ORIGINAL

Mid-term hemodynamic performance of INSPIRIS RESILIA aortic bioprosthesis for severe aortic stenosis

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Abstract : We investigated mid-term outcomes after aortic valve replacement (AVR) with INSPIRIS RESILIA (IR) aortic bioprosthesis for severe aortic stenosis (AS). A total of 60 patients with a mean age of 73.2±6.2 years underwent AVR with IR bioprosthesis for severe AS. We prospectively followed up on 59 survivors and collected transthoracic echocardiographic data at 3-6 months, and annually thereafter. The mean follow-up period was 3.0±1.5 years, with a 100% follow-up rate. The preoperative mean pressure gradient (PG) and the effective orifice area were 52.5±18.2 mmHg, and 0.73±0.23 cm², respectively, which improved to 10.3±3.5 mmHg (P < 0.001), and 1.85±0.48 cm² (P < 0.001) at discharge. The mean PG at 5 years was 10.2±2.7 mmHg, which was similar to one at discharge (P = 0.307). Left ventricular mass index decreased from 119.6±33.1 g/m² before AVR to 104.0±32.5 g/m² (P < 0.001) at discharge, and further decreased to 78.5±22.2 g/m² at 5 years compared with postoperative one (P = 0.011). Survival rate at 5 years was 97.4±2.6%. Freedom from valve-related events at 5 years was 91.4±5.5%. Incidental cerebral infarction (n = 2) and heart failure (n = 1) were noted. IR bioprosthesis demonstrated a stable hemodynamic performance and few valve-related events. J. Med. Invest. 72 : 390-395, August, 2025

Keywords **:** *hemodynamic performance, aortic bioprosthesis, INSPIRIS RESILIA valve, severe aortic stenosis*

INTRODUCTION

The INSPIRIS RESILIA (IR) aortic bioprosthesis (Edwards Lifesciences LLC, Irvine, USA) introduced in Japan in late 2018 is based on the Carpentier-Edwards Perimount Magna Ease valve (Edwards Lifesciences LLC, Irvine, USA) and combines RESILIA tissue with novel tissue preservation technology including functional capping, glycerolization and a new terminal ethylene oxide sterilization method. The animal models demonstrated anticalcification characteristics on the valves and hemodynamic performance through advancement in preservation technology (1, 2). The Carpentier-Edwards Perimount valve has been widely used with an excellent low structural valve deterioration (SVD) rate at 20 years (3). The IR bioprosthesis was created with the same platform as the Carpentier-Edwards Perimount Magna Ease valve, thus the valve is expected to last a long time.

The COMMENCE trial is a prospective, non-randomized, multi-center clinical evaluation of IR aortic bioprosthesis in 689 patients who require surgical replacement of the diseased native aortic valve across 27 sites in the United States and Europe (4). Five-year data following aortic valve replacement (AVR) with IR bioprosthesis were published. The effective orifice area (EOA) was 1.6±0.5 cm², the mean pressure gradient (PG) was 11.5±6.0 mmHg, and > 96.0% of patients had less than trace paravalvular and transvalvular regurgitation at 5 years (5). The EOA and mean PG remained clinically stable at 7 years (6). Furthermore, freedom from SVD at 5 and 7 years was 100% and 99.3%, respectively (5, 6). Clinical outcomes were encouraging in foreign countries, but whether or not these results fit to Japanese cohort with small body surface area (BSA). We previously reported hemodynamic performance and valve safety in a Japanese cohort with severe aortic stenosis (AS). The mean PG was 11.2±3.3 mmHg, and the left ventricular mass index (LVMI) was decreased at 2 years. SVD was not observed with a mean follow-up duration of 19 months. The use of a 19-mm IR bioprosthesis caused a favorable hemodynamic performance as well (7). Herein, we have extended the follow-up duration to evaluate mid-term hemodynamic performance and valve safety.

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MATERIALS AND METHODS

The Institutional Review Board at Hyogo Prefectural Amagasaki General Medical Center approved this study on 24 March 2023 (No.4-202).

This study included 60 patients who underwent AVR with IR bioprosthesis for severe AS at our hospital from November 1, 2018, to June 30, 2023. Compared with our previous study, we have increased the number of patients included in this study by extending the observational period. The choice of IR bioprosthesis and its size was at the discretion of surgeons' preference. The patients were enrolled while undergoing concurrent procedures including coronary bypass grafting, aortic replacement, and other valvular surgery. We excluded patients with aortic root replacement, pure aortic regurgitation, active infective endocarditis, or a history of prior valvular surgery. The surgical procedure was previously described (7). Patients who underwent AVR received warfarin for 6 months postoperatively. Anticoagulation was discontinued if patients did not have atrial fibrillation.

