

**Original
Article**

Durability of Bioprosthetic Valves in Patients on Dialysis

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Purpose: This study focused on clarifying the durability of bioprosthetic valves in current practice.

Methods: A total of 238 consecutive patients who underwent aortic valve replacement at a single institution from 2011 to 2020 were reviewed. We evaluated valve-related outcomes such as structural valve deterioration (SVD), especially in dialysis patients who received bioprosthetic valve.

Results: Among the tissue valves implanted in 212 patients, 5 SVDs were recorded and 3 valves were replaced. All early valve failures occurred in relatively young dialysis patients and were recorded 3 to 5 years after the initial operation. Freedom from SVD at 6 years was 49.9% in patients on dialysis, compared with 100% in non-dialysis patients. Predictors of better survival in dialysis patients were better preoperative functional class and larger prosthetic valve size.

Conclusions: The durability of bioprosthetic valves in the aortic position was suboptimal in dialysis patients. Mechanical valves can be an option for young, healthy dialysis patients with a large aortic valve annulus.

Keywords: bioprosthetic valve, durability, structural valvular deterioration, dialysis

Introduction

The selection of appropriate prosthetic valves for patients on dialysis poses a dilemma as it should be based on multiple conflicting factors such as limited survival rate, risk of future bleeding complications, and the potential risk of accelerated structural valve

deterioration (SVD) progression. Major academic committees have revised statements in their guidelines and ceased listing specific criteria for valve selection in dialysis patients^{1–3)} because there are no significant survival differences related to the type of valve prosthesis.^{4–7)} Due to changes in prosthetic valve selection criteria, bioprosthetic valves are being chosen more often for young dialysis patients. Although SVD progression in dialysis patients is known to be fast, actual durability has not been well documented.

For optimal valve selection, we evaluated the durability of bioprosthetic valves in the aortic position in patients on dialysis.

Materials and Methods

This was a retrospective observational cohort study approved by the ethics committee of Sapporo City General Hospital (R02-059-700). The consent of individual patients was waived by the committee.

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Between April 2010 and November 2020, 238 consecutive patients underwent aortic valve replacement (AVR) at our institution. Cases involving concomitant procedures and emergencies such as acute aortic dissection and infective endocarditis are also included. Bioprosthetic valves were generally chosen for patients over 65 years old. However, for patients on dialysis, bioprosthetic valves were considered for younger patients (primarily those over 60 years old) to prevent future bleeding or thromboembolic complications.

Postoperative problems associated with prosthetic valves such as SVD and major bleeding and thromboembolic complications were investigated retrospectively. We also reviewed preoperative and operative factors potentially affecting SVD progression. Additionally, preoperative abdominal aortic calcification (AAC) scores were calculated to evaluate the effect of systemic calcium metabolism on SVD progression. As previously described, abdominal aorta was divided into 4 segments and calcific deposits were graded on a scale of 0–3 at anterior and posterior aortic walls in each segment.⁸⁾ We used preoperative computed tomography scan to calculate the AAC score in patients who did not have lateral lumbar X-ray.

Anticoagulation with warfarin sodium was performed in all patients for the first three months after bioprosthetic AVR.

Valve-related complications were defined according to the guidelines for reporting mortality and morbidity after cardiac valve interventions. More than moderate prosthesis–patient mismatch (PPM) was recorded as PPM.^{9,10)} Prosthetic valve function was assessed with periodic echocardiographic surveillance, and substantially increased stenosis over time in the mean transprosthesis pressure gradient of more than 40 mmHg or an indexed aortic valve area of less than 0.80 cm²/m², or the development of severe regurgitation is defined as SVD.¹¹⁾

Midterm survival was analyzed in all included patients. Further investigation was focused on patients who received a bioprosthetic valve to identify predicting factor of future SVD. Survival predictors in hemodialysis (HD) patients with bioprosthetic valve were investigated in multivariate analysis.

