68 (17.0)	87 (15.9)
21–30%	6 (5.6)	2 (5.1)	13 (3.3)	21 (3.8)
<20%	0	0	3 (0.8)	3 (0.5)
Aortic valve lesion, *n* (%)*				
Normal	1 (0.7)	0	29 (7.2)	30 (5.0)
Stenosis	67 (46.9)	28 (48.3)	139 (34.5)	234 (38.7)
Insufficiency	30 (21.0)	11 (19.0)	181 (44.9)	222 (36.8)
Mixed	45 (31.5)	19 (32.8)	54 (13.4)	118 (19.5)
Aetiology, *n* (%)*				
Normal	0	1 (1.7)	3 (0.7)	4 (0.7)
Senile degeneration	82 (57.3)	31 (53.4)	137 (34.0)	250 (41.4)
Rheumatic	8 (5.6)	1 (1.7)	11 (2.7)	20 (3.3)
Congenital	24 (16.8)	17 (29.3)	57 (14.1)	98 (16.2)
Healed endocarditis	5 (3.5)	1 (1.7)	7 (1.7)	13 (2.2)
Active endocarditis	11 (7.7)	0	50 (12.4)	61 (10.1)
Failed aortic valve repair	3 (2.1)	0	1 (0.2)	4 (0.7)
Failed aortic valve prosthesis	7 (4.9)	3 (5.2)	47 (11.7)	57 (9.4)
Aortic dissection	0	0	32 (7.9)	32 (5.3)
Aortic dilatation	2 (1.4)	4 (6.9)	57 (14.1)	63 (10.4)

Variables	SC	RI	FR	Total
Other	1 (0.7)	0	1 (0.2)	2 (0.3)
Bicuspid [native valves (n = 514)], n (%)*	43 (32.1)	33 (60.0)	152 (46.8)	228 (44.2)

*P < 0.05 between groups.
eGFR: estimated glomerular filtration rate; FR: full root replacement; IQT: interquartile range; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RI: root inclusion; SC: subcoronary.

Table 2: Operative details

Variables	SC	RI	FR	Total
Number of patients, n (%)	143 (23.7)	58 (9.6)	403 (66.7)	604
CPB time (min), median (IQR)	150 (120–180)		209 (173–273)	205 (169–266)
Cross-clamping time (min), median (IQR)	95 (83–117)	104 (94–120)	161 (128–212)	137 (106–180)
Circulatory arrest time (min), median (IQR)			43 (29–64)	43 (29–64)
ACP time (min), median (IQR)			40 (24–67)	40 (24–67)
Logistic EuroSCORE I, median (IQR)	4.54 (2.89–7.26)	3.29 (2.22–4.48)	10.91 (5.62–19.88)	7.3 (4.7–16.3)
For elective patients, median (IQR)	4.05 (2.75–6.87)	3.43 (2.19–4.65)	7.37 (4.65–15.60)	6.35 (4.09–11.73)
EuroScore II, median (IQR)	1.63 (1.10–3.44)	1.31 (0.84–2.22)	3.94 (2.19–8.40)	3.1 (1.6–6.7)
For elective patients, median (IQR)	1.51 (1.04–2.85)	1.28 (0.82–2.08)	3.03 (1.83–5.57)	2.31 (1.36–4.47)
Urgent settting, n (%)	7 (4.9)	1 (1.7)	82 (20.3)	90 (14.9)
Emergent setting, n (%)	8 (5.6)	1 (1.7)	33 (8.2)	42 (7.0)
Prosthesis size, n (%)				
21mm	20 (14.0)	6 (10.3)	37 (9.2)	63 (10.4)
23mm	51 (35.7)	21 (36.2)	62 (15.4)	134 (22.2)

Variables	SC	RI	FR	Total
25mm	35 (24.5)	17 (29.3)	90 (22.3)	142 (23.5)
27mm	36 (25.2)	14 (24.1)	108 (26.8)	158 (26.2)
29mm	1 (0.7)		106 (26.3)	107 (17.7)
Concomitant surgery, *n* (%)	48 (33.6)	13 (22.4)	290 (72.0)	351 (58.1)
Coronary artery bypass grafting, *n* (%)	31 (21.7)	5 (8.6)	62 (15.4)	98 (16.2)
Mitral valve surgery, *n* (%)	8 (5.6)	2 (3.4)	66 (16.4)	76 (12.6)
Tricuspid valve surgery, *n* (%)	2 (1.4)	1 (1.7)	24 (6.0)	27 (4.5)
Ascending aorta/hemiarch replacement, *n* (%)	0	0	129 (32.0)	129 (21.4)

ACP: antegrade cerebral perfusion; CPB: cardiopulmonary bypass; FR: full root replacement; IQR: interquartile range; RI: root inclusion; SC: subcoronary.

Early postoperative course

In total, there were 48 (7.9%) early deaths. The early mortality rate decreased over time from 10.6% before 2000 to 5.1% in the last 5 years (Table 3). In elective, isolated AVR or root replacement patients, the early mortality rate decreased from 7.2% to 0% (Table 3). Multivariable risk factor analysis showed that age, surgical period, previous cardiac surgery, previous cerebrovascular accident, chronic obstructive pulmonary disease, concomitant coronary artery bypass grafting, concomitant mitral valve surgery and urgent/emergent surgery were independent risk factors for early mortality (Supplementary Material, File A). Postoperative complications for the whole group and the subgroups are listed in Table 3. Echocardiography taken at discharge showed mild patient–prosthesis mismatch (indexed effective orifice area between 0.65 cm^2/m^2 and 0.85 cm^2/m^2) in 37 (6%) patients.

Table 3: Postoperative complications

Variables	SC	RI	FR	Total
Early complications, *n* (%)				
(Temporary) dialysis	9 (6.3)	2 (3.4)	18 (4.5)	29 (4.8)
Low cardiac output	9 (6.3)	4 (6.9)	13 (3.2)	26 (4.3)
Surgical re-exploration for bleeding/tamponade	19 (13.3)	12 (20.7)	33 (8.2)	64 (10.6)

Variables	SC	RI	FR	Total
Myocardial infarction	4 (2.8)	0	8 (2.0)	12 (2.0)
Multiorgan failure	0	1 (1.7)	8 (2.0)	9 (1.5)
CVA	3 (2.1)	0	10 (2.5)	13 (2.2)
Prolonged intubation (>48 h)	6 (4.2)	4 (6.9)	30 (7.4)	40 (6.6)
Intra-aortic balloon pump	2 (1.4)	0	12 (3.0)	14 (2.3)
Extracorporeal membrane oxygenation	0	0	4 (1.0)	4 (0.7)
Permanent pacemaker placement	7 (4.9)	2 (3.4)	33 (8.2)	42 (7.0)
De novo arrhythmia at discharge	15 (10.5)	5 (8.6)	54 (13.4)	74 (12.3)
Late complications				
Mode of structural valve deterioration				
Leaflet tear	19	7	10	36
Leaflet perforation	2	0	2	4
Stenosis	5	2	0	7
Dilatation	0	1	0	1
Valve-related events				
Valve thrombosis	0	0	0	0
Embolism	0	0	0	0
Stroke	6	3	9	18
Ischaemic	4	3	6	13
Haemorrhagic	2	0	3	5
TIA	8	0	6	14
Bleeding event	1	0	2	3
Endocarditis	4	3	12	19
Mortality	**Total group *(n = 604)***	**Elective patients *(n = 472)***	**Elective, isolated AVR/ARR patients *(n = 316*)**	
Early mortality, *n* (%)				
Total	48 (7.9)	29 (6.1)	13 (4.1)	
Before 2000	21/199 (10.6)	18/186 (9.7)	10/138 (7.2)	
2000–2010	13/128 (10.2)	7/102 (6.9)	3/64 (4.7)	
2010–2014	14/277 (5.1)	4/184 (2.2)	0/114 (0)	
Late mortality				
All cause	221			
Late valve related	52			
Sudden, unexplained	14			
Unknown	27			
Late non-valve related	121			

AVR: aortic valve replacement; ARR: aortic root replacement; CVA: cerebrovascular accident; FR: full root replacement; RI: root inclusion; SC: subcoronary; TIA: transient ischaemic attack.

Follow-up

A flow diagram on follow-up data of the study population is shown in Supplementary Material, File B. Clinical follow-up was 96% complete, with recent echocardiography (<1 year prior to the last follow-up) in 91% and 94% of all and surviving patients, respectively. Total follow-up comprised 3293 patient-years. The median follow-up period was 4.3 years (IQR 2.1–8.1 years; maximum 20.5 years), with 114 (19%) patients having a follow-up period exceeding 10 years and 46 (8%) exceeding 15 years.

Structural valve deterioration

SVD developed in 48 (7.9%) patients, of whom 43 underwent reintervention. Four patients did not undergo reintervention because of severe comorbidity (3 of them died during follow-up). One patient was under echocardiographic surveillance to determine the timing of reintervention. The mode of deterioration was leaflet tear in 36 patients, leaflet perforation in 4 patients, calcific stenosis in 7 patients and insufficiency due to dilatation of the ascending aorta in 1 patient. The prosthesis became stenotic due to calcification only after SC or RI implantation. After FR implantation, torn leaflets or valve insufficiency without leaflet tear were the mechanisms of SVD. In most of these cases, the valve leaflets had no-to-mild calcifications, but the aortic root wall was calcified instead. Competing risk analysis showed a cumulative incidence of SVD occurrence in hospital survivors of 7.1% (95% confidence interval 4.5–11.0%) and 16.9% (12.7–22.4%) at 10 and 15 years, respectively.

Valve-related events

Nineteen (3.1%) patients developed prosthetic valve endocarditis; 5 of whom underwent surgery for endocarditis during initial AVR. Late postoperative stroke occurred in 18 (3.0%) patients: 13 ischaemic and 5 haemorrhagic. Haemorrhagic stroke was associated with anticoagulant therapy for arrhythmias in 3 patients. Seventeen patients were diagnosed with a transient ischaemic attack. There were no non-cerebral embolic events. Upper gastrointestinal bleeding was seen in 3 patients (2 on oral anticoagulation). The linearized occurrence rates for prosthesis endocarditis, thromboembolic events (non-cerebral embolism, stroke and transient ischaemic attack combined) and bleeding events were 0.5%, 0.9% and 0.1% per patient-year, respectively. Valve-related events are listed in Table 3.