The mean age was 73.2±6.2 years old, and the participants included 38 females. BSA was 1.57±0.19 m². One patient on dobutamine support was at NYHA functional class IV preoperatively. Preoperative patients' characteristics is summarized in Table 1.

Definition of valve-related events was based on the guidelines for reporting mortality and morbidity after cardiac valve interventions (8).

Experienced sonographers performed follow-up transthoracic echocardiography (TTE) at 3-6 months, and annually thereafter to assess the hemodynamic performance of IR aortic bioprosthesis. The 3-6-month, 1-, 2-, 3-, 4-, and 5-year follow-up data were obtained in 40, 48, 47, 28, 20 and 13 patients, respectively.

The mean follow-up time was 3.0±1.5 years (maximum 5.6 years), with a 100% follow-up rate. Data collection closed on 30 June, 2024.

Statistical analysis

All statistical analyses were conducted with StatView version 5.0 software (SAS Institute, Cary, NC, USA). Categorical variables were analyzed using the χ^2 test and are expressed as percentages. Continuous variables were analyzed using Wilcoxon signed-rank test and are expressed as the mean ± standard deviation (SD). The Kaplan–Meier method was applied to calculate estimates of survival and freedom from valve-related events. P value less than 0.05 indicates statistically significant difference.

RESULTS

Early outcomes

The valve size implanted was 19 mm (n = 12), 21 mm (n = 26), 23 mm (n = 12), 25 mm (n = 9), and 27 mm (n = 1) (Table 2).

The 30-day mortality was zero, but a 71-year-old patient on hemodialysis receiving preoperative dobutamine support died in the hospital because of refractory heart failure. Preoperative left ventricular function was severely reduced by 24% and none of the major complications occurred (7).

Additionally, valve explant, thromboembolism, valve thrombosis, significant paravalvular leakage, and prosthetic valve endocarditis were not observed as clinical occurrences during hospitalization.

Table 1. Preoperative patients' profile (n = 60)

Variables	Mean±SD or number (%)
Age, years	73.2±6.2
Female	38 (63.3)
BSA, m^2	1.57±0.19
BMI, kg/m^2	24.3±4.0
Hypertension	43 (71.7)
Hyperlipidemia	29 (48.3)
Diabetes mellitus	26 (43.3)
COPD	1 (0)
PAD	11 (18.3)
Stroke	11 (18.3)
CAD	10 (16.7)
Atrial fibrillation	11 (18.3)
Creatinine>1.5mg/dL/No HD	3 (5.0)
HD	5 (8.3)
Liver cirrhosis	0 (0)
NYHA	
I/II	50 (83.3)
III/IV	10 (16.7)

BMI, body mass index ; BSA, body surface area ; CAD, coronary artery disease ; COPD, chronic obstructive pulmonary disease ; HD, hemodialysis ; NYHA, New York Heart Association ; PAD, peripheral artery disease

Hemodynamic performance of IR bioprosthesis

Preoperative mean PG, peak velocity, and EOA were 52.5±18.2 mmHg, 4.7±0.94 m/sec, and EOA 0.73±0.23 cm^2, respectively. They improved at 10.3±3.5 mmHg ($p < 0.001$), 2.2±0.3 m/sec ($p < 0.001$) and 1.85±0.48 cm^2 ($p < 0.001$) at discharge, respectively. The peak velocity at 5 years was 2.3±0.3 m/sec. The peak velocity remained stable throughout the follow-up period (P = 0.529) (Fig. 1A). Consistently, the mean PG at 5 years was 10.2±2.7 mmHg, which was not statistically significant compared with the mean PG at discharge (P = 0.307) (Fig. 1B).

The EOA increased with a statistically significant difference following AVR. The EOA at 5 years was 1.60±0.40 cm^2. The EOA remained stable throughout 5 years (P = 0.213) (Fig. 1C).

LVMI decreased from 119.6±33.1 g/m^2 preoperatively to 104.0±32.5 g/m^2 ($P < 0.001$) at discharge. It dropped to 78.5±22.2 g/m^2 at 5 years, which significantly reduced compared with LVMI at discharge (P = 0.011) (Fig. 1D).