To ensure thorough collection of follow-up data, we reviewed all medical charts and called patients, members of their families, and/or dialysis clinics. Continuous variables were presented as mean \pm standard deviation and were compared using the two-sample Student's t-test. Categorical variables were expressed as numbers and

percentages and compared using the chi-squared test. The time-related events were evaluated according to the Kaplan–Meier method and compared using the log-rank test. Predictors of mortality were identified in univariate analysis using a P-value cutoff of 0.1 and then entered into a multivariate analysis. Statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA).

Results

Among the 238 patients enrolled in this study, 68 patients were on chronic HD preoperatively. Of the 68 dialysis patients, 60 patients (88.2%) received bioprosthetic valves based on patient age (mean age 71 years, 53–85 years) and surgeon discretion. The remaining 8 patients (mean age 59 years) received mechanical prostheses. Of the 170 non-dialysis patients during the same period, bioprosthetic valves were implanted in 152 patients (89.4%) (**Fig. 1**).

Although there was no difference between the groups in terms of implanted valve type, the average size of the implanted valve was smaller in the mechanical valve group than in the bioprosthetic valve group ($P = 0.03$). Twenty-two patients were lost to follow-up, and the follow-up rate was 90.8%. The average follow-up period was 3.6 years. In patients who received tissue valve AVR, the mean follow-up period was 2.7 years for the dialysis patient group and 4.0 years for the non-dialysis patient group ($P < 0.01$). More thromboembolic events were recorded in dialysis patients during the follow-up period ($P = 0.02$). Meanwhile, the rate of major bleeding events was not statistically different between the groups ($P = 0.28$). In the mechanical valve group, no major embolic or bleeding events were recorded. The patient characteristics, operative details, and the follow-up data for each patient group are listed in **Tables 1** and **2**.

The overall survival rate of 68 dialysis patients at 6 years was 32.4%, which is significantly worse than that for non-dialysis patients ($P < 0.01$; **Fig. 2A**). In addition, there was no difference in the survival rate for each group regardless of the type of prosthetic valve received (**Fig. 2B**).

In hemodialysis patients who received bioprosthetic valve, preoperative New York Heart Association (NYHA) functional score and prosthetic valve size were identified as independent survival predictors by multivariate analysis (**Table 3**). Other factors such as young age (**Fig. 3A**), high AAC score (a median score

