Surgical solutions for complex aortic root pathology

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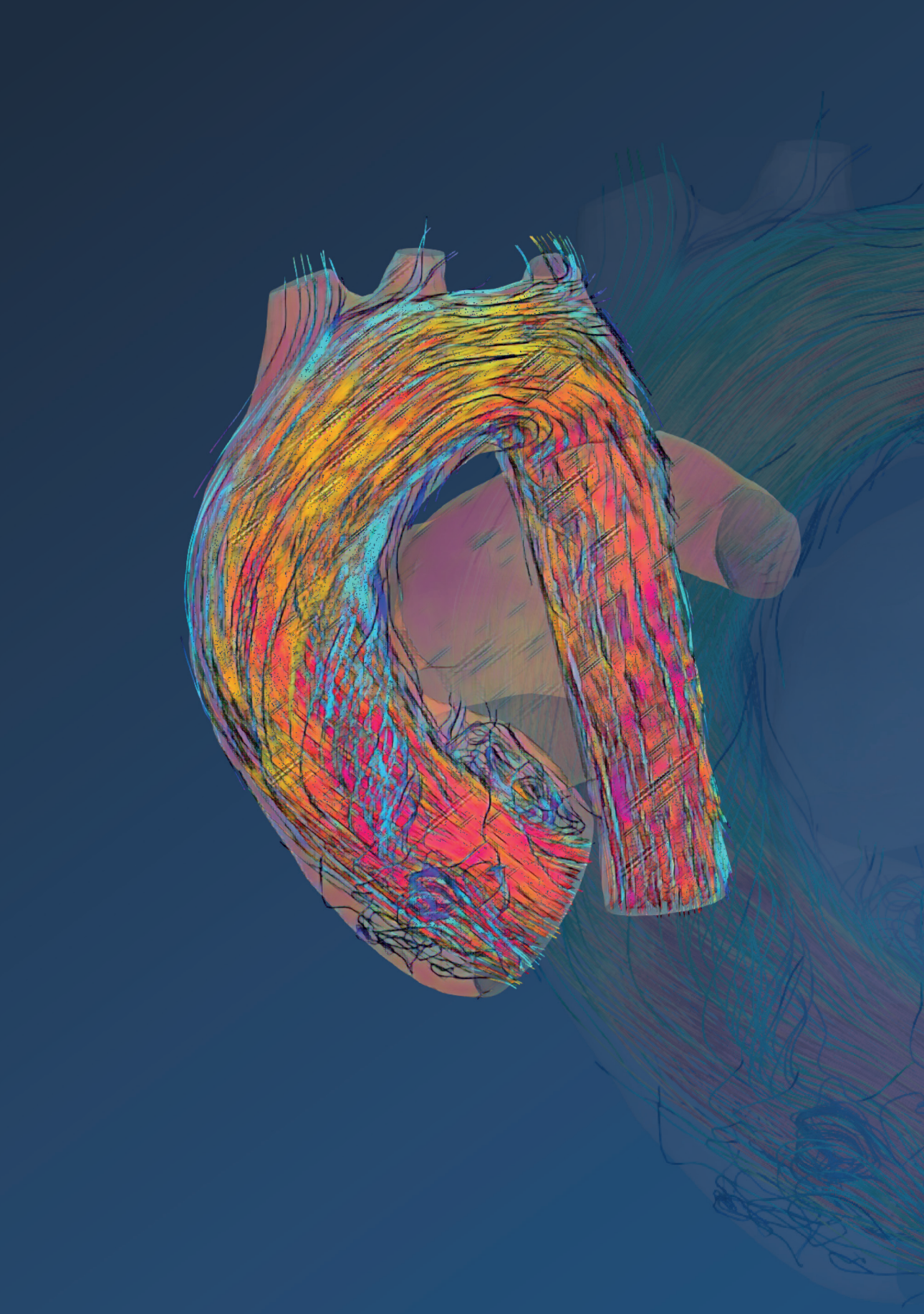

A MULTI-CENTER, PROPENSITY SCORE MATCHED COMPARISON BETWEEN STENTLESS BIOLOGICAL AND MECHANICAL COMPOSITE GRAFT AORTIC ROOT REPLACEMENT.