Transvalvular regurgitation of IR bioprosthesis at 5 years was absent (n = 9) and only trace (n = 4). Transvalvular regurgitation more than mild was not noted.

Mean PG at 4 and 5 years according to the size of implanted IR valve was shown (Fig. 2A and B).

Table 2. Operative details and outcomes (n = 60)

Variables	Mean±SD or number (%)
Valve size, mm	
19	12 (20.0)
21	26 (43.3)
23	12 (20.0)
25	9 (15.0)
27	1 (1.7)
Concomitant procedures	
Coronary bypass	10 (16.7)
LAA closure	12 (20.0)
Aortic repair	3 (5.0)
Surgical approach	
Full sternotomy	46 (76.7)
Partial sternotomy	10 (16.7)
MICS	4 (6.7)
Cardiopulmonary bypass, minutes	165.4±45.5
Cross clamp, minutes	117.7±34.9
Early outcomes	
30-day death	0 (0)
Hospital death	1 (1.7)
Ventilator>72 hours	1 (1.7)
Chest reopening for bleeding	1 (1.7)
Cerebral hemorrhage	0 (0)
Thromboembolism	0 (0)
Valve thrombosis	0 (0)
Mediastinitis	0 (0)
Prosthetic valve endocarditis	0 (0)
PPM implantation	0 (0)
Afib requiring cardioversion	4 (6.7)
Hemodialysis	0 (0)

Afib, atrial fibrillation ; LAA, left atrial appendage ; MICS, minimally invasive cardiac surgery ; PPM, permanent pacemaker

Hemodynamic performance of 19-mm IR bioprosthesis

The pre- and postoperative mean PGs in a 19-mm valve were 56.3±14.2 mmHg and 12.5±2.6 mmHg (P = 0.002), respectively. The peak velocity decreased, and remained stable during the follow-up period (Fig. 3A).

The mean PG at 5 years was 12.0±2.4 mmHg, which remained unchanged during the follow-up period (P = 0.402) (Fig. 3B).

The pre- and postoperative EOA in the 19-mm group was 0.68±0.18 cm^2 and 1.28±0.17 cm^2, respectively (P = 0.005). EOA at 5 years was 1.22±0.13 cm^2, which remained stable since AVR (P = 0.893) (Fig. 3C).

Preoperative LVMI with a 19-mm valve was 114.7±22.5 g/m^2, and 95.9±20.0 g/m^2 at discharge (P = 0.019). LVMI gradually dropped to 75.1±26.2 g/m^2 at 5 years despite statistical insignificance compared with one at discharge (P = 0.116) (Fig. 3D).

Mid-term outcomes

Survival rates at 5 years were 97.4%±2.6% (Fig. 4A). As previously reported, a 68-year-old female patient on hemodialysis died of unknown etiology 2.1 years after AVR (7).

Freedom from valve-related events at 5 years were 91.4%±5.5% (Fig. 4B). Prosthetic valve endocarditis, major paravalvular leakage, and SVD were not observed. We report three cases of valve-related events.

The first case was a 78-year-old female who developed heart failure 1.3 years after AVR due to constrictive pericarditis. She underwent pericardiectomy and recurrent heart failure did not develop. The second case was a 70-year-old female who incidentally found to have an ischemic stroke 3.9 years after AVR. The patient was neurologically intact. The third case was a 57-year-old man who complained about lightheadedness. Magnetic resonance imaging revealed an ischemic stroke approximately three months following AVR. He was on anticoagulation prior to the chief complain, and other symptoms were not noted. Thus, new medication was not added.

DISCUSSION

The present progress report of IR bioprosthesis confirmed three main results. First, hemodynamic performance remained stable throughout mid-term period. Even a 19-mm bioprosthesis generated favorable hemodynamic performance in Japanese cohort. Second, LVMI has gradually decreased throughout the follow-up period. Third, the mid-term follow-up period demonstrated no case of SVD, major paravalvular leakage, or prosthetic valve infection.