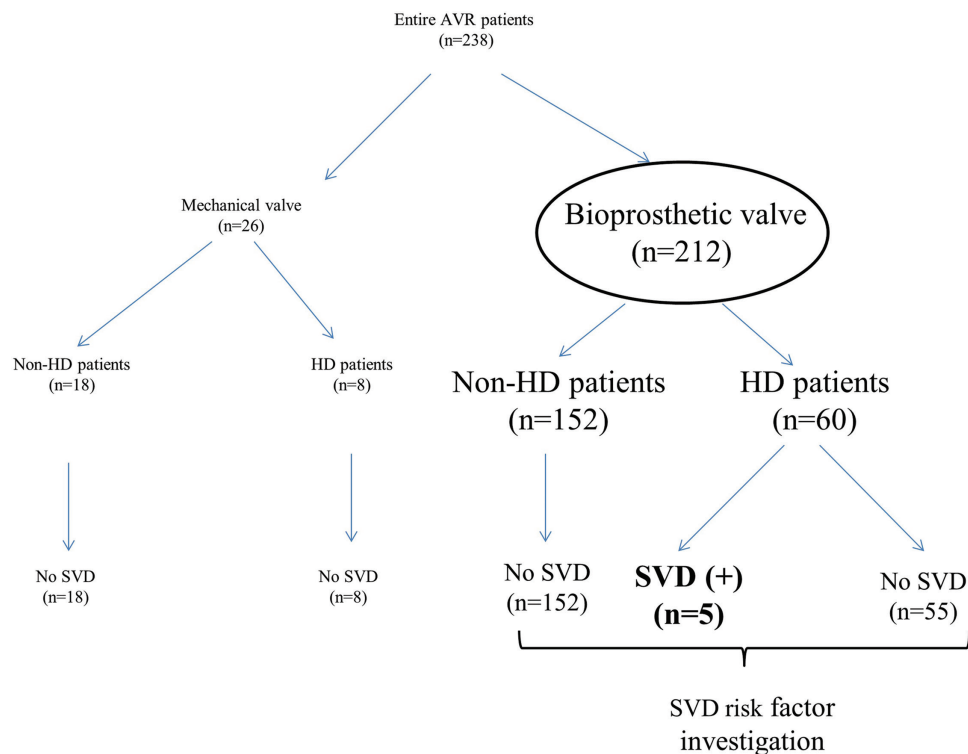


Fig. 1 Enrolled patients in this study. AVR: aortic valve replacement; HD: hemodialysis; SVD: structural valvular deterioration

Table 1 Patients' characteristics in this study

	Bioprosthetic valve			Mechanical valve		
	HD patients (n = 60)	Non-HD patients (n = 152)	P-Value	HD patients (n = 8)	Non-HD patients (n = 18)	P-Value
Age, years	71 (53–85)	75 (65–86)	<0.01 ^a	59 (33–68)	59 (29–71)	0.55
Male (%)	38 (63)	81 (53)	0.18	4 (50)	8 (44)	0.56
BSA (m ²)	1.53 ± 0.16	1.58 ± 0.17	0.87	1.55 ± 0.21	1.60 ± 0.23	0.60
Smoking history (%)	35 (58)	71 (47)	0.43	2 (25)	6 (33)	0.52
Hypertension (%)	46 (77)	123 (81)	0.72	7 (88)	11 (61)	0.19
Diabetes mellitus (%)	18 (30)	40 (26)	0.61	2 (25)	3 (17)	0.50
Hypercholesterolemia (%)	17 (28)	68 (45)	0.02 ^a	1 (13)	6 (33)	0.51
History of CVD (%)	13 (22)	20 (13.2)	0.40	1 (13)	5 (28)	0.38
History of CAD (%)	20 (33)	38 (25)	0.53	0 (0)	1 (6)	0.22
Ejection fraction (%)	50	54	0.21	62	62	0.20
NYHA class ≥3 (%)	14 (23)	26 (17)	0.32	1 (13)	6 (33)	0.27
Preop Ca (mg/dl)	9.1 ± 0.8	9.3 ± 0.7	0.07	9.1 ± 0.7	9.3 ± 0.2	<0.01 ^a
Preop P (mg/dl)	4.5 ± 1.1	3.4 ± 0.5	<0.01 ^a	5.0 ± 2.0	3.2 ± 0.6	<0.01 ^a
Oral vitamin D (%)	26 (43)	8 (5)	<0.01 ^a	4 (50)	0 (0)	<0.01 ^a
AAC score	13.1 ± 6.5	6.5 ± 2.9	<0.01 ^a	11.6 ± 8.2	0.7 ± 0.9	<0.01 ^a

Values are mean ± SD or n (%) unless otherwise specified.

^aStatistically significant (P <0.05)

HD: hemodialysis; BSA: body surface area; CVD: cerebrovascular disease; CAD: cardiovascular disease; NYHA: New York Heart Association; Preop Ca: preoperative serum calcium level; Preop P: preoperative serum phosphate level; AAC: abdominal aorta calcification; SD: standard deviation

