CLINICAL STUDY

Early Safety and Efficacy of Transcatheter Aortic Valve Implantation for Asian Nonagenarians (from KMH Registry)

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Summary

As Japan has one of the most rapidly aging populations in the world, transcatheter aortic valve implantation (TAVI) is likely to be performed in increasing numbers of older people. There is little information on either the efficacy or the safety of TAVI in nonagenarians in Asia.

From October 2013 to June 2015, 112 consecutive patients underwent TAVI with Edwards SAPIEN XT valves in our institution. We compared 25 patients aged at least 90 years (mean 91.6 ± 1.7 years) with 87 patients aged under 90 years (mean 82.5 ± 6.0 years) at the time of TAVI. All definitions of clinical endpoints and adverse events were based on the Valve Academic Research Consortium 2 definitions.

The median follow-up interval was 561.5 days (the first and third quarters, 405.0 and 735.8 days). Nonagenarians had a higher logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), Euro II score, and the Society of Thoracic Surgeons predictive risk of mortality (STS) score, and a prevalence of clinical frailty scale. The rate of device success, and the 30-day and 6-month mortalities were not different between patients aged ≥ 90 years and < 90 years (96.0% versus 92.0%, P = 0.68; both 0%, P = 1.00; 4.0% versus 3.5%, P = 0.32, respectively). At six months, clinical efficacy and time-related valve safety were also similar in the two groups (12.5% versus 13.4%, P = 1.00; 4.5% versus 10.3%, P = 0.68, respectively). The cumulative 1-year mortalities were not significantly different between the two groups (8.4% versus 9.4%, P = 0.94, respectively).

TAVI can contribute to acceptable clinical results and benefits in a carefully selected group of nonagenarians in Asia.

Key words: Aortic stenosis, Elderly people, TAVI

Aortic stenosis (AS) is a common condition associated with major morbidity and mortality, due to both progressive valve narrowing and consequent left ventricular hypertrophy. As a consequence of the aging of the population, the number of very elderly patients with severe AS has been increasing. In Japan, the Cabinet Office predicts that the percentage of people aged > 75 years will more than double in the next 40 years: 12.5% in 2014 and 26.1% in 2055. In such an aging society, transcatheter aortic valve implantation (TAVI), which is an alternative option for severe patients with AS considered inoperable or at high risk for surgical aortic valve replacement (SAVR),1-3 was officially initiated in Japan in October 2013. Although TAVI was gradually introduced for elderly patients who were considered to have too high risk to undergo SAVR, there are few reports of clinical data after TAVI in very elderly patients, especially in Asia. The aim of this study was to compare nonagenarians and other Asian people, who tend to have small bodies, with respect to the early outcome and safety of TAVI.

Methods

Subjects: Kokura Memorial Hospital (KMH) registry is a single-center registry enrolling high-risk or inoperable patients with severe AS. The subjects in this study were consecutive patients who had undergone balloon-expandable TAVI between October 2013 and June 2015 in our institution. We divided them into two groups: those aged ≥ 90 years and those aged < 90 years. Severe AS was defined as aortic valve area < 0.8 cm², a mean pressure gradient ≥ 40 mmHg, or a peak aortic jet velocity ≥ 4.0 m/s.

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4.0 m/second. All patients were considered high risk or inoperable for SAVR by the institutional heart team, which consists of cardiologists, cardiac surgeons, anesthesiologists, nurses, clinical engineering technologists, and radiation technologists. Exclusion criteria were a bicuspid or non-calcified aortic valve, life expectancy less than one year because of diseases other than AS, acute myocardial infarction (MI) during the month prior to the procedure, active gastrointestinal hemorrhage, a recent transient ischemic attack or stroke during the month prior to the procedure, severe dementia, very severely frail patients (Clinical Frailty scale ≥ 8), sepsis, and endocarditis. Peripheral artery disease (PAD) was defined as a history of treatment for PAD or already known significant stenosis of a peripheral artery.