Reinterventions

In total, 75 (12.4%) patients underwent aortic valve or root reintervention, with a median time to reintervention of 7.9 years (IQR 3.2–11.5 years). Primary implantation technique was SC in 34 patients, RI in 15 patients and FR replacement in 26 patients. Thirty-two (5.3%) patients were reoperated for other causes than SVD at a median time to reintervention of 2.7 years (IQR 0.8–5.5 years). Indications for non-SVD reoperation were prosthesis endocarditis in 15 patients, suture line dehiscence in 9 patients, pseudoaneurysm in 4 (2 at the proximal suture line and 2 at a coronary button) patients, (para)valvular leakage in 3 patients and Type A aortic dissection in 1 patient. One patient underwent mitral valve repair 10 years after the Freestyle implantation; the Freestyle prosthesis with normal function was replaced pre-emptively. Competing risks regression analysis showed a cumulative incidence of prosthesis explant for other causes than SVD of 6.5% (3.9–9.1%) at 10 years and 8.1% (4.9–11.0%) at 15 years.

Survival

Overall survival rates for the total patient cohort at 10, 15 and 20 years were 58.8% (53.2–63.9%), 42.4% (36.3–48.3%) and 29.1% (21.4–37.3%), respectively. Causes of late mortality were non-valve-related in 121 (70%) patients, valve-related in 11 (6%) patients and sudden unexplained in 14 (8%) patients. In 27 (16%) patients, the cause of death could not be retrieved.

Prediction model for shared decision-making

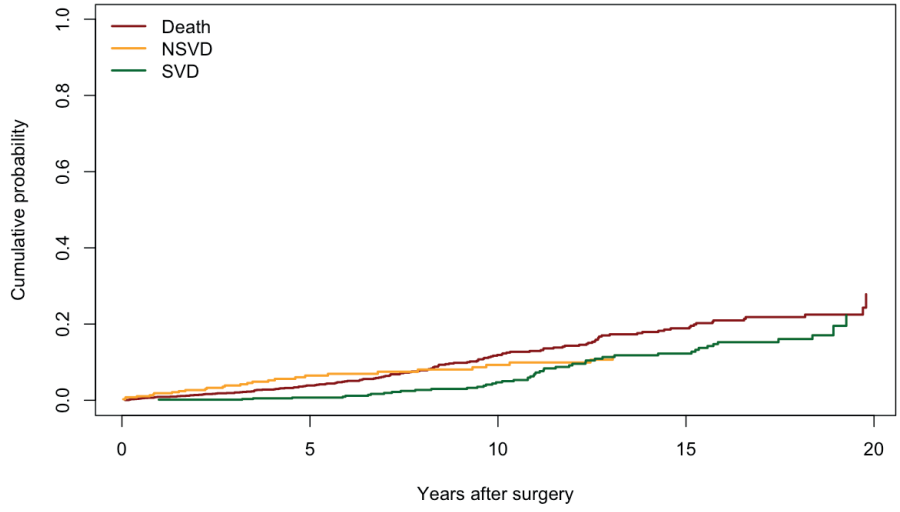
A prediction model using a competing risk regression formula was constructed to predict mortality, the chance of developing SVD and the chance of prosthesis reoperation for other causes than SVD based on age, renal function and implantation technique. Internal validation of the model showed good to fair predictive performance for SVD, with a concordance index of 80.5 at 15 years. Regression coefficients and the estimated concordance indices of the internal validation analysis are listed in Table 4. An example of predicted outcomes for a 55-year-old patient with good renal function after root replacement is shown in Fig. 1. An extensive overview of the outcomes from the predictive model is shown in Supplementary Material, Files C and D.

Table 4: Competing risks regression model with internal validation

	Death			**Reoperation for other causes than SVD**			**SVD**		
	B	**SE**	***P*-value**	*B*	**SE**	***P*-value**	*B*	**SE**	***P*-value**
Implantation technique									
Non-root									
Root	0.060	0.189	0.750	−0.495	0.433	0.250	−0.912	0.313	0.004
Age group (years)									
<40									
40–50	0.871	0.630	0.170	0.627	0.762	0.410	−0.864	0.415	0.037
50–60	0.548	0.614	0.370	0.7449	0.677	0.270	−1.306	0.411	0.002
60–70	1.522	0.543	0.005	0.540	0.654	0.410	−2.648	0.482	<0.001
>70	2.172	0.568	<0.001	−0.431	0.761	0.570	−2.481	0.507	<0.001
eGFR (ml/kg/min)									
>85									
50–85	0.121	0.275	0.660	−0.371	0.446	0.41	−0.074	0.342	0.830
<50	0.778	0.313	0.013	0.046	0.713	0.95	−0.970	0.743	0.190
Estimated concordance index									
5-year	63.6			47.2					
10-year	69.5			50.5			81.0		
15-year	70.6			51.8			80.5		
19-year	71.5			51.8			76.4		

eGFR: estimated glomerular filtration rate; SE: standard error; SVD: structural valve deterioration.

Figure 1:



Results from the competing risks regression model for a 55-year-old patient with normal renal function after root replacement. NSVD: non-structural valve deterioration; SVD: structural valve deterioration.

DISCUSSION

This article describes over 20 years of experience with the Freestyle stentless bioprosthesis, which has been used for various pathologies with different implantation techniques at our institution. This report provides predictive data that can aid patients, cardiologists and surgeons in their shared decision-making on using this prosthesis for AVR, giving a comprehensive summary of both the risks in the short (perioperative) term and on the occurrence of SVD and other valve-related events during follow-up. The Freestyle prosthesis can be used with an acceptable early mortality rate, given the often complex patient group. The early mortality rate decreased over time from ~10% in the beginning to ~5% in recent years. Since 2010, elective procedures have been performed with an early mortality rate of ~2% for patients with concomitant surgery and 0% for isolated surgery. During follow-up, fewer valve-related events were observed. Furthermore, the relatively large effective orifice area of the Freestyle prosthesis, as reflected by the low incidence of moderate patient–prosthesis mismatch (i.e. a risk factor for

all-cause and cardiac mortality [12, 13]), enables future valve-in-valve procedures. The elective patient with an indication for aortic root replacement with or without the ascending aorta replacement can therefore be treated with this prosthesis with a minimal risk.

As with all bioprostheses, the Freestyle prosthesis will degenerate in time. The cumulative incidence of SVD at 15 years was 17% in this series. Leaflet tear was the predominant mode (75%) of SVD. As a result of the sudden failure of the prosthesis, patients presented mostly with subacute symptoms of moderate decompensation.

FR replacement was associated with higher freedom from SVD compared with other implantation techniques in our competing risks model. Since late 2005, the FR implantation technique has been used exclusively at our institution. Increased durability of the Freestyle prosthesis after FR replacement was previously reported by Mohammadi *et al.* [4]. In a randomized trial, El-Hamamsy *et al.* [14] have reported higher freedom from SVD and reoperation for SVD of the Freestyle prosthesis compared with homografts.

SVD developed earlier in younger patients. In patients <40 years of age, 57% had developed SVD 15 years after surgery. For these patients, other alternatives offer a better solution. In a previous series published by our group on young patients (median age 12 years, all under 40 years of age) undergoing the Ross procedure [15], an analysis with death as a competing risk for autograft reoperation showed a cumulative incidence of autograft reoperation at 20 years of 31%. For patients <40 years of age, the pulmonary autograft appears to be the best bioprosthesis available for AVR in terms of durability [16].

There is an increasing recognition that patients' wishes and expectations regarding valve prostheses have to be taken into account in the process known as shared decision-making. Korteland *et al.* [17], in their study among patients aged <60 years and who received either a mechanical or a biological aortic valve prosthesis, reported that the majority of the patients consider it important that they are involved in deciding on the type of prosthesis. Furthermore, they found that patients who were more actively involved in choosing the prosthesis type showed better mental health after surgery, as measured with the 36-Item Short Form Health Survey.

Recent guidelines underscore that the choice of valve intervention and type of valve prosthesis should be a shared decision [1, 2]. Yet for patients to be able to make a good decision, they need to be informed with full disclosure about all benefits and risks that accompany certain interventions. A study in patients undergoing AVR in the Netherlands analysed patients' knowledge about valve substitutes and patients' numeracy [18]. It was not only found that almost half of the patients felt that they had insufficient knowledge about different valve prostheses after having received information but half of the patients also had impaired numeracy, implying that they experienced difficulty in weighing benefits and risks. Presenting data in pictograms may improve patient understanding of the benefits and risks of different types of valve prostheses [19].

In this study, a competing risks regression model was constructed for the Freestyle bioprosthesis to provide patients, cardiologists and surgeons with information on expected clinical outcomes, given the relevant predictors (age, renal function and implantation technique). Internal validation of this model showed good to fair predictive performance with respect to SVD occurrence up to 19 years and fair predictive performance with respect to mortality. As expected, this model was unable to accurately predict reoperation due to other causes than SVD. Such events may be attributed more to chance than to patient characteristics. The information from this model, showing both risks of events and the probability of remaining event-free, can be presented graphically to patients, improving their understanding of the presented data. This aids patients, cardiologists and surgeons in their shared decision-making in choosing a prosthesis.

Limitations

The retrospective part of this study comes with its accompanying limitations. Changes in (peri)operative management during the long study period may have influenced both early (as shown in this article) and late outcomes. Because of the small number of events, the results of this logistic regression model should be considered with some caution, because the possibility of some overfitting cannot be excluded. The several different indications and patient characteristics make this a heterogeneous series. Although internal validation of our competing risks prediction model showed good predictive capabilities, it needs to be validated externally.