The mean PG of a 19-mm bioprosthesis was 12.5±2.6 mmHg at discharge, and 12.0±2.4 mmHg at 5 years (P = 0.402). These are exceptionally stable and PG was low throughout the 5 years. The 5-year follow-up results from the COMMNECE trial demonstrated a > 20 mmHg mean PG of a 19-mm bioprosthesis at 4 years which had gradually increased since AVR (5). Considering the large body size of subjects in the COMMENCE trial, only 3.2% of participants received a 19-mm bioprosthesis. Another study that included 488 patients who received IR bioprosthesis revealed that only 2% of patients had a 19-mm bioprosthesis (9). In our study, a 19-mm bioprosthesis was implanted in 12 patients (20.0%). The use of a 19-mm bioprosthesis demonstrated a large discrepancy among studies. A 19-mm size would be beneficial to achieve the low mean PG after AVR for the Japanese cohort (7.10). Furthermore, LVMI following AVR with a 19-mm IR bioprosthesis at 5 years was lower than that at discharge despite being statistically insignificant (95.9 g/m^2 vs 75.1 g/m^2, P = 0.116). One study consisting of a Japanese cohort reported that the mean PG in a 19-mm IR bioprosthesis at discharge was 13.3±5.1 mmHg, which was close to our result (10). Thus, we speculated that LVMI would decrease during the follow-up period as our report described in this study, although the authors did not mention LVMI limited to a 19-mm IR bioprosthesis (10).

Figure 1 indicates the stable mean PG and EOA throughout the mid-term period. These results were the same as described in a 5-year follow-up in the COMMENCE trial. The mean PG was between 10 mmHg and 12 mmHg except the mean PG in a 19-mm bioprosthesis (5). Conversely, the mean PG slightly

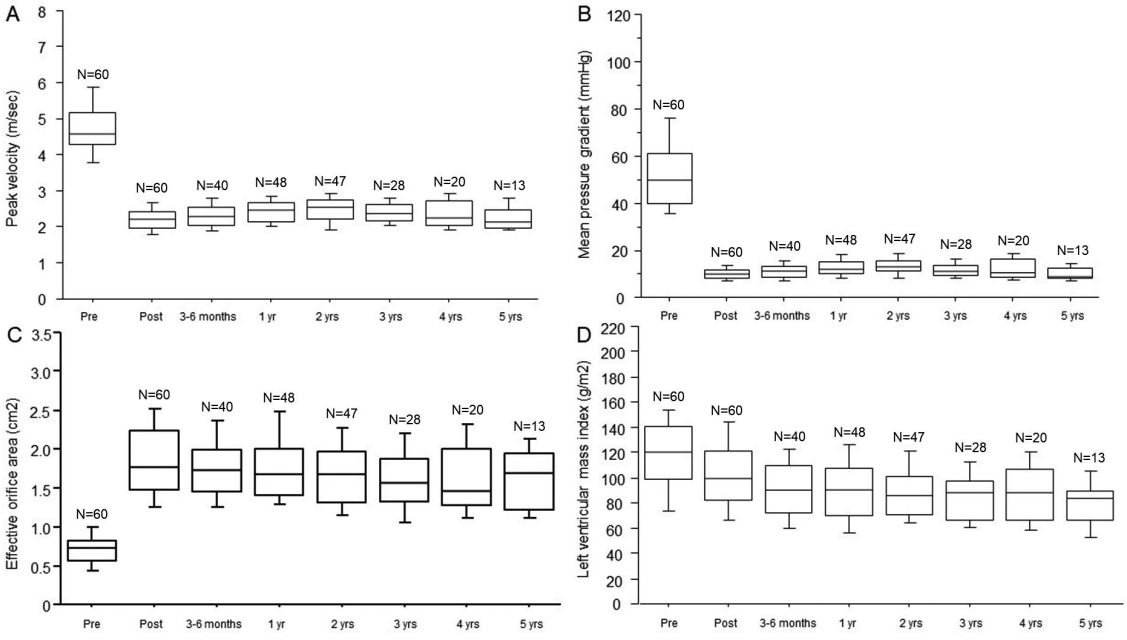

Figure 1. Hemodynamic performance of The INSPIRIS RESILIA aortic bioprosthesis is summarized. The peak velocity (A), mean pressure gradient (B), effective orifice area (C) and left ventricular mass index (D) throughout follow-up period are described.