Routine right cardiac catheterization and coronary angiography were performed before TAVI. Before the procedure, all patients were given contrast computed tomography for assessments of the anatomy and dimensions of the aortic valve, aorta, and iliofemoral arteries. The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), the Euro II Score, and the Society of Thoracic Surgeons predictive risk of mortality (STS) score were used to evaluate pre-operative risk. In addition to them, we used pre-operative risk assessment combining STS risk estimate, frailty, major organ system dysfunction, and procedure-specific impediments from 2014 in accordance with the AHA/ACC guidelines for the management of patients with valvular heart disease.

Device and procedure: Technical aspects of the TAVI procedure have been reported in detail. We used a balloon-expandable valve, the Edwards SAPIEN XT (Edwards Lifesciences, Irvine, California). The transfemoral (TF) approach was first chosen as an access route, but the transapical (TA) approach was considered in patients with aortic dissection, marked shaggy aorta, or small iliofemoral diameters. The femoral artery was punctured percutaneously and closed using a hemostatic device (PERCLOS, Abbott, Chicago, Illinois), or surgically cut down and closed. The TA approach was managed surgically. All procedures were performed by a team of cardiologists, cardiac surgeons, and anesthesiologists in a hybrid operating room, under general anesthesia and rapid ventricular pacing. Transesophageal echocardiography (TEE) was used in all cases. Intravenous heparin was administered, targeting an activated clotting time of 250-300 seconds. After successful completion of the procedure, antiplatelet therapy consisted of aspirin 100 mg and clopidogrel 75 mg daily for three to six months.

Data collection and endpoints: We extracted medical histories from the hospital records of eligible patients. Data included patient characteristics, coronary angiography, computed tomography, transthoracic echocardiography, TEE, procedural data, transfusion, and the length of hospital and intensive care unit (ICU) stays. Information on prognosis was obtained from regular hospital visits or through direct calls to the patients. All definitions of clinical endpoints and adverse events were based on the Valve Academic Research Consortium 2 (VARC-2) definitions: all-cause mortality, early safety, clinical efficacy, time-related valve safety, device success, peri-procedural MI, stroke, life-threatening bleeding, acute kidney injury, coronary obstruction, major vascular complications, minor vascular complications, two-valve deployment, and conversion to open surgery.

Statistical analysis: Categorical variables were compared between groups with the chi-square test or Fisher’s exact test, as appropriate. The descriptive results were displayed in patients aged ≥ 90 years, and the continuous safety variables presented as mean ± SD or the median and interquartile range. Differences between the two groups in demographics, clinical characteristics, device and procedures, echocardiographic data, and laboratory data were analyzed by the Student t test or the Wilcoxon rank sum test, as appropriate. All analyses were two-tailed, with clinical significance defined as $P < 0.05$. All-cause mortality analysis was performed by the Kaplan-Meier method. Differences in mortality between the two groups were estimated by the log-rank test. To identify the predictive values of one-year survival after TAVI, we performed Cox multivariate regression analysis. The multivariate model was adjusted for nonagenarian or not, and general risk factors were adjusted for death of patients who had undergone surgery for valvular heart disease or TAVI: body mass index (BMI), STS score, diabetes mellitus, clinical frailty scale (≥ 4) (which means no walking or assistance required), chronic kidney disease (CKD), chronic obstructive pulmonary disease, and reduced ejection fraction. All statistical analyses were performed using SPSS version 19 (IBM, Armonk, NY).

Results

Baseline patient characteristics: From October 2013 to June 2015, 112 patients underwent balloon-expandable TAVI, using the Edwards SAPIEN XT (Edwards Lifesciences, Irvine, California) in our institute. The baseline patient characteristics are summarized in Table I, and the distribution of age is presented in Figure 1. From this registry, 25 patients (22.3%) were aged at least 90 years at the time of the procedure (91.6 ± 1.7 years and range 90-96 years). The other 87 patients aged under 90 years had a mean age of 82.5 ± 6.0 years. There was no significant difference in gender. On average, the ≥ 90-year group was shorter and lighter. In the ≥ 90-year group, logistic EuroSCORE, Euro II score, STS score, and clinical frailty scale were significantly higher than those in the < 90-year group (20.0 [IQR 16.0-25.5] versus 14.0 [11.0-22.0], $P = 0.002$; 5.0 [4.0-9.5] versus 4.0 [3.0-6.0], $P = 0.002$; 10.0 [7.5-12.0] versus 6.0 [3.0-7.0], $P = 0.002$; 83.3% versus 54.0%, $P = 0.009$; respectively). Medical history, cardiac history, laboratory findings, and medications were almost the same in the two groups. The ≥ 90-year group tended to have severe AS, but there were no significant differences between the ≥ 90-year group and the < 90-year group, except for effective orifice area (EOA). Patients aged < 80 years were 23.2% of the total (Figure 1), and comorbidities and technical inoperability accounted for major reasons why they were selected as TAVI candidates.

