Bileaflet mechanical valve replacement: an assessment of outcomes with 30 years of follow-up

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Abstract

OBJECTIVES: Heart valve replacement with a bileaflet mechanical valve is a well-established procedure. However, the long-term results of valve replacement using the bileaflet mechanical valve remain unclear, especially for follow-up periods over 30 years. Additionally, it is important to identify predictors of long-term mortality and valve-related events.

METHODS: We performed a retrospective cohort analysis of 2727 patients (mean ± standard deviation age, 52.8 ± 1.6 years) who underwent valve replacement with a St. Jude Medical valve at our institute from 1978 to 2012. Data were collected using a questionnaire and chart review or physician contact. The cohort included 950 aortic valve replacements (AVRs), 1255 mitral valve replacements (MVRs) and 522 double valve replacements (DVRs). Follow-up was 91% complete, and the analysis included a total of 39 187 patient-years.

RESULTS: Operative mortality rates were 2.3% for AVR, 2.2% for MVR and 3.6% for DVR. The 30-year survival rate (actuarial method) was 38.0% (AVR, 44.5%; MVR, 34.9%; and DVR, 37.5%). The 30-year rates of freedom from valve-related mortality, thromboembolic events and bleeding events were 86.3% (AVR, 88.6%; MVR, 85.4%; and DVR, 84.3%), 83.5% (AVR, 89.8%; MVR, 80.0%; and DVR, 81.4%) and 91.5% (AVR, 94.4%; MVR, 90.1%; and DVR, 90.2%), respectively. The incidence rates of valve-related morbidity, thromboembolic events and bleeding events were significantly higher among patients with MVR and DVR than among those with AVR. Significant risk factors for late death and other late events included male sex, age >65 years and atrial fibrillation.

CONCLUSIONS: Low late mortality and a low incidence of valve-related events can be achieved for at least 30 years using mechanical bileaflet valve replacement. Persistent atrial fibrillation is a significant risk factor for morbidity and mortality.

Keywords: Valve replacement surgery • Prosthetic valve • Long-term results

INTRODUCTION

Mechanical valves are useful prostheses for the surgical treatment of valvular heart disease. Nonetheless, the use of bioprostheses has increased in the context of patient preference to avoid lifetime anticoagulation therapy, and an improvement in the durability of bioprostheses [1, 2]. Recently, transcatheter valve implantation has evolved as a primary alternative treatment, especially for elderly patients who face greater risks [3]. In this context, it is important to evaluate and analyse the long-term results of mechanical bileaflet valve replacement over the course of 30 years, particularly as it has classically been a standard treatment option.

The St. Jude Medical valve prosthesis (SJM) is a bileaflet low-profile mechanical valve that is capable of excellent haemodynamic performance, especially for smaller-sized valves. Since the first clinical implantation of this valve in 1977, investigators in the USA have reported excellent durability in the analyses of long-term outcomes. Furthermore, the use of this valve is associated with a low incidence of valve-related complications [4, 5]. At our institution, we have implanted SJMs in more than 2700 patients since 1978, when the first implantation of this prosthesis was performed [6].

The primary aims of this study were to document patient survival and valve-related events over the course of 30 years and to identify risk factors for both mortality and valve-related events. This review of cases at our institution was designed to follow the guidelines for reporting morbidity and mortality after valvular surgery, as published in the European Journal of Cardiothoracic Surgery [7].

MATERIALS AND METHODS

Patient population

This study involved human subjects and was reviewed and approved by the Institutional Review Board of Tokyo Women's
Medical University. Between July 1978 and December 2012, SJMs were implanted in 2727 adult patients (all older than 16 years; 1322 men and 1405 women) who were included in this study. Pertinent demographic data on patients who underwent SJM implantation by surgeons from our institute were maintained in an independent database at The Heart Institute of Japan Research Foundation. This database was continuously updated from 1978 to 2012 for all patients undergoing valve implantation with SJMs. Interim reports were issued during this period.