Table 2 Operative and postoperative data

	Bioprosthetic valve			Mechanical valve		
	HD patients (n = 60)	Non-HD patients (n = 152)	P-Value	HD patients (n = 8)	Non-HD patients (n = 18)	P-Value
Bicuspid valve ^b (%)	6 (10)	25 (16)	0.16	2 (25)	5 (28)	0.64
Isolated AVR (%)	26 (43)	68 (45)	0.87	2 (25)	7 (39)	0.41
Concomitant procedure						
CABG (%)	14 (23)	26 (17)	0.32	3 (38)	0 (0)	<0.01 ^a
Valve (%)	14 (23)	26 (17)	0.30	1 (13)	7 (39)	0.07
Mitral (%)	8 (13)	20 (13)	1.00	1 (13)	7 (39)	0.07
Tricuspid (%)	9 (15)	12 (8)	0.41	1 (13)	3 (17)	0.45
Aorta (%)	5 (8)	24 (16)	0.19	2 (25)	2 (11)	0.26
Emergency (%)	5 (8)	10 (7)	0.76	0 (0)	3 (17)	0.31
Prosthetic valve type						
CEP ^d (%)	21 (35)	56 (37)	0.83	–	–	
Magna ^e (%)	23 (38)	61 (40)	0.87	–	–	
Resilia (%)	8 (13)	16 (11)	0.74	–	–	
Trifecta (%)	2 (3)	3 (2)	0.61	–	–	
Mosaic (%)	5 (8)	15 (10)	0.75	–	–	
Mitroflow (%)	1 (2)	0 (0)	0.44	–	–	
Crown (%)	0 (0)	1 (1)	0.52	–	–	
SJM (%)	–	–	–	5 (63)	14 (78)	0.71
ATS (%)	–	–	–	0 (0)	1 (6)	0.55
On-X (%)	–	–	–	3 (38)	3 (17)	0.16
Prosthetic valve size (mm)						
<19	16 (27)	26 (17)	0.22	6 (75)	11 (61)	0.84
21	21 (35)	63 (41)	0.71	2 (25)	4 (22)	0.75
23	20 (33)	46 (30)	0.75	0	2 (11)	0.23
>25	3 (5)	17 (11)	0.46	0	1 (6)	0.12
Average prosthetic valve size (mm)	21 ± 2	22 ± 2	0.19	19.3	20.2	0.08
		21 ± 2	0.03 ^a		20 ± 2	0.03 ^a
CPB time (min)	241.2	226.9	0.77	278.6	276.4	0.83
Cross-clamp time (min)	159.7	151.0	0.85	185.3	187.7	0.49
Postop PPM ^e (%)	14 (23)	41 (27)	0.72	1 (13)	2 (11)	0.76
Hospital death (%)	2 (3)	2 (1)	0.13	1 (13)	1 (6)	0.53
Average follow-up year	2.7 (0–7.9)	4.0 (0–10.0)	<0.01 ^a	3.1 (0–9.7)	4.1 (0–9.9)	0.02 ^a
Thromboembolic events	4	3	<0.02 ^a	0	0	–
Major bleeding events	2	2	0.28	0	0	–
Deep sternal wound infection	1	0	0.63	0	0	–

Values are mean ± SD or n (%) unless otherwise specified.

^aStatistically significant (P < 0.05)

^bIncluding monocuspid aortic valve

^cAll recorded PPM were moderate (0.65 ≤ EOAi ≤ 0.85).

^dCarpentier-Edwards Perimount pericardial aortic bioprosthesis

^eCarpentier-Edwards Perimount Magna Ease pericardial aortic bioprosthesis

HD: hemodialysis; AVR: aortic valve replacement; CABG: coronary artery bypass grafting; SJM: St. Jude Medical; CPB: cardiopulmonary bypass; PPM: patient-prosthesis mismatch; SD: standard deviation; Postop: postoperative; EOAi: Effective Orifice Area index