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CHAPTER 7

ABSTRACT

Objective

Comparison of clinical outcome after mechanical versus biological aortic root replacement (ARR) in a propensity score matched cohort.

Methods

Propensity score matching was applied in 117 patients after mechanical ARR and 260 after biological ARR between 2004 and 2014 in 2 centers and resulted in 101 matched pairs. Primary endpoint was freedom from the composite endpoint of thromboembolic event, bleeding, reintervention and valve related mortality. Secondary endpoints were freedom all-cause mortality and the primary endpoints separately.

Results

After matching, patient characteristics were comparable between both groups, with a median age of 65-years. The median follow-up time was 4 years. Besides more reinterventions for bleeding in the mechanical prosthesis (MP) group, there were no differences in perioperative complication rates. At 8 years, freedom from thromboembolic event, bleeding, reintervention and valve related death (primary endpoint) was 60.9% (48.9 – 75.7%) in the MP group and 66.7% (49.8 – 89.1%) in the bioprosthesis (BP) group (P = 0.030). Overall survival was higher in the BP group (P = 0.032). The competing risks analysis showed a higher event-free survival probability during follow-up in the BP group (90.1% at 4 years) compared to the MP group (77.9% at 4 years).

Conclusions

Aortic root replacement with a bioprosthesis had better overall survival compared to a mechanical prosthesis in patients over 60 years of age, with a higher valve related mortality after mechanical valve replacement. Event-free survival during the first years of follow-up was higher after biological root replacement.

INTRODUCTION

Several options are available to replace a diseased aortic valve and root. Mechanical composite grafts have been the "gold standard" for several decades. The most important benefit is an excellent durability of mechanical prostheses. This comes, however, at the cost of lifelong anticoagulant therapy to prevent thromboembolism, which is related with higher hemorrhagic event risk. Bioprostheses do not need anticoagulant treatment, but structural degeneration, especially in young patients, limit their durability with the risk of a reintervention in time. In recent years, the use of bioprostheses has increased[1]. This increase might be explained by improved durability of modern bioprostheses and the advances in less invasive transcatheter valve-in-valve reinterventions to replace a degenerated bioprosthesis.

Regarding aortic valve prosthesis choice, recent American and European guidelines state that bioprostheses should be considered in older patients (aged >70[2] and >65[3]), and mechanical prostheses should be considered in younger patients (aged <50[2] and <60[3]). However, the lack of scientific support for these class IIa recommendations is demonstrated by the level of evidence C (expert opinion). Furthermore, these recommendations create a gray area in which prosthetic valve selection is less straightforward, and patient preferences, considering risks of reoperation and risks of anticoagulant treatment, play a more important role. Moreover, in case of aortic root disease there might be additional risks due to the more extensive surgery, especially in the perioperative period. In this light there is even less evidence on outcomes related to the type of prosthesis.

In this light we conducted a propensity score matched cohort study after aortic valve and root replacement with either a mechanical composite graft or a stentless aortic root bioprosthesis, to search for differences in clinical outcome between both types of prostheses.

METHODS

Patients

Between 2004 and 2014, 352 patients underwent aortic valve and root replacement (ARR) with a mechanical composite graft (MP) at the Erasmus Medical Center, and 366 patients underwent ARR with a Freestyle stentless bioprosthesis (BP) (Medtronic Inc., Minneapolis, MN, USA) at the Leiden University Medical Center. Since some etiologies of aortic valve and root disease are relatively rare and there were differences between the 2 groups (i.e. congenital cardiac anomalies like hypoplastic left heart, atrioventricular septal defect, and tetralogy of Fallot were overrepresented in the biological valve group), these patients were excluded from the study. Additionally, all patients with emergent surgery were excluded, resulting in 117 patients with a MP and 260 with a BP in the study population.

Anticoagulant treatment

Patients with mechanical AVR postoperatively received lifelong vitamin K antagonists (VKA) with a target International Normalized Ration of 2.0 – 3.0. Patients who received a biological AVR were treated with aspirin for 3 months (unless VKA treatment was warranted for other indications).

Data collection

Data were collected retrospectively from the departments' databases. Follow-up data was obtained using outpatient clinic visits, questionnaires, or through direct telephone contact. Data on death causes were obtained from hospital records or patients general practitioners. Valve related events were defined according to current guidelines[4]. The ethical committees of the centers approved of this study and waived the need of patients informed consent.