Clinical charts were reviewed to ensure that postoperative events and complications during the original operative period were captured. To ensure that the SJM itself had been evaluated, we reviewed 5619 patients in our database who had valves of other types in addition to an SJM, as well as patients with composite graft replacements. The primary objectives of this study were to document patient survival and valve-related events over the course of 30 years and to identify risk factors for both valve-related mortality and events. Single aortic valve replacement (AVR) was performed in 950 patients, single mitral valve replacement (MVR) in 1255 patients and aortic and MVR (double valve replacement, DVR) in 522 patients (Table 1). The original SJM standard model, Hemodynamic Plus model and Regent models were used in 1112, 276 and 584 patients with AVR. The SJM Silzone model is not used in Japan. Among this cohort, patients who underwent aortic root replacement (the Bentall operation) were excluded to ensure simplicity of analysis.

### Operative technique

Details of the surgery and patient care have been described previously. In brief, all patients underwent surgery using standard cardiopulmonary bypass with moderate hypothermia (at 28–34°C). Either cold crystalloid or blood cardioplegia, associated with ice slush topical cooling, was delivered using an antegrade approach, a retrograde approach or both. To suture the valves, surgeons predominantly used the everting mattress suture technique with 2-0 braided polyester sutures reinforced with polytetrafluoroethylene (Teflon) felt pledgets. Since 2004, AVR of the small aortic annulus has been predominantly performed using the horizontal mattress suture technique.

### Follow-up

Follow-up was conducted via questionnaires and telephone contact with the patient. If warranted, and if valve-related

### Table 1: Demographics and operative procedures for patients who underwent aortic, mitral or both aortic and mitral valve replacement with the St. Jude Medical cardiac valve prosthesis during the 30-year period of this study

<table>
<thead>
<tr>
<th>Variable</th>
<th>AVR</th>
<th>MVR</th>
<th>DVR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>950</td>
<td>1255</td>
<td>522</td>
<td>2727</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.7±12.9</td>
<td>52.8±11.2</td>
<td>52.9±10.3</td>
<td>52.8±11.6</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>616/334 (65/35)</td>
<td>490/765 (39/61)</td>
<td>216/306 (41/59)</td>
<td>1322/1405 (49/51)</td>
</tr>
<tr>
<td>Total follow-up (patient-years)</td>
<td>13187.0</td>
<td>18646.8</td>
<td>7352.9</td>
<td>39186.6</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operative</td>
<td>22 (2.3)</td>
<td>27 (2.2)</td>
<td>19 (3.6)</td>
<td>68 (2.5)</td>
</tr>
<tr>
<td>Late</td>
<td>293 (30.8)</td>
<td>488 (38.9)</td>
<td>184 (35.2)</td>
<td>965 (35.4)</td>
</tr>
<tr>
<td>Valve-related</td>
<td>84 (8.8)</td>
<td>138 (11.0)</td>
<td>48 (9.2)</td>
<td>270 (9.9)</td>
</tr>
</tbody>
</table>

AVR: aortic valve replacement; CI: confidence interval; DVR: double valve replacement; MVR: mitral valve replacement.

### Figure 1: Distribution of valve sizes implanted for patients with an aortic or mitral valve position. Results are shown for patients who received a St. Jude Medical cardiac valve prosthesis during the 30-year duration of this study.
complications occurred, contact was made with the primary physician or the patient’s hospital records were accessed. Owing to the extended time frame of this study, any clinical study documents that had been obtained in prior studies were cross-checked to ensure that all events were captured. Causes of patient deaths were determined from hospital records. All sudden or unknown causes of death were considered to be valve-related, in accordance with standards described by Akins et al. [7]. In total, 273 patients were lost to follow-up. The number of patients at risk on 10 December 2013 was 1291.

Anticoagulation

Chronic warfarin sodium (Coumadin) anticoagulation was recommended for all patients. The international normalized ratio (INR) has been recommended exclusively for anticoagulation follow-up. The target INR was 1.6–2.5 for AVR and 2.0–3.0 for MVR. If atrial fibrillation was present, the target INR was 2.0–3.0.

Statistical analysis

Descriptive statistics are summarized as frequencies and percentages for categorical variables. Continuous variables are reported as mean ± standard deviation (SD). Groups were compared using Pearson’s χ² test for categorical variables, and the Mann–Whitney U-test or Student’s t-test for continuous variables.