CONCLUSION

The choice of the aortic valve prosthesis is a shared decision between patients, cardiologists and surgeons. For patients to make a well-informed decision, clinicians need to fully disclose the risks and benefits accompanying the different treatment options and present them in a comprehensible manner. The Freestyle stentless bioprosthesis is a valuable option for patients with an indication for aortic root replacement, with low incidence of SVD and valve-related events, especially in older patients. The competing risk regression model of this study can be used to clearly and fully inform patients about their expected individual trajectory after the implantation of this prosthesis. This improves the shared decision-making process between patients and clinicians.

FUNDING

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Conflict of interest: none declared.

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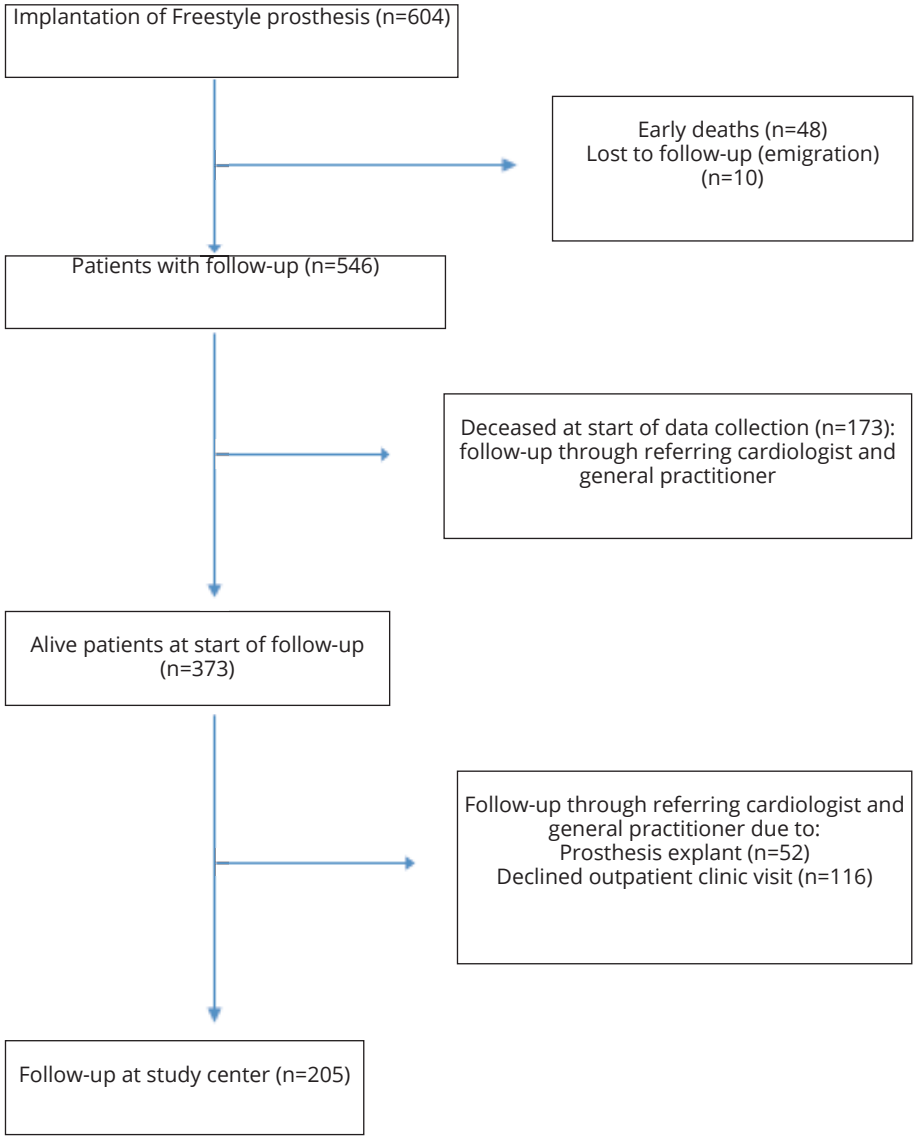
Supplementary Material

Supplemental File A. Risk factor analysis

	Univariable analysis (Student's T-test or Chi-square test)	Multivariable logistic regression		
Variable	**P-value**	**Odds Ratio**	**95% CI**	**P-value**
Isolated surgery	0.063			
NYHA class III or IV	0.10			
Previous cardiac surgery	0.19	2.465	1.090 – 5.573	0.030
Previous AVR	0.62			
Previous MVR	0.16			
Active endocarditis	0.093			
Previous MI	0.002			
Previous revascularization	0.005			
Diabetes	0.97			
Periferal artery disease	0.095			
CVA	<0.001	4.590	2.105 – 10.008	<0.001
COPD	0.002	2.714	1.115 – 6.607	0.028
Renal impairment (eGFR < 85ml/kg/min)	<0.001			
Impaired left ventricular function	0.85			
Urgent/emergent surgery	<0.001	9.471	3.701 – 24.238	<0.001
Root replacement	0.11			
Concomitant CABG	<0.001	2.329	1.120 – 4.843	0.024
Concomitant MV surgery	0.024	3.363	1.374 – 8.228	0.008
Surgical era	0.053			0.003
Before 2000		-	-	-
2000 – 2010		0.748	0.378 – 2.012	0.75
After 2010		0.246	0.103 – 0.585	0.002
Age (continuous)	<0.001	1.058	1.025 – 1.092	<0.001

Multivariable logistic regression model: Hosmer and Lemeshow goodness-of-fit: P = 0.955; AUC: 0.850

Supplemental File B. Flow diagram on follow-up



Supplemental File C. Predicted probabilities from the competing risks regression model at 5, 10 and 15 years.

5 Year

	>85			**50-85**			**<50**		
Root	Death	NSVD	SVD	Death	NSVD	SVD	Death	NSVD	SVD
<40	2.26	3.13	2.58	2.54	2.17	2.40	4.85	3.27	0.99
40-50	5.31	5.77	1.10	5.97	4.02	1.02	11.20	6.03	0.42
50-60	3.87	6.47	0.71	4.35	4.51	0.66	8.23	6.76	0.27
60-70	9.93	5.31	0.19	11.12	3.69	0.17	20.36	5.55	0.07
>70	18.15	2.04	0.22	20.22	1.41	0.20	35.34	2.14	0.08
	>85			**50-85**			**<50**		
Non-root	Death	NSVD	SVD	Death	NSVD	SVD	Death	NSVD	SVD
<40	2.13	5.08	6.30	2.40	3.53	5.87	4.57	5.31	2.44
40-50	5.01	9.29	2.71	5.63	6.51	2.52	10.58	9.70	1.03
50-60	3.65	10.39	1.75	4.11	7.29	1.62	7.77	10.85	0.67
60-70	9.38	8.55	0.46	10.51	5.98	0.43	19.29	8.93	0.17
>70	17.19	3.33	0.54	19.17	2.31	0.50	33.68	3.48	0.21

10 Year

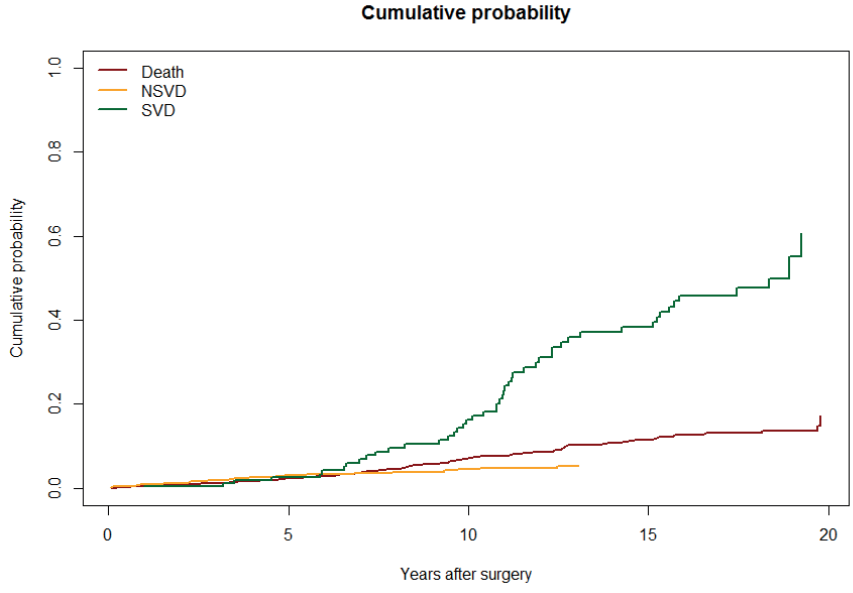
	>85			**50-85**			**<50**		
Root	Death	NSVD	SVD	Death	NSVD	SVD	Death	NSVD	SVD
<40	7.06	4.52	16.28	7.92	3.14	15.21	14.73	4.72	6.51
40-50	16.05	8.29	7.22	17.91	5.80	6.72	31.67	8.66	2.80
50-60	11.89	9.27	4.70	13.30	6.50	4.37	24.08	9.69	1.81
60-70	28.49	7.62	1.25	31.49	5.33	1.16	51.81	7.97	0.48
>70	47.39	2.96	1.48	51.55	2.05	1.37	75.30	3.09	0.56
	>85			**50-85**			**<50**		
Non-root	Death	NSVD	SVD	Death	NSVD	SVD	Death	NSVD	SVD
<40	6.66	7.30	35.74	7.48	5.10	33.68	13.93	7.63	15.43
40-50	15.19	13.22	17.01	16.96	9.33	15.89	30.14	13.80	6.82
50-60	11.24	14.75	11.29	12.58	10.43	10.53	22.86	15.39	4.44
60-70	27.08	12.19	3.08	29.97	8.59	2.87	49.72	12.73	1.18
>70	45.39	4.80	3.63	49.47	3.34	3.38	73.21	5.02	1.39