Study endpoints

The primary endpoint was freedom from the composite endpoint of thromboembolic (TE) event, bleeding, reintervention and valve related mortality. Secondary endpoints were freedom all-cause mortality, and the primary endpoints separately. Study endpoints are reported for both the unmatched, and the matched study cohorts.

Statistical analysis

The cohort was matched using propensity score matching, considering 15 variables (Table 1). Matching was performed 1:1 without replacement, with a caliper width of 0.05 and priority to exact matches, resulting in 103 matched pairs. Continuous data are expressed as means ± standard deviation (SD) and compared using the Students T-test or as medians (interquartile range [IQR]) and compared with the Mann-Whitney U-test where appropriate. Categorical data are expressed as counts (%) and compared using the Chi-squared test or Fishers exact test. Freedom from events were calculated using the Kaplan-Meier estimator and compared using the log-rank test. To provide insights in the time related occurrence of valve related events, a competing risks analysis was performed using the mstate package[5] in R (version 3.5.0, R foundation for statistical computing, Vienna, Austria). Analyzed competing risks were death, reoperation and thromboembolic/bleeding event. All other analyses were performed with IBM SPSS Statistics version 24 (IBM Inc., Armonk, NY, USA).

RESULTS

Baseline characteristics

Baseline characteristics of the total group before matching, and the matched cohort are shown in Table 1. After matching, there were no preoperative differences between both groups, indicating an adequate performance of the matching process. Median follow-up in the MP group was 4.2 (2.3 – 6.3) years in the unmatched and 4.3 (2.3 – 6.7) years in the matched cohort, and in the BP group 4.3 (2.5 – 5.7) years in the unmatched and 4.6 (2.8 – 6.2) in the matched cohort, and was 100% complete.

Table 1. Patient characteristics

	Entire cohort			Matched cohort		
	Bentall	**Freestyle**	**P-value**	**Bentall**	**Freestyle**	**P-value**
Number of patients	117	260		103	103	
Male sex	86 (73.5)	180 (69.2)	0.400	74 (71.8)	79 (76.7)	0.425
Age at operation (y) (median [IQR])	65.5 (61.1 – 70.1)	64.1 (58.9 – 71.4)	0.355	65.6 (61.3 – 70.0)	65.2 (61.8 – 72.1)	0.577
Redo surgery	31 (26.5)	67 (25.8)	0.882	25 (24.3)	28 (27.2)	0.633
LVEF			0.006			0.836
>50	82 (70.1)	197 (75.8)		79 (76.7)	77 (74.8)	
30 – 50	19 (16.2)	53 (20.4)		19 (18.4)	19 (18.4)	
21 – 30	12 (10.3)	8 (3.1)		5 (4.9)	7 (6.8)	
20 or less	4 (3.4)	2 (0.8)		…	…	
Prior myocardial infarction	5 (4.3)	13 (5.0)	0.760	4 (3.9)	4 (3.9)	1
Urgent timing	30 (25.6)	66 (25.4)	0.958	22 (21.4)	28 (27.2)	0.330
Diabetes mellitus	3 (2.6)	34 (13.1)	0.002	3 (2.9)	4 (3.9)	0.701
Creatinine (median [IQR])	89 (75 – 104)	81 (72 – 96)	0.007	87 (73 – 101)	82 (74 – 99)	0.329
Prior CVA	3 (2.6)	37 (14.3)	0.001	3 (2.9)	6 (5.8)	0.307
Coronary artery disease	18 (15.4)	56 (21.5)	0.164	18 (17.5)	16 (15.5)	0.707
Aortic valve stenosis	61 (52.1)	142 (54.6)	0.655	49 (47.6)	56 (54.4)	0.780
Aortic valve insufficiency	87 (74.4)	192 (73.8)	0.916	73 (70.9)	74 (71.8)	0.878
COPD	13 (11.1)	26 (10.0)	0.743	12 (11.7)	13 (12.6)	0.831
Hypertension	55 (47.0)	169 (65.3)	0.001	53 (51.5)	55 (53.4)	0.780
NYHA functional class			0.337			0.944
I	48 (41.7)	97 (37.3)		45 (43.7)	43 (41.7)	
II	29 (25.2)	87 (33.5)		29 (28.2)	33 (32.0)	
III	33 (28.7)	68 (26.2)		22 (26.2)	25 (24.3)	
IV	5 (4.4)	8 (3.1)		2 (1.9)	2 (1.9)	

Values depict count (%) unless stated otherwise
COPD: chronic obstructive pulmonary disease, CVA: cerebrovascular accident, IQR: interquartile range, LVEF: left ventricular ejection fraction

Perioperative details

Perioperative details are shown in Table 2. There were more reinterventions for bleeding in the MP group. Early mortality, postoperative conduction block requiring a pacemaker, postoperative stroke, and postoperative myocardial infarction were not statistically significantly different between both groups.