Procedural results: Procedural data are presented in Table II. Operating time, fluoroscopy time, and amount of contrast agent were similar in the two groups. The TF and
TA approaches were performed in 78 (69.6%) and 34 (30.4%) patients, respectively. There was no significant difference in approach site between the ≥ 90-year group and the < 90-year group. We performed all TAVI procedures under general anesthesia. Valves of 23, 26, and 29 mm were implanted in 77 patients (68.8%), 32 patients (27.5%), and three patients (2.7%), respectively. Implanted valve size was similar in the two groups.
Of 112 patients, 104 achieved device success (92.9%). Eight patients did not achieve correct positioning of a single prosthetic heart valve into the proper anatomical location; three continued to have moderate aortic regurgitation; three had prosthesis-patient mismatch; and one continued to have a mean aortic valve gradient ≥ 20 mmHg at post-procedural echocardiography. There was no significant difference in device success between the ≥ 90-year group and the < 90-year group (96.0% and 92.0%, respectively, P = 0.68, Table III). Changes in mean EOA and PG among the two groups at baseline and after valve implantation are summarized in Figure 2. After valve implantation, changes in mean EOA and PG were similar in the two groups.

**Follow-up at 30 days:** Outcomes at 30 days are presented in Table III. Our registry revealed that all-cause mortality at 30 days was zero. The VARC-2 defined 30-day early safety and device success rates as 15.3% and 92.9% in 112 patients. There were no significant differences in them between the ≥ 90-year and < 90-year groups. Peri-procedural MI, stroke, life-threatening bleeding, acute kidney injury stage 2 or 3, major vascular complications, minor vascular complications, two-valve deployment, and conversion to open surgery were rare and similar in the two groups. But in the cases of stroke, nonagenarians tended to develop TIA more frequently than the < 90-year subjects. Length of stay in the ICU, in the hospital, and

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**Table II. Procedural Data**

| Characteristic                      | Overall (n = 112) | ≥ 90 (n = 25) | < 90 (n = 87) | P  |
|------------------------------------|-------------------|--------------|--------------|----|
| Operating time (minutes)           | 93.5 ± 41.3       | 97.5 ± 44.4  | 92.3 ± 40.6  | 0.58 |
| Fluoroscopy time (minutes)         | 20.2 ± 7.9        | 21.1 ± 8.9   | 19.9 ± 7.6   | 0.51 |
| Amount of contrast agents (mL)     | 175.5 ± 60.8      | 183.0 ± 65.6 | 173.3 ± 59.5 | 0.49 |
| Approach                           |                   |              |              | 0.70 |
| Transfemoral                       | 69 (61.6)         | 15 (62.5)    | 53 (60.9)    |     |
| Transapical                        | 34 (30.4)         | 8 (32.0)     | 26 (29.9)    |     |
| Transiliac                         | 9 (8.0)           | 1 (4.2)      | 8 (9.2)      |     |
| General anesthesia                 | 112 (100.0)       | 25 (100.0)   | 87 (100.0)   | 1.00 |
| Implanted valve size               |                   |              |              | 0.51 |
| 23 mm                              | 77 (68.8)         | 19 (76.0)    | 58 (66.7)    |     |
| 26 mm                              | 32 (28.6)         | 6 (24.0)     | 26 (29.9)    |     |
| 29 mm                              | 3 (2.7)           | 0 (0.0)      | 3 (3.4)      |     |