15 year

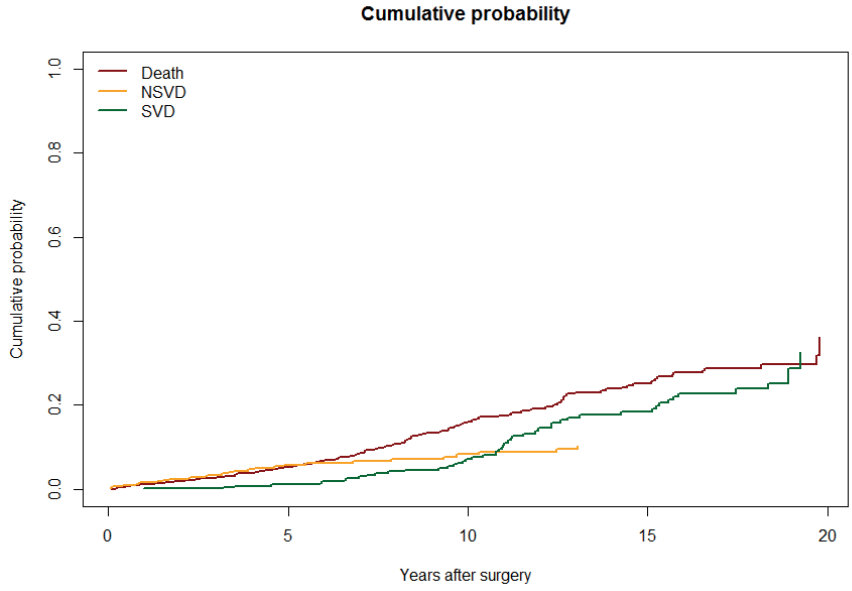
	>85			50-85			<50		
Root	Death	NSVD	SVD	Death	NSVD	SVD	Death	NSVD	SVD
<40	11.39	5.57	38.38	12.76	3.88	36.12	23.15	5.82	16.71
40-50	25.11	10.18	18.41	27.84	7.14	17.21	46.72	10.63	7.42
50-60	18.88	11.38	12.26	21.02	8.00	11.43	36.58	11.87	4.83
60-70	42.55	9.37	3.36	46.49	6.57	3.12	70.08	9.79	1.29
>70	65.42	3.66	3.96	69.82	2.54	3.68	90.09	3.82	1.52
	>85			**50-85**			**<50**		
Non-root	Death	NSVD	SVD	Death	NSVD	SVD	Death	NSVD	SVD
<40	10.77	8.98	69.91	12.06	6.28	67.22	21.97	9.37	36.56
40-50	23.84	16.14	39.73	26.45	11.44	37.51	44.73	16.83	17.45
50-60	17.88	17.97	27.77	19.93	12.78	26.08	34.88	18.72	11.60
60-70	40.67	14.90	8.15	44.51	10.54	7.59	67.91	15.54	3.17
>70	63.22	5.93	9.56	67.64	4.13	8.91	88.67	6.19	3.74

Supplemental File D. Cumulative probability curves from the competing risks regression model for all covariates.

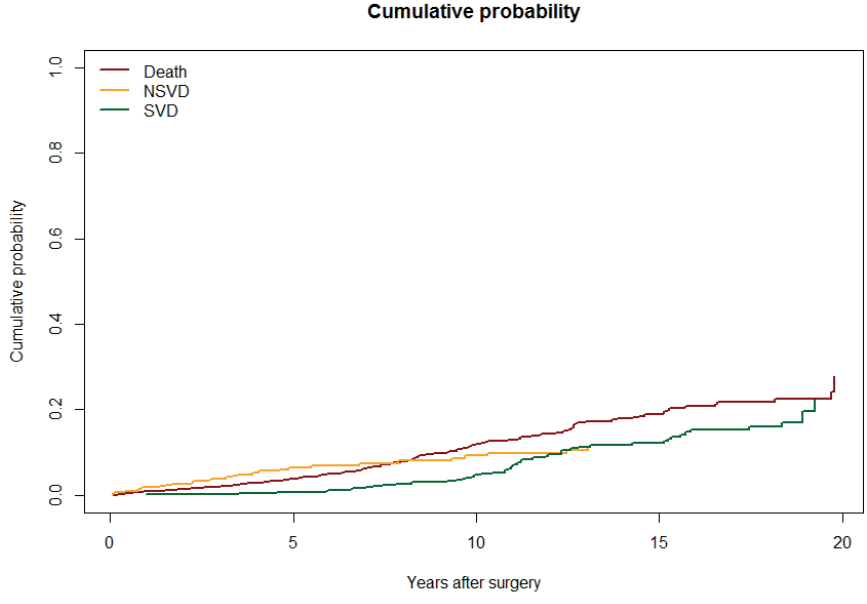
Root, normal renal function, <40 year



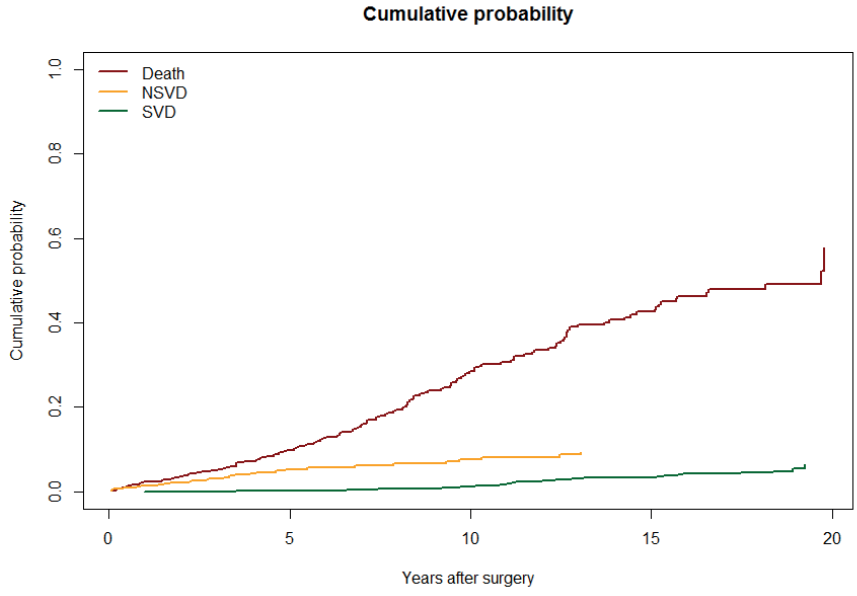
Root, normal renal function, 40-50 years



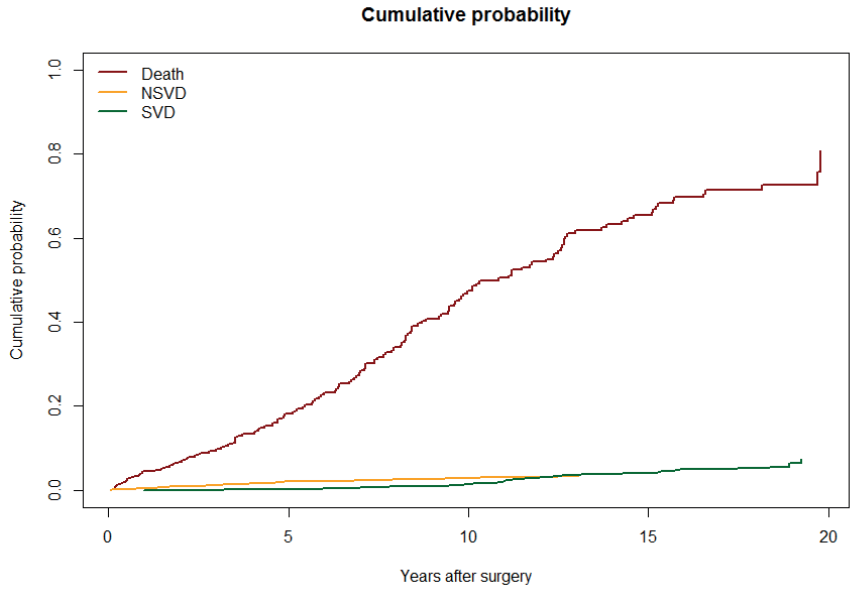
Root, normal renal function, 50-60 years



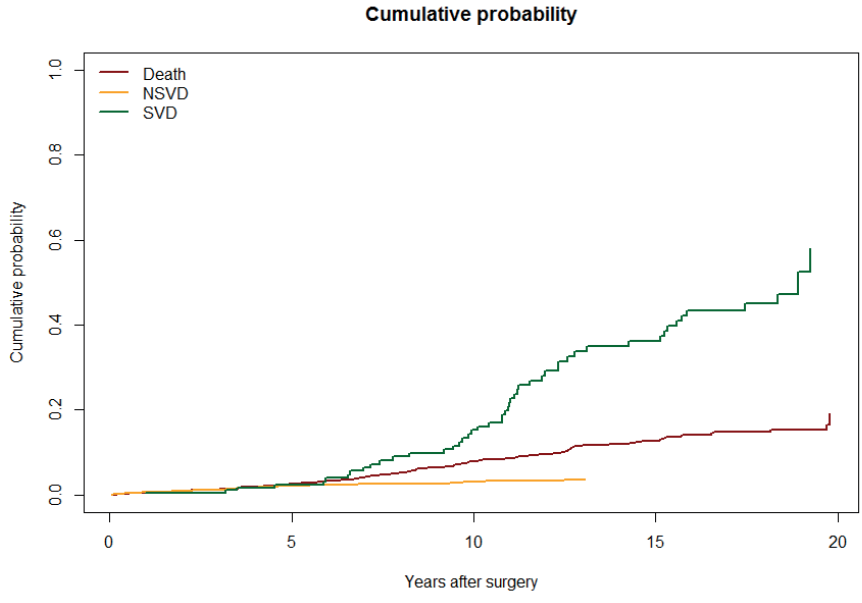
Root, normal renal function, 60-70 years