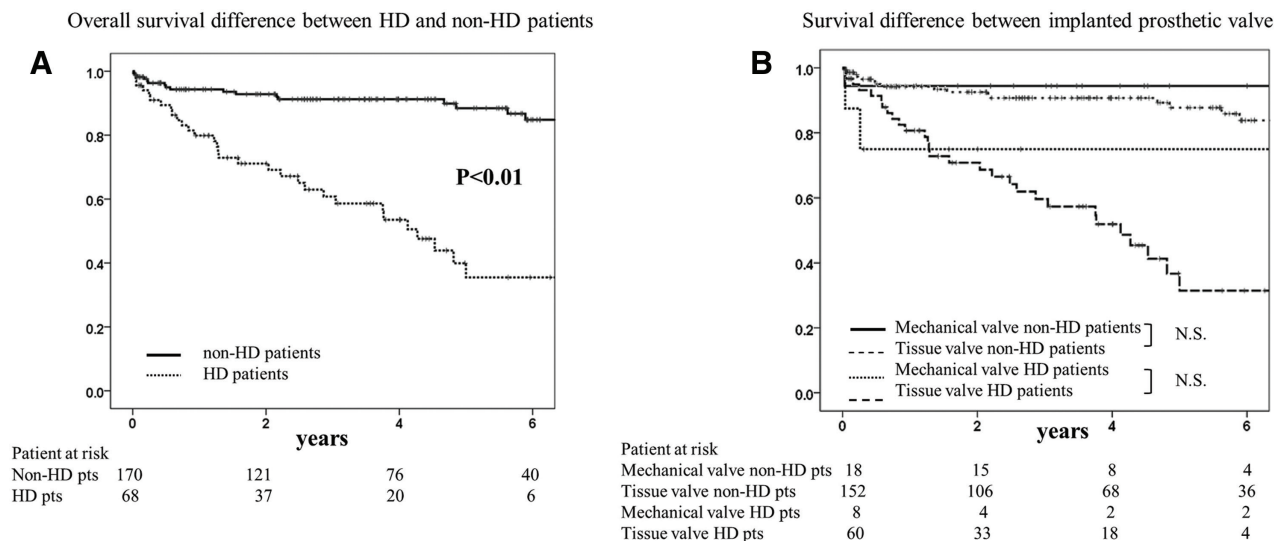


Fig. 2 Survival curve comparison of overall patients. (A) Overall survival comparison between HD and non-HD patients. (B) Survival curve comparison of mechanical and bioprosthetic valve in HD and non-HD patients. HD: hemodialysis; NS: not significant

Table 3 Survival predictors in HD patients (n = 60)

Factors	Univariate analysis	Multivariate analysis	
	P-Value	HR (95% CI)	P-Value
AAC score (>14)	0.072	4.40 (0.98–19.8)	0.054
NYHA class (≥3)	0.064	2.96 (1.12–7.84)	0.029 ^a
Valve size (≥23 mm)	0.017 ^a	0.35 (0.14–0.87)	0.023 ^a
Oral vitamin D3	0.078	0.57 (0.25–1.33)	0.196

^aStatistically significant (P <0.05)

HD: hemodialysis; AAC: abdominal aorta calcification; NYHA: New York Heart Association; HR: hazard ratio; CI: confidence interval

of 14 was used as the cut-off value), diabetes mellitus, and type of bioprosthetic valve were not related to the survival difference. Patients meeting two predictors (i.e., NYHA class ≤2 and prosthetic valve ≥23 mm) showed better survival than other dialysis patients (Fig. 3B).

During the follow-up in the dialysis patient group, five SVDs were recorded between three and five years after the initial AVR. Four out of five SVD cases were in relatively young (i.e., younger than 65 years) patients, and re-AVR operations using mechanical valves were conducted in three cases without major surgical complications. Meanwhile, SVD was not recorded in the non-dialysis group during the follow-up period. Two

re-AVRs were conducted in the non-dialysis group for prosthetic valve endocarditis. Freedom from SVD was 49.9% in the dialysis group and 100% in the non-dialysis group at six years post surgery (P <0.01; Fig. 4A). Among the 60 dialysis patients with a bioprosthetic valve, 11 patients were younger than 65 years. Freedom from SVD at six years was 20.8% in the young dialysis group and 66.7% in the older dialysis group (P <0.01; Fig. 4B). Meanwhile, neither SVD nor reoperation was recorded in mechanical valve patients.