RESULTS

Surgical procedures

The study cohort included 950 single AVRs, 1255 single MVRs and 522 DVRs. The distribution of valve types and sizes is shown in Figure 2:

Figure 2: (A) Survival rates for all causes of death in the total study cohort; (B) survival rates for all causes of death in patients with AVR, MVR and DVR; (C) cause-specific survival rates for valve-related death in the total study cohort and (D) cause-specific survival rates for valve-related death in patients with AVR, MVR and DVR. AVR: aortic valve replacement; MVR: mitral valve replacement; DVR: double valve replacement.
For both the aortic and mitral positions. A previous valve replacement had been performed in 375 patients. Concomitant procedures were performed in 448 (16.4%) of the patients included. In the AVR, MVR and DVR groups, concomitant coronary artery bypass grafting (CABG) was performed in 46 (4.8%), 27 (2.1%) and 5 (1.0%) patients, respectively.

Patient characteristics and follow-up

The mean patient age was 52.8 ± 11.6 years (range, 16–83 years).

The mean duration of follow-up was 14.4 ± 8.5 years and the longest patient follow-up was 34.8 years. Follow-up was 91.0% complete. The analysis included a total of 39,187 patient-years of follow-up. Patient demographics and operative procedures are given in Table 1.

Operative mortality

In total, 68 (2.5%) deaths occurred either within 30 days of surgery or in the hospital at any time interval after surgery. The early mortality rate was 2.9% for AVR, 2.2% for MVR and 3.6% for DVR. Low-output syndrome was the most common cause of early death, and all other early deaths were attributed to sepsis or mediastinitis.

Late mortality

During the 34-year follow-up period, there were an additional 965 patient deaths, of which 270 (28% of deaths and 9.7% of the patient population) were valve-related. Actuarial freedom from all death and valve-related death is shown in Fig. 2 for AVR, MVR and DVR. No significant differences were observed between the AVR, MVR and DVR groups for either actuarial survival (Fig. 2A and B) or freedom from valve-related death (Fig. 2C and D).

Valve-related morbidity

The linearized rates of valve-related complications for AVR, MVR and DVR were 1.1, 2.26 and 1.7% per patient-year, respectively (Table 2). Thromboembolism, haemorrhage, valve thrombosis, valve dysfunction, haemolysis, valve infection and reoperation were associated with valve-related morbidity. The linearized ratios for each event are listed in Table 2.

The 30-year freedom from valve-related events was significantly greater in patients with AVR (82.9 ± 1.4%) than in those with MVR (73.2 ± 8.3%) and DVR (72.6 ± 5.4%; P < 0.0001; Fig. 3A and B).

Thromboembolism and haemorrhage

When compared with the MVR and DVR groups, the AVR group showed significantly higher freedom from valve-related events (P < 0.0001; Fig. 3B), freedom from bleeding events (P = 0.0279; Fig. 4D) and freedom from thromboembolism events (P < 0.0001; Fig. 4D). At 30 years, the AVR, MVR and DVR groups exhibited 95.6 ± 3.2, 93.0 ± 5.6 and 90.4 ± 4.0% freedom from bleeding, respectively (P = 0.0279; Fig. 4C and D). The corresponding rates of freedom from thromboembolism were 88.6 ± 5.4, 79.8 ± 7.9 and
80.8 ± 45.4%, respectively (P < 0.0001; Fig. 4A and B). No significant differences were observed between the AVR, MVR and DVR groups in terms of freedom from valve thrombosis, valve dysfunction, haemolysis, valve infection or reoperation (Figs 3C and D).

Reoperation

During the 34 years of follow-up, 130 patients (4.7%) required reoperation. Causes included valve thrombosis (n = 9), prosthetic valve infection (n = 16), haemolysis due to paravalvular leak (n = 9) and pannus formation (n = 8). There was 1 structural failure early in our experience resulting from embolization of 1 leaflet of a mitral prosthesis. At 30 years, the cumulative rate of freedom from reoperation was 85.9 ± 15.9% for AVR, 89.6 ± 12.6% for MVR and 89.4 ± 8.2% for DVR. Freedom from reoperation is shown in Fig. 3C and D.

Valve thrombosis and valve dysfunction

Thrombosis of the prosthetic valve occurred in 9 patients, including 3 patients with AVR (0.3%), 6 with MVR (0.48%) and none with DVR. Subsequent reoperation was reported in 6 patients. The incidence rate of valve thrombosis was 0.02% per patient-year for AVR, 0.02% per patient-year for MVR and 0% per patient-year for DVR (Table 2).