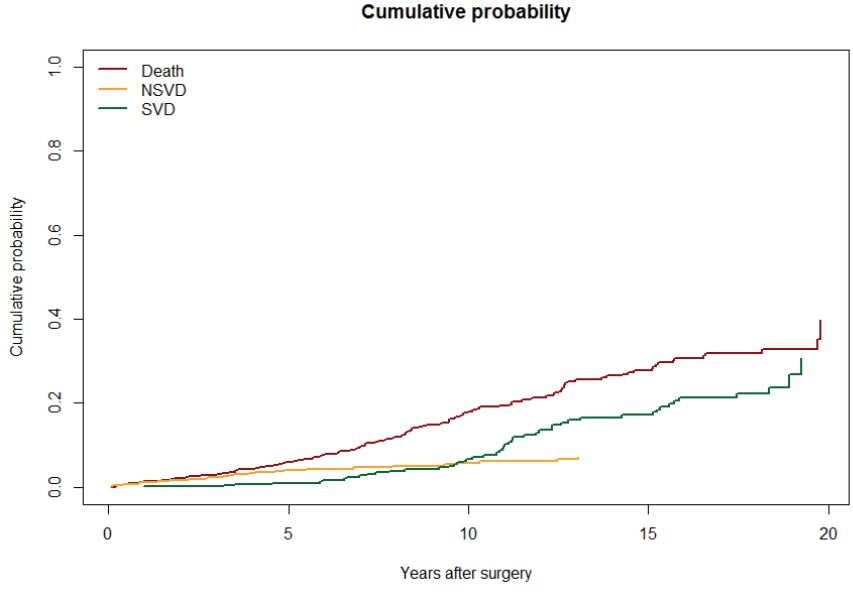
Root, normal renal function, >70 years



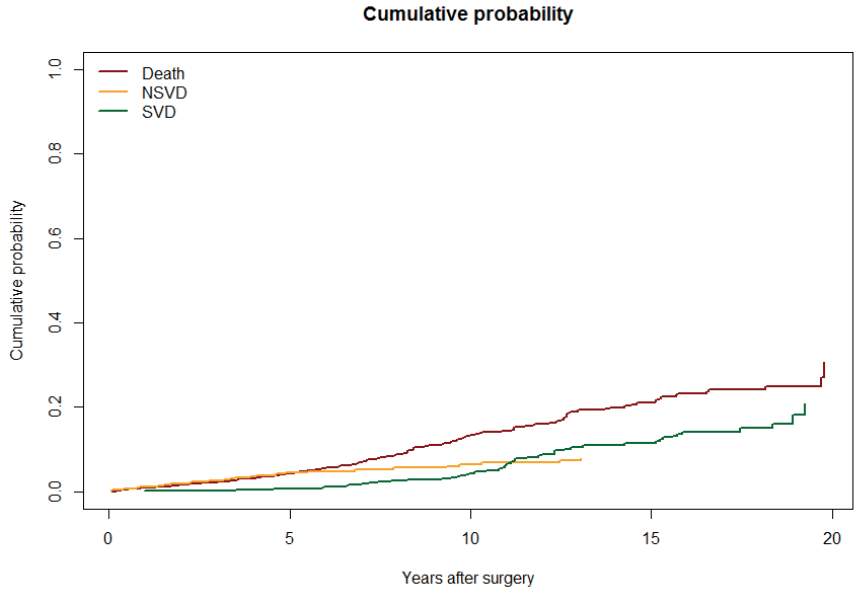
Root, moderately impaired renal function, <40



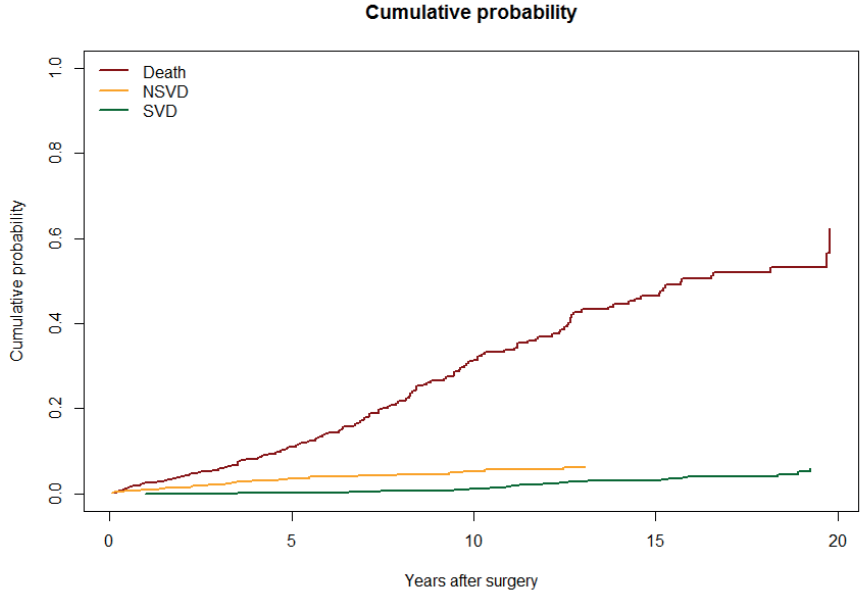
Root, moderately impaired renal function, 40-50



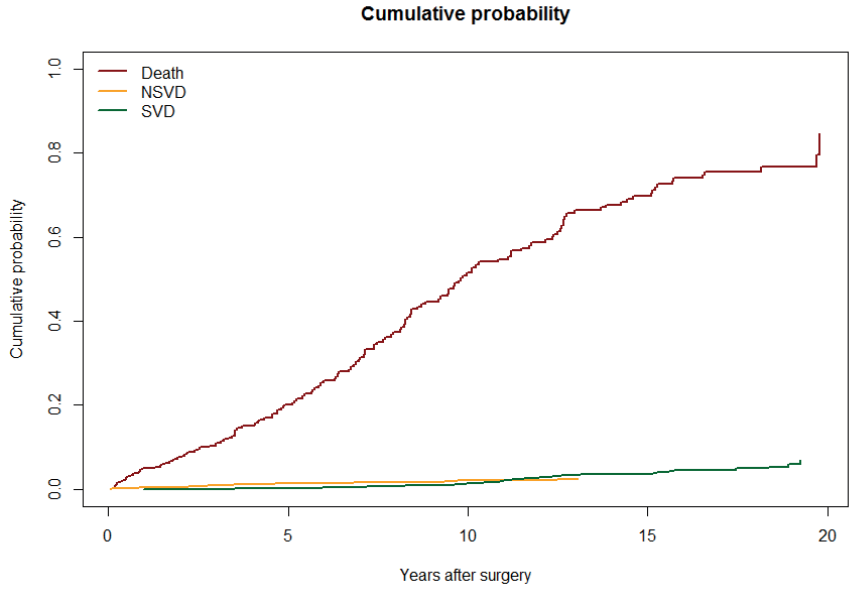
Root, moderately impaired renal function, 50-60



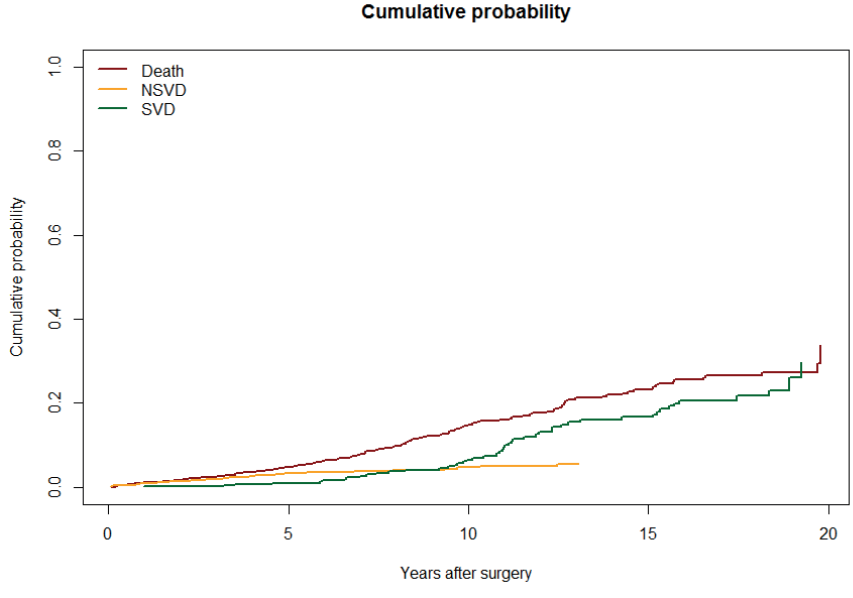
Root, moderately impaired renal function, 60-70



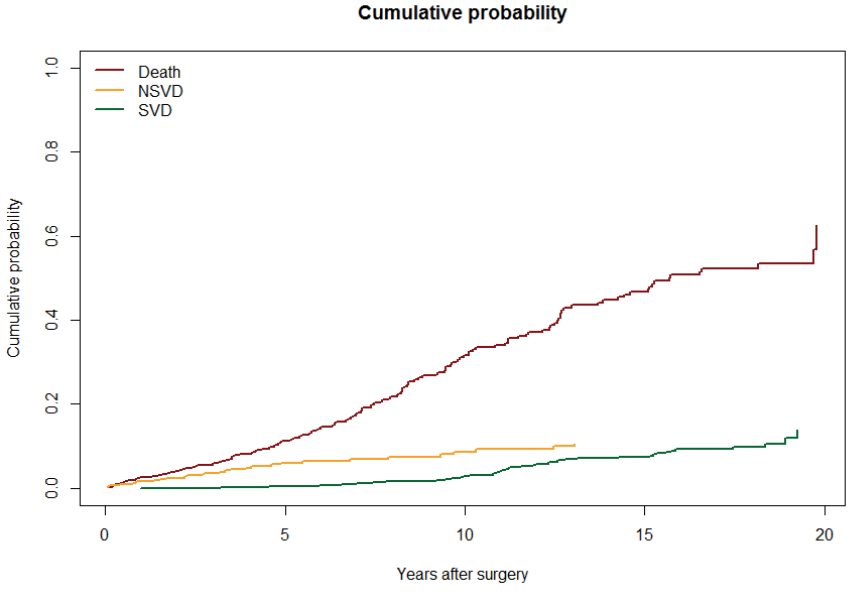
Root, moderately impaired renal function, >70