Table 2. (Peri)operative details

	Entire cohort			**Matched cohort**		
	Bentall	**Freestyle**	**P-value**	**Bentall**	**Freestyle**	**P-value**
Bypass time (median [IQR])	189 (153 – 231)	206 (171 – 271)	0.011	183 (146 – 224)	207 (171 – 260)	0.010
Crossclamp time (median [IQR])	128 (100 – 157)	166 (132 – 213)	<0.001	125 (100 – 156)	167 (136 – 211)	0.010
Concomitant CABG	14 (12.0)	49 (18.8)	0.098	13 (12.6)	18 (17.5)	0.330
Concomitant mitral valve surgery	8 (6.8)	46 (17.7)	0.005	7 (6.8)	15 (14.6)	0.071
Reintervention for bleeding	24 (20.5)	17 (6.5)	<0.001	22 (21.4)	8 (7.8)	0.006
Perioperative myocardial infarction	1 (0.9)	5 (1.0)	0.444	1 (1.0)	1 (1.0)	1
Permanent pacemaker	5 (4.3)	21 (8,1)	0.175	3 (2.9)	8 (7.8)	0.134
Perioperative stroke	-	5 (1.9)	0.132	-	2 (1.9)	0.498
Early mortality	5 (4.3)	11 (4.2)	0.985	4 (3.9)	0	0.121

Values depict count (%) unless stated otherwise

CABG: coronary artery bypass grafting

Primary endpoint

The 8 year freedom from combined TE event, bleeding, reintervention and valve related death (primary endpoint) was 60.9% (48.9 – 75.7%) in the MP group and 66.7% (49.8 – 89.1%) in the BP group, respectively (P = 0.030) in the matched

population. Figure 1 shows the freedom from the primary endpoint in both the matched and the unmatched group.

Secondary endpoints

There was a survival benefit in favor of the BP group, with an 8 year estimated overall survival of 79.8% (68.5 – 92.9%) vs. 66.3% (55.1 – 79.8%) in the MP group (P = 0.032).

Freedom from TE events and bleeding combined, and freedom from reintervention did not differ significantly between both groups. Figure 1 shows a detailed freedom from the secondary endpoints in the matched and unmatched group.

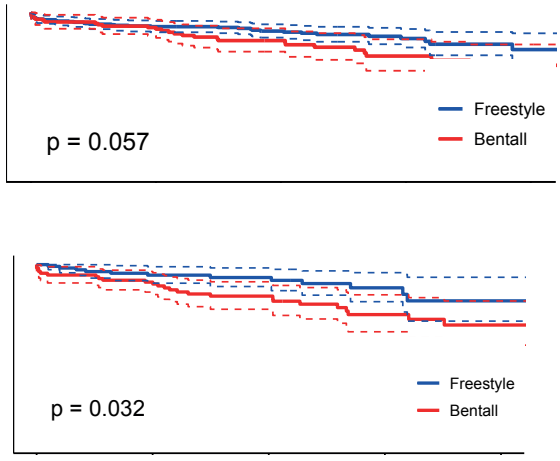

Figure 1. Kaplan-meier of overall survival (A), freedom from thromboembolic (TE) events and bleeding (B), freedom from reintervention (C) and freedom from the composite endpoint of TE events, bleeding, explant and valve related mortality in the unmatched (top) and matched (bottom) cohorts.