Valve dysfunction occurred in 11 patients, including 3 patients with AVR (0.3%), 4 with MVR (0.3%) and 4 with DVR (0.8%). Pannus formation was confirmed in 4 aortic positions and thrombosis was suspected in 4 mitral positions. Subsequent reoperation was reported in 8 patients. The incidence of valve thrombosis was 0.02% per patient-year for AVR and 0.02% per patient-year for MVR, valve thrombosis in patients with DVR was not observed.

Valve infection

A total of 26 patients had infection events. Valve infection developed in 11 patients with AVR (1.1%), 9 patients with MVR (0.7%) and 6 patients with DVR (1.2%). Sixteen of these patients required reoperation. The overall incidence rate of valve infection was 0.08% per patient-year for AVR, 0.05% per patient-year for MVR and 0.08% per patient-year for DVR.

Haemolysis

A total of 14 (0.5%) patients had haemolysis due to paravalvular leakages. Haemolysis developed in 2 patients with AVR (0.2%), 10 with MVR (0.8%) and 2 with DVR (0.3%); all of these patients required reoperation. The overall incidence rate of valve haemolysis was 0.02% per patient-year for AVR, 0.05% per patient-year for MVR and 0.03% per patient-year for DVR (Table 2).
Risk factors for valve-related deaths

Cox regression analysis revealed that advanced age (older than 70 years), male sex, previous operation and emergency operation were independent predictors of valve-related mortality. The only independent predictor of thromboembolism was the presence of atrial fibrillation, whereas the independent risk factors for anticoagulation-related haemorrhage were age older than 70 years and previous operation (Table 3).

DISCUSSION

This retrospective study represents one of the largest and longest reports on bileaflet prosthetic valves. Emery et al. [8] have also reported on their extensive experience with SJM, demonstrating its excellent function in the mitral or aortic position for up to 25 years. Grunkemeier et al. [9] also described their 35-year experience with aortic and mitral replacement; however, multiple valve models were included.

In this report, we found that low late mortality and a low incidence of valve-related events can be achieved for more than 30 years with mitral, aortic or simultaneous mechanical bileaflet valve replacement. No significant differences in early or late mortality (valve-related mortality) were observed between patients with AVR, MVR and DVR. However, the incidence of valve-related morbidity was significantly higher in the MVR and DVR groups than in the AVR group. Similarly, the incidence rates of thromboembolic and bleeding events were also higher in the MVR and DVR groups than in the AVR group. The significant risk factors for all deaths and events included older age (>65 years), male sex, emergency operation and atrial fibrillation.

Because of the long time frame of this study, the importance of our efforts to capture valve-related events cannot be overemphasized. All living patients and related physicians were contacted. Although attempts to contact these persons were made repeatedly, 9% of the original cohort of patients was unavailable for follow-up, which represents a major limitation to this study. The present study included patients with relatively younger ages, who underwent concomitant procedures (such as CABG) less frequently, and who mostly had disease of a rheumatic aetiology. These characteristics may not reflect the modern population of patients undergoing valvular surgery. Because this Japanese study of the long-term outcomes of SJMs differs from previously published studies in a number of aspects, direct comparisons with the results of these previous studies may be unfeasible.

Nevertheless, the results of the present study, including those for hospital mortality, represent a substantial update to our previous investigation of SJMs at 12 years of follow-up [6]. Furthermore, the results of the present study show survival rates that are similar to those observed for various other bileaflet mechanical valves, such as CarboMedics valves and ATS valves [10–12]. The excellent durability of the SJM prosthesis is confirmed by the observation of only 1 structural valve deterioration in this study.
Figure 5: (A) Rates of freedom from valve leakage in the total study cohort; (B) rates of freedom from valve leakage in patients with AVR, MVR and DVR; (C) rates of freedom from valve infection in the total study cohort and (D) rates of freedom from valve infection in patients with AVR, MVR and DVR. AVR: aortic valve replacement; MVR: mitral valve replacement; DVR: double valve replacement.