Data are given as n (%) or mean ± SD.
Table III. Outcomes at 30 Days, 6 Months, and 1 Year

| Characteristic                      | Overall (n = 112) | ≥ 90 (nT = 25) | < 90 (nT = 87) | P   |
|------------------------------------|-------------------|---------------|---------------|-----|
| All-cause mortality                | 0/112 (0.0)       | 0/25 (0.0)    | 0/87 (0.0)    | 1.00|
| Early safety                       | 17/111 (15.3)     | 5/24 (20.8)   | 12/87 (13.8)  | 0.52|
| Device success                     | 104/112 (92.9)    | 24/25 (96.0)  | 80/87 (92.0)  | 0.68|
| Peri-procedural MI                 | 1/112 (0.9)       | 0/25 (0.0)    | 1/87 (1.1)    | 1.00|
| Stroke                             |                   |               |               |     |
| Ischemic                           | 4/112 (3.6)       | 1/25 (4.0)    | 3/87 (3.4)    | 1.00|
| Hemorrhagic                        | 0/112 (0.0)       | 0/25 (0.0)    | 0/87 (0.0)    | 1.00|
| TIA                                | 2/112 (1.8)       | 2/25 (8.0)    | 0/87 (0.0)    | 0.05|
| Life-threatening bleeding           | 2/112 (1.8)       | 1/25 (4.0)    | 1/87 (1.1)    | 0.40|
| Acute kidney injury stage 2 or 3   | 2/112 (1.8)       | 0/25 (0.0)    | 2/87 (2.3)    | 1.00|
| Coronary obstruction               | 2/112 (1.8)       | 0/25 (0.0)    | 2/87 (2.3)    | 1.00|
| Major vascular complications       | 6/112 (5.4)       | 2/25 (8.0)    | 4/87 (4.6)    | 0.61|
| Minor vascular complications       | 5/112 (4.5)       | 1/25 (4.0)    | 4/87 (4.6)    | 1.00|
| Two-valve deployment               | 1/112 (0.9)       | 0/25 (0.0)    | 1/87 (1.1)    | 1.00|
| Conversion to open surgery         | 1/112 (0.9)       | 1/25 (4.0)    | 0/87 (0.0)    | 0.22|
| Length of stay in ICU (days)       | 1.0 (1.0-2.0)     | 1.0 (1.0-2.5) | 1.0 (1.0-2.0) | 0.93|
| Length of stay in hospital (days)  | 15.0 (12.0-20.0)  | 18.0 (12.0-24.5) | 15.0 (12.0-20.0) | 0.88|
| Hospital stay after the procedure  | 11.5 (8.0-15.8)   | 14 (9.5-21.5) | 11.0 (8.0-15.0) | 0.96|

Data are given as n (%), mean ± SD, or median (IQR). MI indicates myocardial infarction; TIA, transient ischemic attack; and ICU, intensive care unit.

follow-up at six months: Outcomes at six months are presented in Table III. All-cause mortality was four of 112 (3.6%). The VARC-2 defined 6-month clinical efficacy and time-related valve safety were 13.2% and 9.0%, respectively. There were no significant differences between patients aged ≥ 90 years and < 90 years.

follow-up at one year: The cumulative Kaplan-Meier survival curves are presented in Figure 3 (median 561.5 days; the first and third quarters, 405.0 and 735.8 days). All-cause mortality at one year was 8.4% for patients aged ≥ 90 years and 9.4% for patients aged < 90 years (P = 0.94). In patients who underwent TA-TAVI, the groups had similar all-cause mortalities at one year (14.3% versus
12.1%, \( P = 0.90 \)). In the Cox regression analysis, age ≥ 90 years was not significantly related to all-cause mortality at one year (hazard ratio 1.79, 95% CI 0.37-8.73, \( P = 0.47 \), Table IV). Diabetes was significantly related to all-cause mortality at one year (hazard ratio 4.48, 95% CI 1.13-14.7, \( P = 0.033 \)).