Discussion

In accordance with the current guidelines, bioprosthetic valves were chosen for the majority of AVR cases in our study, and the rate was similar between the non-dialysis and dialysis groups (89.6% and 87.4%, respectively). Among the 60 dialysis patients, five bioprosthetic valves exhibited accelerated progression of SVD within five years of implantation. While freedom from SVD at six years in dialysis patients was 49.9%, it was only 20.8% in the young age subgroup (Fig. 4C). Since the follow-up period in this group was limited, more SVDs would likely have been recorded in a longer follow-up period. As the cost of transcatheter aortic valve implantation for dialysis patients is not generally covered by health insurance in Japan, the percentage of dialysis patients requiring surgical AVR is increasing. In the case of postoperative SVD, redo replacement is the only surgical option in the current practice, which is often

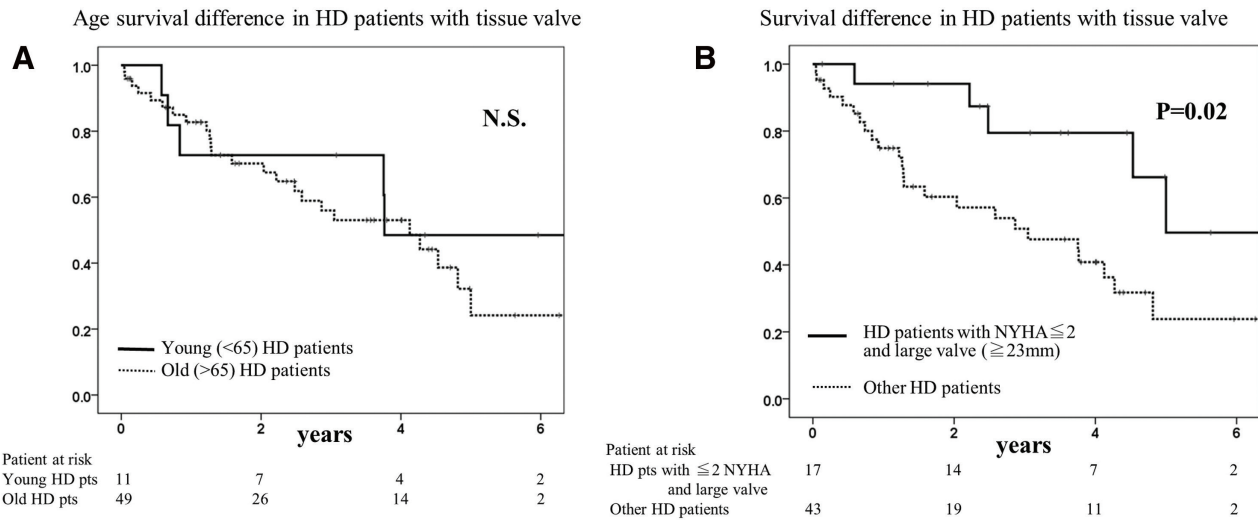


Fig. 3 Survival curve comparison in HD patients who received bioprosthetic valve. **(A)** Survival comparison between young (≤ 65 years) and old (> 65 years) HD patients. **(B)** Survival difference in HD patients with preoperative NYHA class ≤ 2 and large (≥ 23 mm) bioprosthetic valve. Tissue valve: bioprosthetic valve; HD: hemodialysis; NYHA: New York Heart Association; NS: not significant