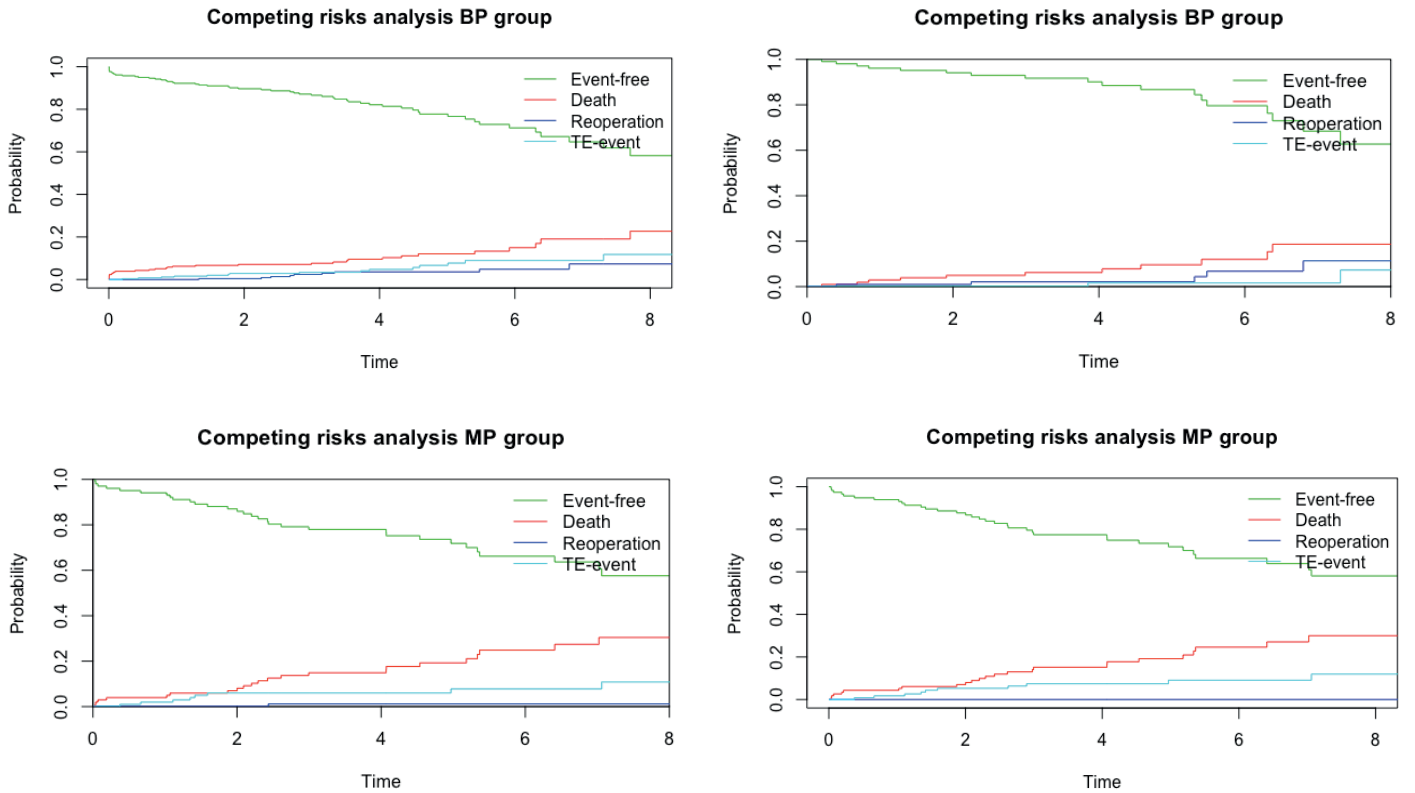

Figure 2. Competing risks analysis in the unmatched (left 2)) and matched (right 2) patient cohorts in the bioprosthesis group and mechanical prosthesis group. The increased probability of being event-free in the BP group decreases during follow-up.

Competing risks analysis

The competing risks analysis showed a higher event-free survival probability during at 4 years: 94% in the BP group (90.1% at 4 years) compared to 78% in the MP group. During the first years after surgery, a higher death rate and incidence of TE events in the MP group is responsible for this difference (Figure 2). At 8 years, however, the event-free rates of both groups converge (62.7% vs. 57.6% in the BP vs. MP groups in the matched cohort, respectively), mostly due to increased probability of death, and to a lesser extent reoperation, in the BP group (Figure 2).

DISCUSSION

This study reports on valve related outcomes after mechanical and biological aortic root replacement. Both prosthesis types seem to be safe and durable during the first decade after implantation. Mechanical valve replacement is associated with a higher valve related mortality, possibly due to more fatal bleeding events.