Table 3: Factors associated with all death, thromboembolic events and anticoagulant-related haemorrhage

<table>
<thead>
<tr>
<th>Factor</th>
<th>Alive (n = 1694)</th>
<th>Death (n = 1033)</th>
<th>P-value</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>777 (46%)</td>
<td>545 (53%)</td>
<td>0.0003</td>
<td>1.25 (1.11–1.42)</td>
</tr>
<tr>
<td>Age ≥70</td>
<td>263 (16%)</td>
<td>175 (17%)</td>
<td>&lt;0.0001</td>
<td>2.06 (1.74–2.44)</td>
</tr>
<tr>
<td>Previous operation</td>
<td>202 (12%)</td>
<td>198 (19%)</td>
<td>&lt;0.0001</td>
<td>1.47 (1.26–1.71)</td>
</tr>
<tr>
<td>Emergency</td>
<td>21 (1%)</td>
<td>23 (2%)</td>
<td>0.014</td>
<td>1.68 (1.11–2.54)</td>
</tr>
<tr>
<td>Concomitant CV surgery</td>
<td>279 (16%)</td>
<td>169 (16%)</td>
<td>0.956</td>
<td>1.01 (0.85–1.18)</td>
</tr>
<tr>
<td>Censored (n = 2396)</td>
<td></td>
<td>Thromboembolism (n = 331)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1162 (48%)</td>
<td>160 (48%)</td>
<td>0.856</td>
<td>1.02 (0.82–1.27)</td>
</tr>
<tr>
<td>Age ≥70</td>
<td>140 (6%)</td>
<td>9 (3%)</td>
<td>0.134</td>
<td>0.60 (0.31–1.17)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>400 (17%)</td>
<td>83 (25%)</td>
<td>0.003</td>
<td>1.47 (1.14–1.88)</td>
</tr>
<tr>
<td>Censored (n = 2576)</td>
<td></td>
<td>Haemorrhage (n = 151)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1258 (49%)</td>
<td>64 (42%)</td>
<td>0.178</td>
<td>0.80 (0.58–1.11)</td>
</tr>
<tr>
<td>Age ≥70</td>
<td>138 (5%)</td>
<td>11 (7%)</td>
<td>0.033</td>
<td>1.96 (1.06–3.63)</td>
</tr>
<tr>
<td>Previous operation</td>
<td>369 (14%)</td>
<td>31 (21%)</td>
<td>0.019</td>
<td>1.60 (1.08–2.38)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>457 (18%)</td>
<td>26 (17%)</td>
<td>0.536</td>
<td>0.88 (0.57–1.34)</td>
</tr>
</tbody>
</table>

CI: confidence interval; CV: cardiovascular.
In the present study, the incidence of haemorrhagic events and thromboembolism resembled that reported for other current era devices, such as ATS valves [12, 13]. Nonetheless, haemorrhage and thromboembolism were the major causes of valve-related morbidity in the present study. Based on the higher incidence rates of thromboembolic and haemorrhagic events in the MVR and DVR groups, patients with SJMs in the mitral position (MVR and DVR) are at a greater risk for valve-related events than those with SJMs in the aortic position (AVR). Emery et al. reported that patients with AVR and MVR had equal incidence rates of thromboembolic events for the first 10 years, but that their incidence rates differed thereafter, likely because of the increased incidence of atrial fibrillation in patients with MVR [14, 15]. In the present study, the incidence rates of thromboembolic events in the AVR, MVR and DVR groups differed after the first year of post-operative follow-up. The separation of these incidence rates may be associated with the role of preoperative atrial fibrillation as a significant risk factor for valve-related events over the entire follow-up period.

The effect of atrial fibrillation on survival and valve-related events has been reported repeatedly in previous studies [16]. The present study confirmed that atrial fibrillation is a significant risk factor for thromboembolism, but not for anticoagulation-related haemorrhage. This finding also suggests that the overall long-term outcomes after prosthetic valve replacement may be influenced more strongly by pre-existing comorbidities prior to surgery than by the presence of the mechanical valve. It has been reported that patients undergoing valve replacement surgery do not survive at the same rates as the general population, mainly because of patient-related factors, rather than the prosthesis itself [14, 15]. In the present study, older age, previous operation and male sex were the other significant risk factors for valve-related deaths or events, and each of these factors is patient-related, rather than prosthesis-related.