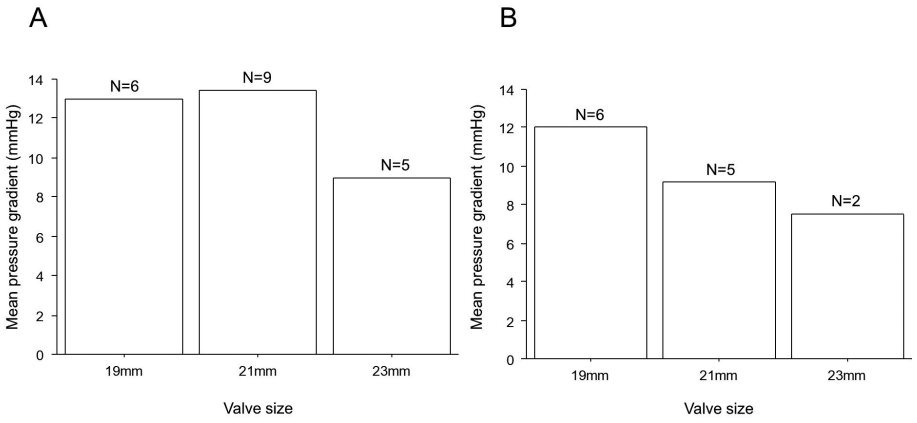

Figure 2. Mean pressure gradient at 4 (A) and 5 years (B) according to size of implanted bioprosthesis is shown.

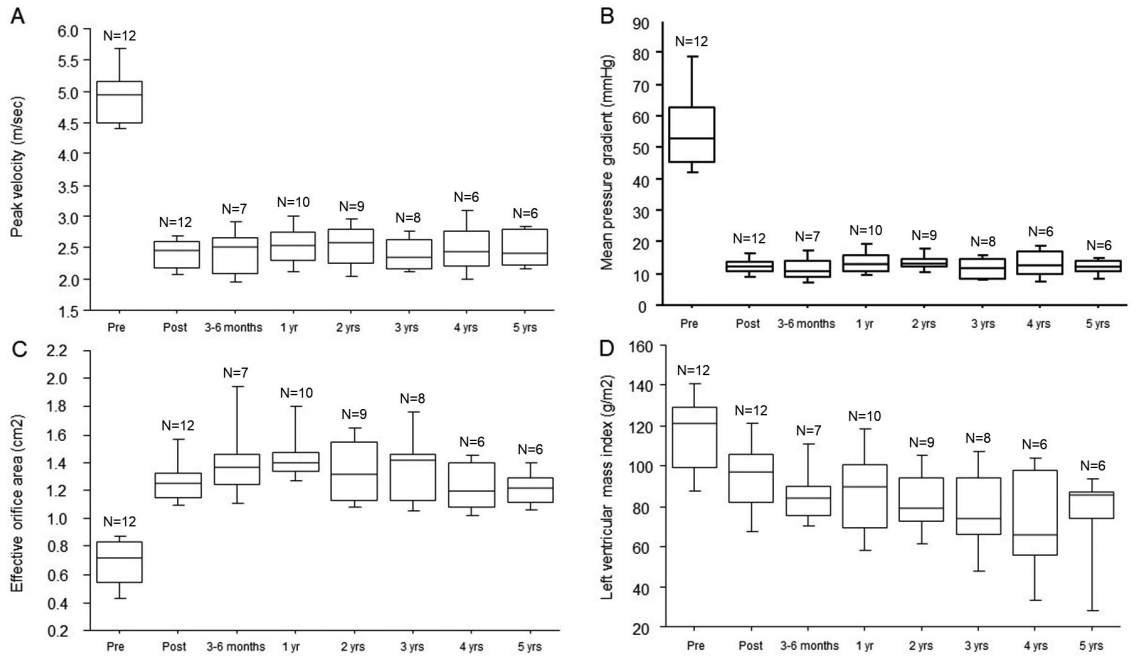

Figure 3. Hemodynamic performance of a 19-mm INSPIRIS RESILIA aortic bioprosthesis is summarized. The peak velocity (A), mean pressure gradient (B), effective orifice area (C) and left ventricular mass index (D) throughout follow-up period are described.