Early mortality and postoperative complications did not differ between both groups. This is in line with previously reported data.[6]These results emphasize that both treatment options can be performed safely, and that the choice between biological or mechanical aortic root replacement is a choice between the long-term risks accompanying both types of prostheses, and that preoperative informing of patients should focus on these aspects.

However, freedom from TE, bleeding, reintervention and valve related mortality was in favor of BP. This difference was already present in the unmatched group, but became more evident after propensity score matching. The most important separate endpoint contributing to this difference was the high rate of valve related mortality during follow-up in the MP group.

Freedom from the individual endpoints only differed significantly in terms of all-cause mortality. This difference is remarkable, considering the higher number of concomitant bypass and mitral valve surgery in the BP group. Several previous studies comparing biological versus mechanical AVR found either no difference, or higher survival rates in the mechanical prosthesis group, however, patients in most of these series were younger.[7-13] A possible explanation for this survival benefit in the BP group might be more concealed bleeding events in the sudden unexplained deaths.

Freedom from reinterventions did not differ significantly between both groups in the first postoperative decade. However, the rate of structural deterioration of bioprostheses increases after approximately 10 years in patients aged > 60 yrs. Longer follow-up of this series is needed to assess this event, as increased reoperation rates after biological AVR are expected.[8,12,14]

The incidence of TE- and bleeding events were comparable. Fatal bleeding events not diagnosed as such in the MP group, however, might be disguised as sudden valve related deaths, which leads to the significant difference in the primary outcome of this study. Although we cannot be completely certain, it is less likely that these sudden deaths were cardiac deaths, since there was no sign of progressive (ventricular or valvular) dysfunction in the outpatient clinic. Unfortunately, only few pathology reports were available as autopsy, especially after deaths outside of the hospital, are not performed routinely due to objection from the patients family.

The median age of 65 years in this study population is relatively old for mechanical prostheses. Higher age is associated with more bleeding complications of anticoagulant treatment with vitamin K antagonists[15,16]. In this study, the increased mortality in the MP group was attributable to the high number of sudden, unexplained deaths. These deaths might be explained due to undiagnosed fatal bleeding events due to anticoagulant treatment. The higher bleeding risk in older patients is one of the considerations of the recent guidelines on valvular heart disease, which state that bioprostheses should be considered in older patients.[2,3] Although this is still a level of evidence C recommendation, the results of this study provide data to support this recommendation. In a meta-analysis by Mookhoek et al., the reported linearized occurrence rate of hemorrhage and thromboembolism after the Bentall procedure was estimated at 1.2% per patient-year[17]. A recent study on long-term outcomes after aortic valve and root replacement using the Freestyle prosthesis in a large cohort reports a combined linearized occurrence rate of 1% per patient-year for hemorrhage and thromboembolism (including transient ischemic attacks)[14].

The competing risks analysis showed an increased event-free survival probability in the first 5 years after surgery in the BP group. This difference was mainly attributable to higher mortality rates and increased incidence of TE events during

the first years after surgery in the MP group. At 8 years, however, event-free probabilities were similar between both groups, with increasing death rates in the BP group. Reoperations will further lower event-free rates, probably more so in the BP group than the MP group due to increasing structural degeneration of bioprostheses during longer follow-up.

Limitations

This is a retrospective study comparing 2 treatment options with possible different patient populations, however, propensity score matching provided 2 comparable groups and minimized bias. The follow-up time of the BP might be relatively short, as most SVD of bioprostheses occurs after 10 years, so more reinterventions in the BP group can be expected with longer follow-up. Although both centers act according to the guidelines, local preferences in peri-operative care may have influences outcomes.

CONCLUSIONS

Both mechanical and biological aortic root replacement can be performed safely. Mid-term freedom from TE events, bleeding and reintervention is similar between both types of prostheses. The results of this study show better survival after root replacement using a bioprosthesis compared to a mechanical prosthesis in patients over 60 years of age, with a higher valve related mortality after mechanical valve replacement, probably due to sudden death from hemorrhagic CVA. Event-free survival during the first years of follow-up seems to be higher after biological root replacement.

FUNDING

None

CONFLICT OF INTEREST

None.

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