Table IV. Multivariate Cox Regression Analysis of 1-Year All-Cause Mortality

| Variable                              | Univariate analysis | P     | Multivariate analysis |
|---------------------------------------|---------------------|-------|-----------------------|
|                                       | HR (95% CI)         |       | HR (95% CI)           | P         |
| Age ≥ 90 years                        | 1.19 (0.32-4.39)    | 0.80  | 1.79 (0.37-8.73)      | 0.47      |
| BMI (kg/m²)                           | 1.01 (0.87-1.18)    | 0.85  | 0.97 (0.83-1.14)      | 0.71      |
| STS score (%)                         | 1.14 (1.00-1.29)    | 0.044 | 1.07 (0.91-1.25)      | 0.43      |
| DM                                    | 3.91 (1.26-12.1)    | 0.018 | 4.48 (1.13-14.7)      | 0.033     |
| Clinical Frailty Scale ≥ 4           | 2.12 (0.57-7.83)    | 0.26  | 1.84 (0.45-7.55)      | 0.40      |
| CKD ≥ stage 3A                        | 2.25 (0.61-8.32)    | 0.22  | 1.20 (0.28-5.22)      | 0.81      |
| COPD                                  | 1.77 (0.48-6.54)    | 0.39  | 1.43 (0.30-6.70)      | 0.65      |
| EF                                    | 0.97 (0.92-1.02)    | 0.25  | 0.97 (0.92-1.02)      | 0.25      |

BMI indicates body mass index; STS, Society of Thoracic Surgeons; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; and HR, hazard ratio.

Discussion

The most important result of this study is that balloon-expandable TAVI for selected nonagenarians is feasible, safe, and effective in this population. Most patients in this study were female, as average life expectancy is increasing more rapidly in females than in males.
Patients aged ≥ 90 years had a higher logistic EuroSCORE, Euro II score, STS score, and clinical frailty scale. We found that the device success rate was high and similar in both groups, and that they also had similar 30-day, six-month, and one-year mortalities, and short-term complications. This observational study from a single high-volume center extends the existing evidence for the benefit of the TAVI procedure in very elderly patients with severe AS in the Japanese population.

TAVI is a new therapeutic option for severe patients with AS considered inoperable or at high risk for SAVR. In the 2014 AHA/ACC guidelines for the management of patients with valvular heart disease, those at high risk were defined as those with an STS predicted risk of mortality > 8%, or a moderate to severe degree of frailty; unable to perform ≥ 2 activities of daily living (independence in feeding, bathing, dressing, transferring, toileting, urinary continence, and independence in ambulation without a walking aid or assistance, and a 5-meter walk in < 6 seconds), or dysfunction of two organ systems (cardiac dysfunction, CKD stage 3 or worse, pulmonary dysfunction, central nervous system dysfunction, gastrointestinal dysfunction, active malignancy, and liver dysfunction), or a possible procedure-specific impediment.

TAVI candidates are also selected on the basis of age, frailty, comorbidities, and technical inoperability (such as porcelain aorta and chest wall radiation). In our registry, most patients had moderate to severe frailty, and this was one of the major reasons why they were selected as TAVI candidates. And the patient’s age is thought to account for a large proportion of the reason of treatment selection. In fact, the number of patients aged ≥ 90 years who underwent SAVR was very small (< 1%). It is expected that the prognosis after TAVI of these patients, who cannot survive SAVR, is very poor, but our findings show that nonagenarians as well as younger patients have good outcomes. We argue that TAVI is a reasonable procedure for a carefully selected group of nonagenarians.

This is the first clinical study of TAVI in nonagenarians in Asia. There have been studies that assessed the safety and effectiveness of TAVI in nonagenarians in Europe and the USA. In this study, 22.3% of patients were at least 90 years old. This is higher than the reported percentage of patients who underwent TAVI in the FRANCE-2 Registry (10.1%) and the STS/ACC TVT Registry in the USA (15.7%). And in our registry, most patients aged ≥ 90 years had moderate to severe frailty compared with a previous single high-volume center report in the USA (83.3% versus 59.6%, respectively). Interestingly, mortalities of nonagenarians at 30 days after the procedure in our registry (0.0%) were lower than in the foregoing reports (11.2% in the FRANCE-2 Registry and 8.8% in the STS/ACC TVT Registry). At one year, mortalities in patients aged ≥ 90 years in our registry were also lower than in the foregoing reports (8.4% in the KMH registry, 26.1% in the FRANCE-2 Registry, and 24.8% in the STS/ACC TVT Registry). These results also compare favorably with the 7.6% 30-day mortality rate and 21.0% 1-year mortality rate reported for SAVR in selected nonagenarians.