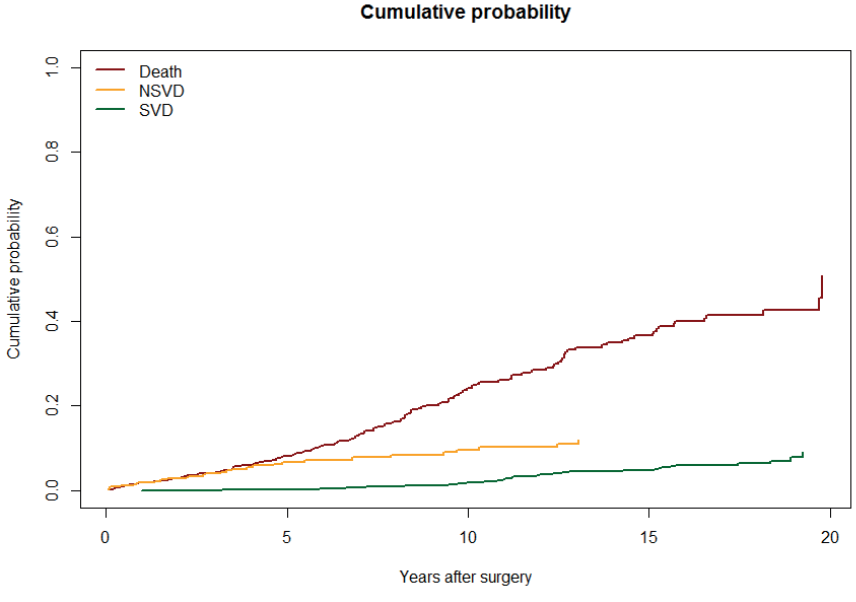
Root, severely impaired renal function, <40



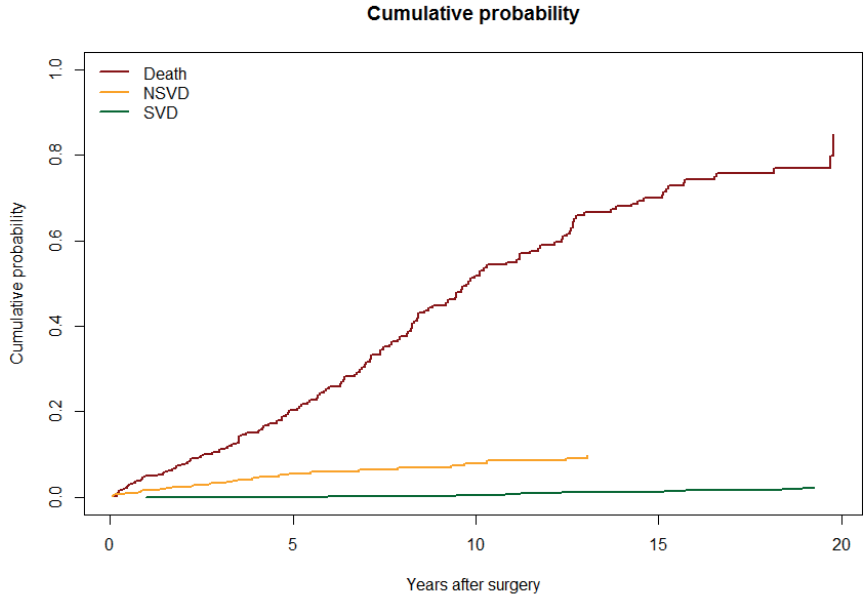
Root, severely impaired renal function, 40-50



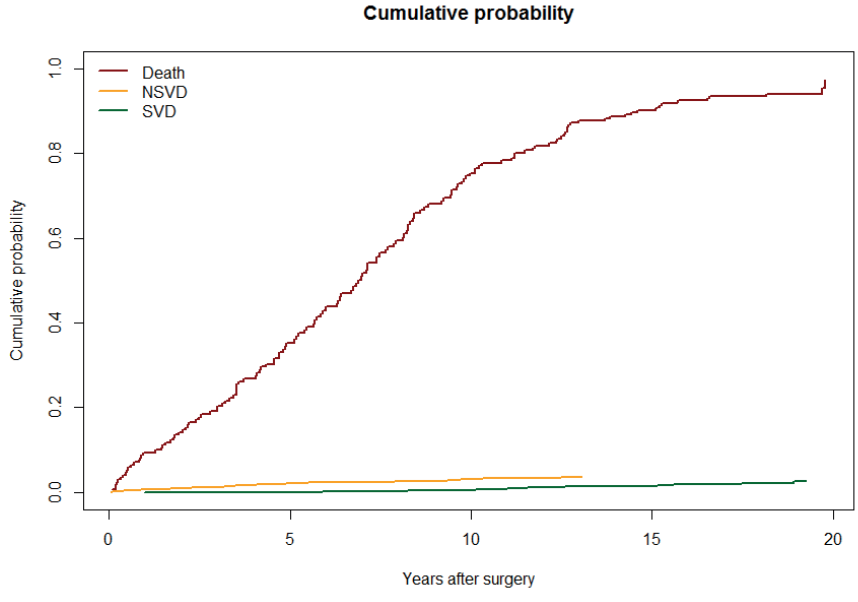
Root, severely impaired renal function, 50-60



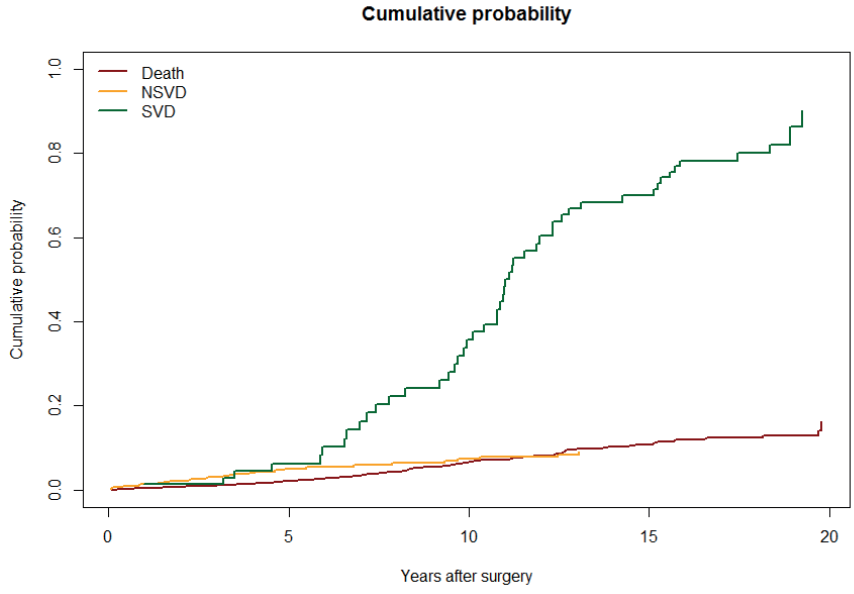
Root, severely impaired renal function, 60-70



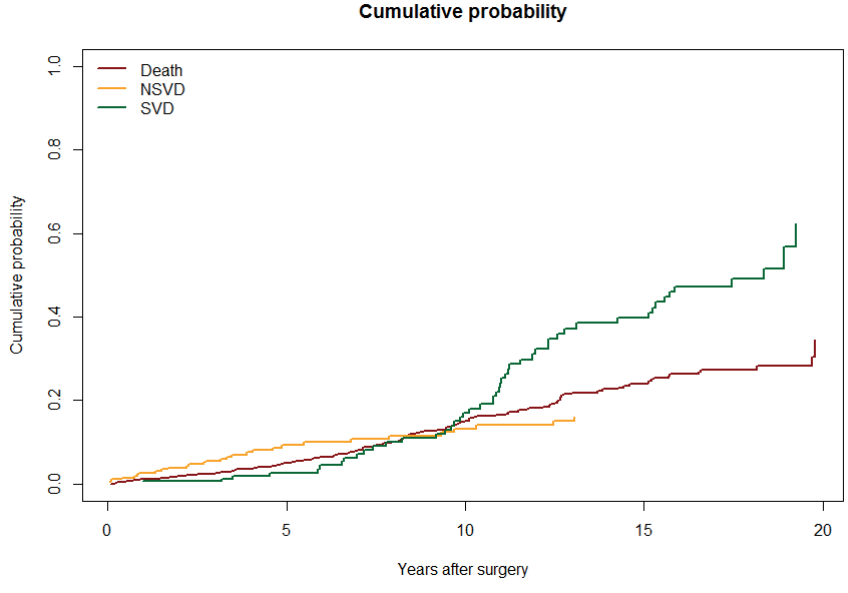
Root, severely impaired renal function, >70



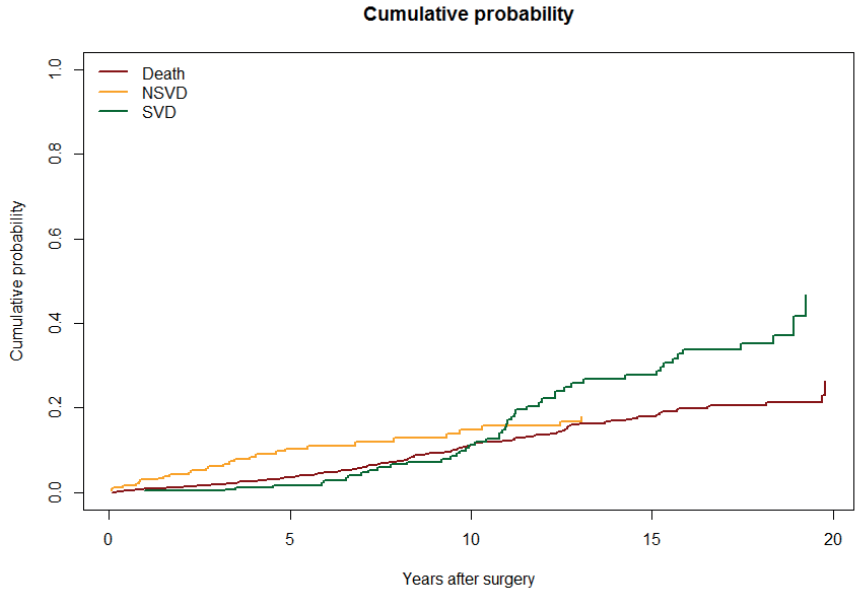
Non-root, normal renal function, <40 year