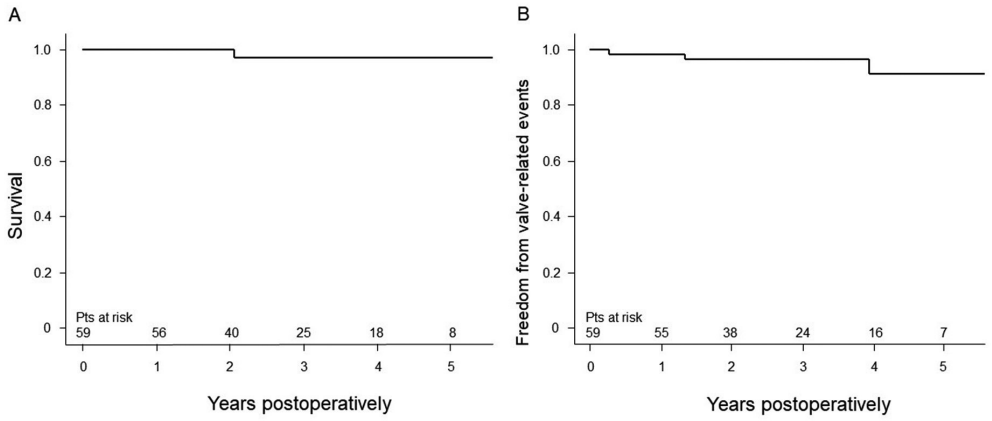

Figure 4. Survival (A) and freedom from valve-related events (B) are demonstrated.

increased during the 2-year follow-up (9). The mean PG at 2 years was 11.1±0.5 mmHg in the study. The PG remains favorable. Therefore, further follow-up is required to investigate changes in PG after 2 years.

We have reported subvalvular pannus formation to have possibly caused SVD of the St. Jude Epic bioprosthesis (St. Jude Medical Inc., St Paul, MN, USA) (11). In the case, the opening of the valve leaflets worked. An increased mean PG coincided with a decreased EOA after 5 years. IR bioprosthesis has the RESILIA tissue, which is thought to be protective against calcification, but there is nothing to prevent subvalvular pannus formation. A prospective follow-up is mandatory to detect the changes in the mean PG and EOA in IR bioprosthesis because the relationship between an increased mean PG and a decreased EOA may be associated with SVD (11).

The COMMENCE trial did not mention LVMI, but we investigated LVMI on TTE because LV hypertrophy was associated with survival after AVR (11, 12). The results revealed that LVMI in the entire cohort had gradually decreased during the follow-up period with statistically significant differences (Fig. 1D). Maeda, *et al*. demonstrated a consistent decreasing trend of LVMI after AVR with IR bioprosthesis in the Japanese cohort (10). This trend observed in our study was similar to that observed in a study, revealing the subsequently decreased LVMI at 1 year after AVR with other bioprosthesis during the next 4-year period (13).

The longest follow-up study revealed that 7-year freedom from all-cause mortality and SVD was 85.4% and 99.3%, respectively (6). Two patients developed SVD within 5-7 years. Both were symptomatic and demonstrated increased mean PG of up to 27 mmHg and decreased EOA of 0.62 and 0.87 cm^2. One patient underwent transcatheter valve-in-valve implantation, and the other received a mechanical aortic valve as a redo surgery. Our series demonstrated no SVD possibly due to the short follow-up period. Follow-up after 5 years would be of importance to suspect SVD. This is an interesting result because Epic bioprosthesis demonstrated a similar trend in developing SVD after AVR (11).

The survival rate at 5 years was 96% in our study and 89.2% at 5 years in the COMMENCE trial (5). One deceased case with unknown etiology in our study was a patient on dialysis. Based on the dialysis background and the literature (14), SVD was believed to be caused by calcification.

This study demonstrated limitations. First, this is a single-center retrospective study with a small number of included patients. Only 13 patients out of 60 patients had 5-year follow-up data. Second, follow-up duration is limited with distribution of implanted valve size being not same at each follow-up timing. These limitations made it difficult to show mid-term clinical outcomes of IR aortic bioprosthesis in the present study. Therefore, data described here should be carefully interpreted in clinical practice. However, IR bioprosthesis was introduced in late 2018 in Japan, and thus the present progress report contains important clinical and hemodynamic data from the Japanese cohort. This is the longest follow-up study of IR bioprosthesis in Japan. Additionally, a homogenous cohort in nationality is crucial to directly implement data on clinical practice as data from foreign countries do not fit the Japanese cohort.

In conclusion, IR bioprosthesis for AVR demonstrated a stable hemodynamic performance throughout the mid-term period without SVD cases. Relatively low mean PG after AVR with IR bioprosthesis was outstanding result in the present study, which led to postoperative decrease in LVMI. Further follow-up is mandatory to confirm stable hemodynamic performance and valve safety.

CONFLICT OF INTEREST

None

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