Lifetime anticoagulation therapy remains the major cause of valve-related events in patients with mechanical prostheses. The 2014 American College of Cardiology/American Heart Association guidelines recommend a target prothrombin time/INR of approximately 2.5–3.0 for both patients with mechanical aortic prostheses and those with mechanical mitral prostheses [17]. It has also been reported that individuals of Asian descent have a substantially higher risk (2- to 4-fold) of warfarin-related intracranial haemorrhage than do Caucasian individuals. A lower target INR for mechanical aortic and mitral prostheses has been proposed in Japan [18]. Considering the low incidences of thromboembolic and haemorrhage events in AVR patients in the present study, the current INR target (1.6–2.5) for AVR can be justified, although the INR targets for MVR and DVR patients may be worth re-evaluating. Koertke et al. [19] reported that early INR home management enables patients to achieve lower target anticoagulation levels. Home INR monitoring can be an important adjunct for more adequate INR control [20].

**CONCLUSION**

In summary, this report describes more than 30 years of experience with SJMs in the mitral and/or aortic position, demonstrating the excellent function and the durability of these prostheses. The mechanical bileaflet valve remains an important prosthesis option that is likely to remain functional throughout the patient’s lifetime. Low late mortality and a low incidence of valve-related events can be achieved for at least 30 years using mechanical bileaflet valve replacement. Bileaflet mechanical heart valve prosthesis is an excellent choice for patients who require mechanical prosthetic valve replacement, even in the modern era. Persistent atrial fibrillation is a significant risk factor for morbidity and mortality in a long-term setting.

**ACKNOWLEDGEMENTS**

We thank Professor Emeritus Hitoshi Koyanagi and all surgeons and medical staff of the Heart Institute of Japan who contributed to this project. Furthermore, we also thank Dr. Kazutaro Mizukami for assistance with the statistical analysis and Ms. Eiko Shirato for assistance with the data collection.

**Conflict of interest:** none declared.

**REFERENCES**


APPENDIX. CONFERENCE DISCUSSION

Dr H. Najm (Riyadh, Saudi Arabia): I consider this paper one of the longest follow-up studies for the St. Jude mechanical valve in the literature. I find this paper important in proving to the cardiac surgical community that this mechanical prosthesis can stand the wear and tear of mechanical forces for over 30 years. This review includes a large number of patients, allowing confidence in the conclusions. Having said this, I wish that the authors had included, in the analysis, the other types of valves. You had mentioned in your manuscript that you had another 3000 valves which had been implanted during the same period. That could also allow us to compare the performance of different mechanical valves.

One important conclusion from long-term studies such as your study is the era effect. This was not included in the analysis and the effect of left ventricle dysfunction on the early and late outcomes was not included. I think this should be included in the final manuscript for publication. In addition, you have 176 patients who had size 17 and size 19 valves, and these are a very important subgroup, because it will allow us to analyse the smaller valve patients and its effect on survival, in particular, the patient-prosthesis mismatch issue.

Lastly, the study spans over 30 years and the indication for surgery was not included in the analysis itself. It was assumed that it might have been rheumatic in origin, but obviously you have patients who are very young and up to 80 years, therefore, you could have also had some degenerative or ischaemic mitral valves and they do survive differently. I have two straightforward questions for you. The first question is, considering the low incidence of thrombosis, especially in the aortic position, would you consider a lower INR target in that position? The second question is, in the current era of percutaneous valve solutions we have now, would you think that the use of mechanical valves would decrease despite the good long-term performance?

Dr Saito: First, because this is a long-term study, the rate of INR control has been changed. Most patients have been controlled with an INR range between 1.6 and 2.5 for aortic valve replacement and between 2.0 and 3.0 for mitral valve replacement. Thinking about a lower incidence of thromboembolic events, especially in the aortic valve replacement patients, we are considering lowering the INR control with a range between 1.6 and 2.0, but in the mitral and the DVR patients, our data showed a significantly higher incidence of bleeding events and also thromboembolic events compared with the aortic valve replacement patients and we have to consider that more carefully.

For the second question, as we have mentioned in the background slide, the number of transcatheter aortic valve replacements is increasing. For the reoperation, there are trends to do transcatheter aortic valve replacement, using it in a bioprosthetic unit. Considering the case of the reoperation, valve-in-valve procedures, this is not the time to think about it now because we really don’t know yet the long-term results of transcatheter aortic valve replacement, and also, without knowing the long-term results, we would have to change our policy against the guideline that has been decided here.