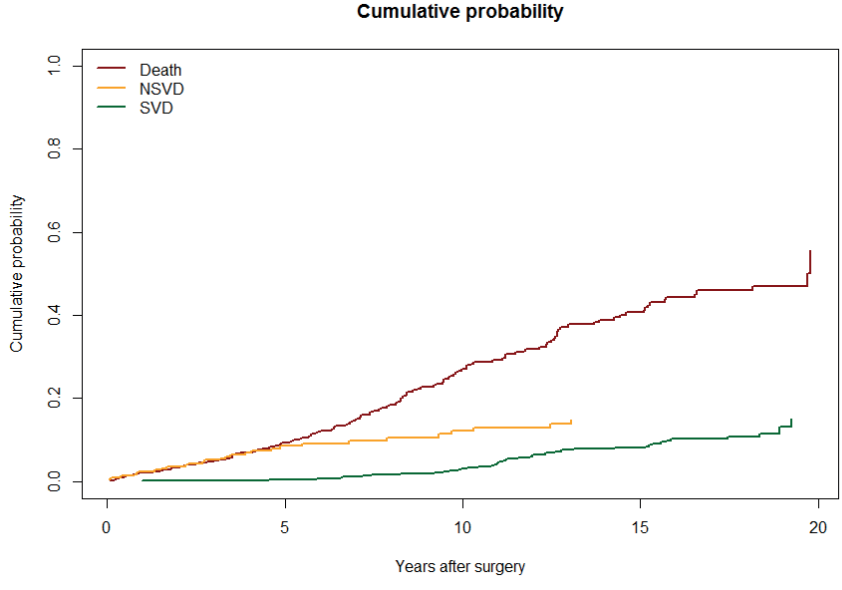
Non-root, normal renal function, 40-50 years



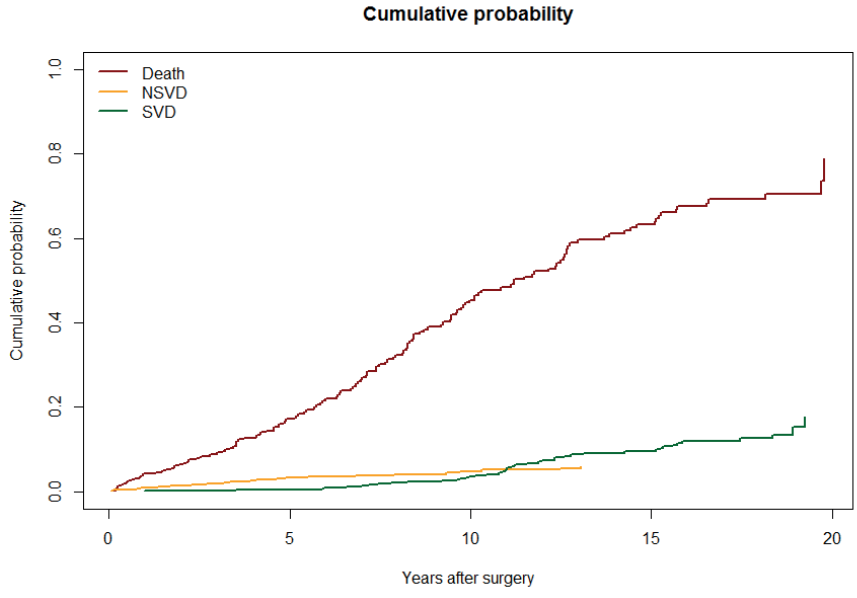
Non-root, normal renal function, 50-60 years



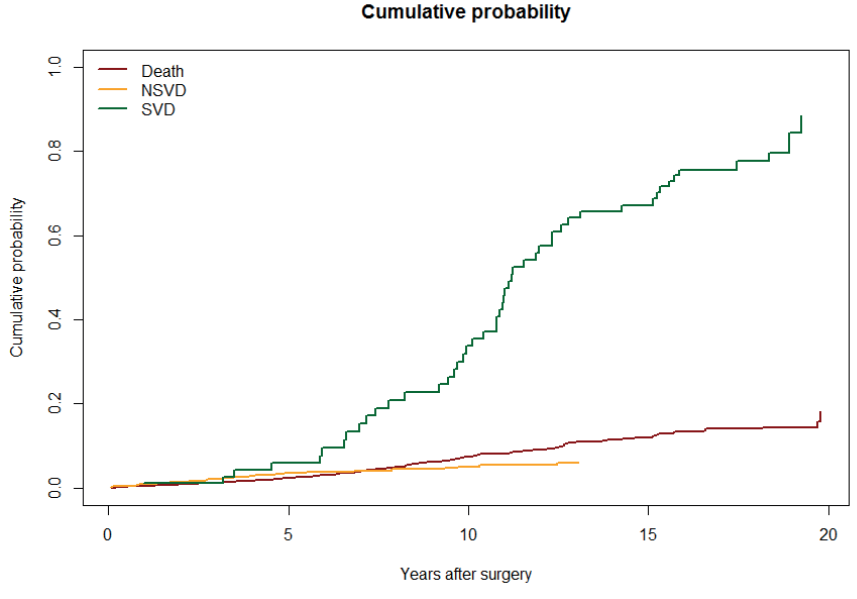
Non-root, normal renal function, 60-70 years



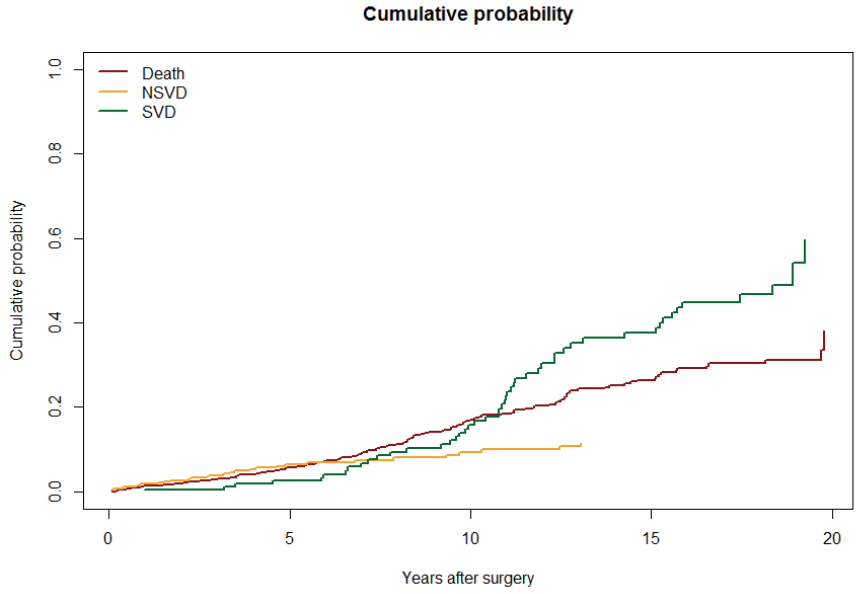
Non-root, normal renal function, >70 years



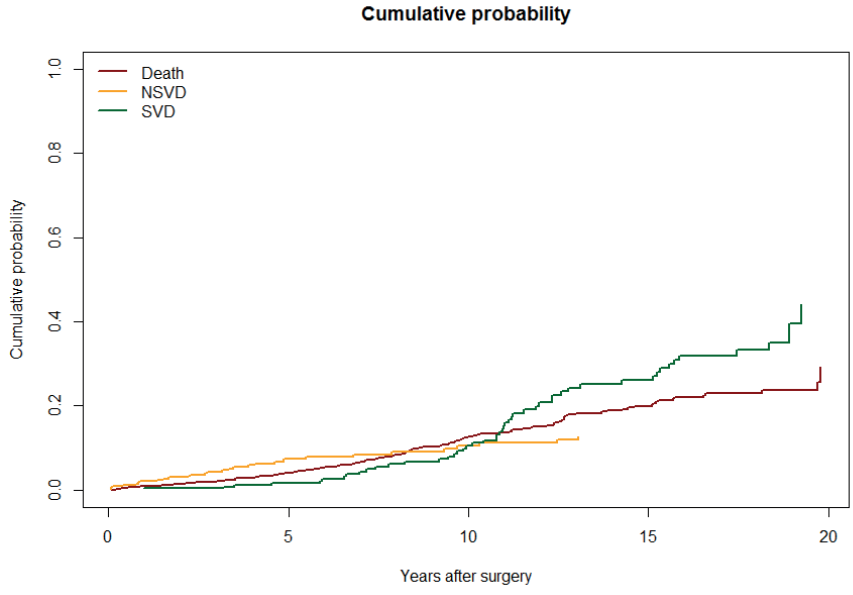
Non-root, moderately impaired renal function, <40