In regard to the comparison of patients aged ≥ 90 and < 90 years after TAVI, the present study showed that there were no significant differences of 30-day and 1-year mortality rates. The FRANCE-2 data on 30-day and 1-year mortality rates also did not achieve statistical significance, but in the STS/ACC TVT data, the 30-day and 1-year mortality rates in nonagenarians were higher than in younger patients (age ≥ 90 years versus < 90 years: 30 days: 8.8% versus 5.9%; P < 0.001; one year: 24.8% versus 22.0%; P < 0.001). These might be reflected in average life expectancy. The World Health Organization’s World Health Statistics 2016 indicated that the USA had the lowest life expectancy among three countries (83.7 years in Japan, 82.4 years in France, and 79.3 years in the USA). In fact, there were no significant differences, but nonagenarians tended to have higher mortality after one year.

This study also showed that there was no significant difference in the rate of stroke at 30 days between patients aged ≥ 90 and < 90 years, but nonagenarians tended to develop more TIA. The FRANCE-2 data did not achieve statistical significance in the rate of stroke (age ≥ 90 years versus 80-89 years: major stroke: 4.0% versus 4.6%; minor stroke: 1.2% versus 2.9%). On the other hand, the STS/ACC TVT data showed that nonagenarians tended to suffer more strokes in hospital than patients aged < 90 years (2.72% versus 2.11%; P = 0.021). In this study, nonagenarians tended to develop TIA more frequently, suggesting that advancing age may influence strokes in patients who have undergone TAVI.

The present study also showed that patients aged ≥ 90 and < 90 years had a low rate of bleeding according to VARC-2 criteria. Previous studies showed that serious bleeding events and blood transfusions were associated with higher 1-year mortality. This point may also reflect high survival rates after TAVI among our population.

In our registry, nonagenarians had lower prevalence rates of several comorbidities, such as NIDDM, CAD, and previous PCI. However, nonagenarians were more frail than younger patients. Previous reports have demonstrated that nonagenarians who underwent TAVI had lower prevalence rates of comorbidities, and were more frail than patients aged < 90 years. These findings supported appropriate patient selection in our registry, and led to good outcomes. In addition, as we have performed TAVI since 2013, we utilized learning curves in Europe and the USA and improvements in devices, providing another reason why nonagenarians had good outcomes in our registry.

The clinical implication of the present study is that TAVI for selected nonagenarians is feasible, safe, and effective in Asia. Asians are generally smaller than Westerners. In fact, patients aged ≥ 90 years in our registry had a lower BMI than those in the FRANCE-2 Registry, and the STS/ACC TVT Registry (21.1 ± 3.1, 24.5 ± 4.8, and 24.67 (22.20-27.56) kg/m², respectively). Yamamoto et al. reported that major morbidity and 1-year mortality after TAVI were less in overweight and obese patients than in those classified as having normal weight. Nevertheless, mortalities in patients in our registry were very low. We used only SAPIEN XT, while SAPIEN 3 might contribute to a better outcome in small patients such as Asians.
Therefore, further work is needed to assess the safety and effectiveness of SAPIEN 3 and other devices in Asia. It will be necessary to evaluate the long-term prognosis of nonagenarians who have undergone TAVI, and to identify those patients who have good outcomes after TAVI, as nonagenarians have a shorter life expectancy than patients aged < 90 years.

There are some limitations of this study. First, it is a single-center observational study. Second, the patient number was relatively small, especially of nonagenarians. The results warrant future multicenter studies with larger samples.

Conclusion
TAVI is feasible, safe, and effective even in a selected population of nonagenarians. TAVI may be a good therapeutic option in very elderly patients in Japan, which is one of the countries in which the population is aging rapidly.

Disclosures
Conflicts of interest: Kenji Ando has a relationship with Medtronic Japan. The remaining authors report no conflicts.

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