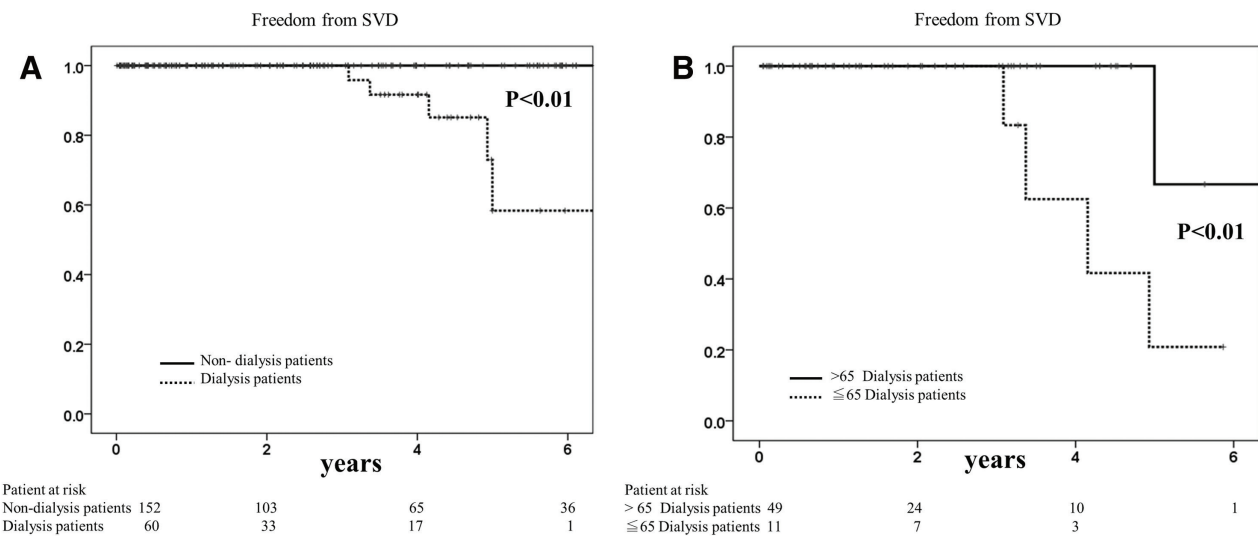


Fig. 4 Comparison of bioprosthetic valve durability between non-dialysis and dialysis patients. **(A)** SVD comparison between HD and non-HD patients. **(B)** SVD comparison between young (≤ 65 years) and old (> 65 years) HD patients. SVD: structural valve deterioration; HD: hemodialysis

difficult to apply for high-risk patients. With the growing number of dialysis patients around the world and improvements being made in their management, further data accumulation regarding these issues is required, as is the development of a new standard for optimal choice of prosthetic valves in patients on dialysis.

End-stage renal disease is associated with bone metabolism dysregulation and is known to lead to a procalcifying phenotype within native vessels and heart

valves.^{8,12-15}) Therefore, we hypothesized that a high AAC score can be a predictor of rapid SVD progression because high AAC is a strong predictor of cardiovascular events in patients with renal disease.⁸) Several other factors such as diabetes, smoking, longer dialysis vintage, hyperparathyroidism, and high circulating calcium and phosphate have also been proposed as contributors to the progression of calcification in patients on dialysis.¹³⁻¹⁵) Although we could not

confirm such a relationship in the investigated factors, the majority of the accelerated SVDs were recorded in young (≤ 65) dialysis patients. As mechanical stress from high exercise tolerance and discrete immunological reaction and active calcium metabolism have been proposed to explain the process of early calcification of bioprosthetic valves in young populations,^{16,17)} we believe that this deterioration process was intensified by procalcifying exposure in dialysis patients. Therefore, we believe that SVD in younger dialysis patients is more common not only because they are supposed to live longer but also because their condition deteriorates at a faster speed.

Given the high incidence of bleeding complications in dialysis patients, bioprostheses appear to be a reasonable choice. However, as determined in our study, there are no differences in bleeding events according to the type of prosthesis in young patients.^{16,18,19)} In addition, several studies have documented that the type of prosthesis does not play a significant contributing role in long-term survival.⁴⁻⁷⁾ If that is indeed the case, the type of prosthesis used for young patients should be based on durability and the patient's preference on anticoagulation. In our study, poor preoperative functional class and small prosthetic valve size were identified as risk predictors for the survival of dialysis patients. Although overall dialysis patient survival following valve replacement is limited and not age dependent, our findings also support another report stating that young, healthy patients without NYHA III or IV symptoms survive long enough to justify placement of a mechanical valve.⁵⁾

Limitations

This study is retrospective, non-propensity matched, and not randomized, thereby allowing for selection bias. Other limitations are small sample size and limited numbers of SVD cases, which prevent us from conducting multivariate analysis to discover independent SVD risk factors. Besides, longer follow-up period is required to compare the prosthetic valve durability.

Conclusion

Mechanical valves is still a good option in young (<65 years) dialysis patients because future SVD risk of bioprosthetic valve is high.

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Disclosure Statement

The authors declare no conflict of interest.

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