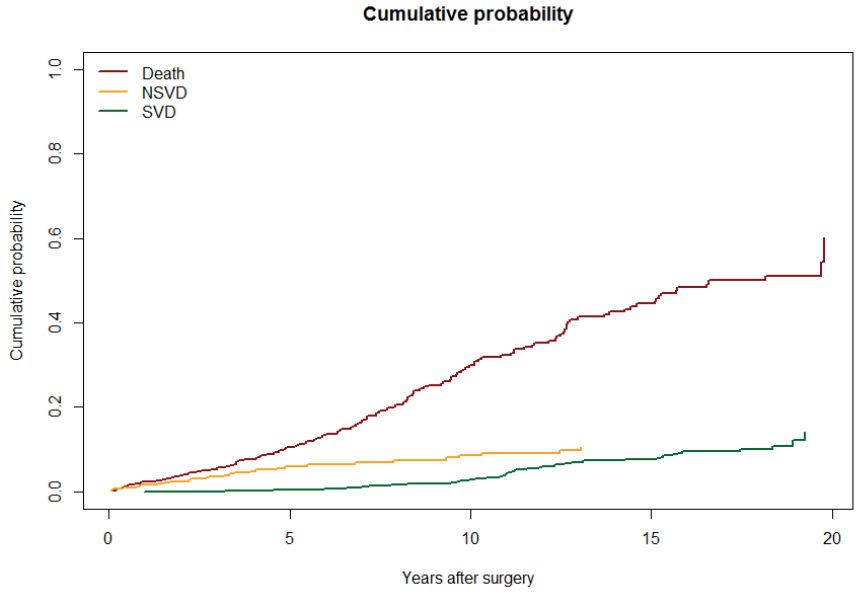
Non-root, moderately impaired renal function, 40-50



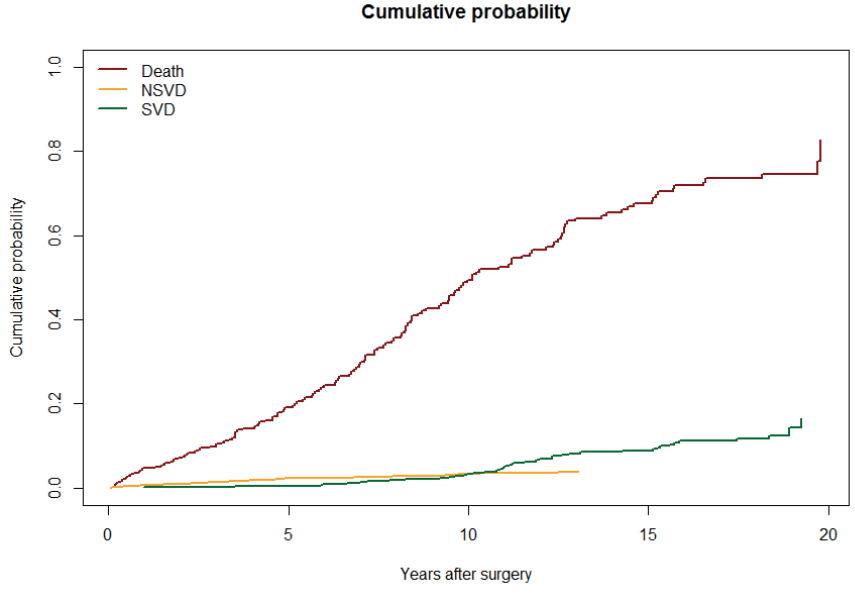
Non-root, moderately impaired renal function, 50-60



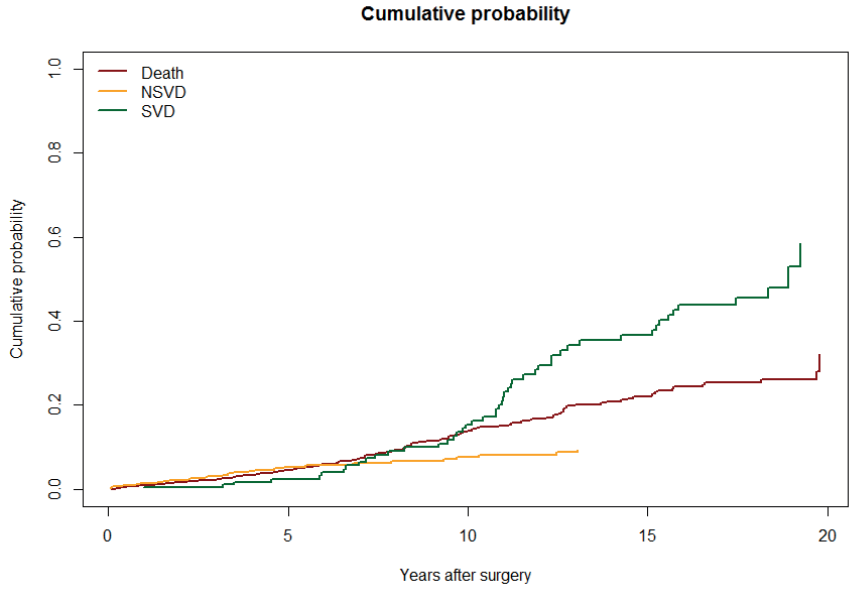
Non-root, moderately impaired renal function, 60-70



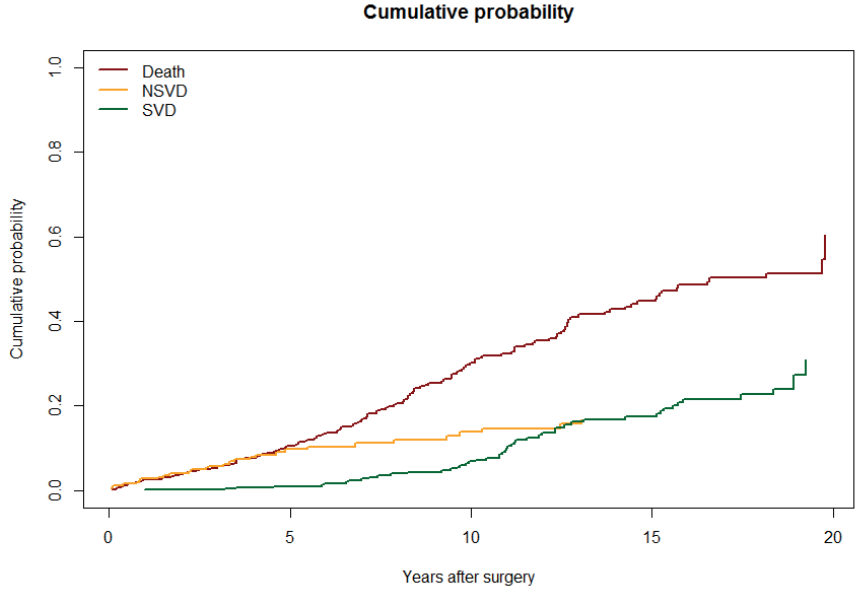
Non-root, moderately impaired renal function, >70



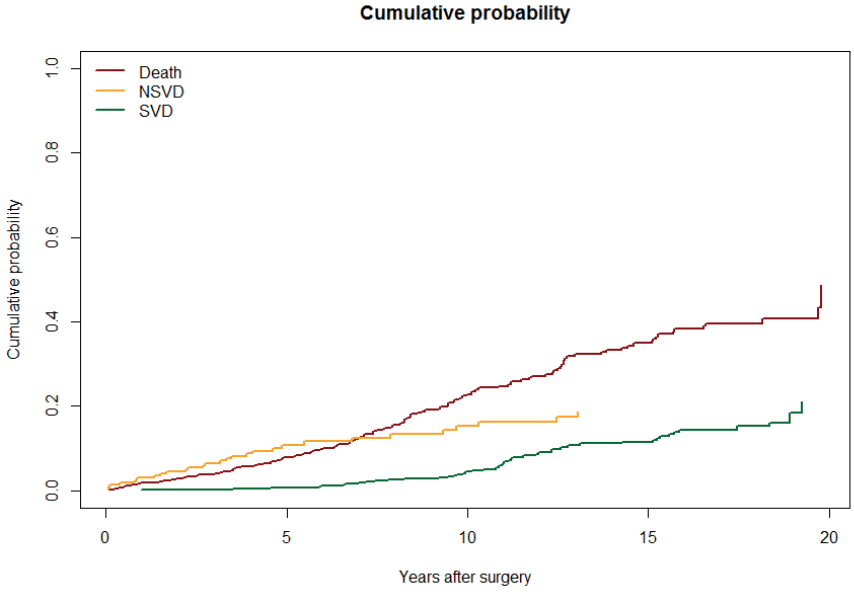
Non-root, severely impaired renal function, <40



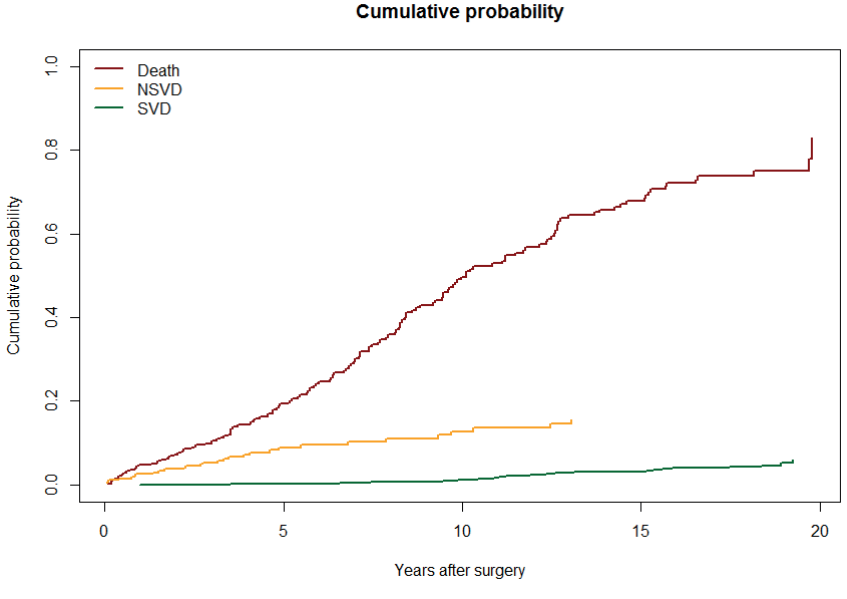
Non-root, severely impaired renal function, 40-50



Non-root, severely impaired renal function, 50-60



Non-root, severely impaired renal function, 60-70



Non-root, severely impaired renal function, >70