Contemporary short- and mid-term outcomes of transcatheter aortic valve replacement for nonagenarians in Japan

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September 16, 2020

Abstract

Objectives: The large-scale adoption of transcatheter aortic valve implantation (TAVI) and aging of the population in Japan have led to an increase in the number of TAVI procedures among elderly patients. However, the clinical outcomes of TAVI for nonagenarians in Japan are unclear. The aim of this study was to clarify the outcomes of TAVI in nonagenarians with severe aortic stenosis in a real-world Japanese setting. Methods: This study retrospectively assessed the early and mid-term clinical outcomes after TAVI in nonagenarians (group N; n=23) in comparison to those of younger patients (group Y; n=117). Results: There were no postoperative deaths in either group. Although patients in group N required longer hospital stays (19±32.1 days vs. 12.1±9.3 days, p=0.04), all other early outcomes were equivalent in the two groups. The overall survival at 5 years tended to be lower in group N but the difference was not statistically significant (29.5% vs. 51.1%, p=0.26). The freedom from cardiac events at 5 years rate was equivalent in both groups (69.5% vs. 66.0%, p=0.68). There were no late cardiac deaths in group N. The freedom from late cardiac death rate at 5 years was 100% in group N and 84.6% in group Y. Conclusions: The early and mid-term clinical outcomes of TAVI in nonagenarians were comparable to those in younger patients. These results indicate that TAVI is effective for aortic stenosis in Japanese nonagenarians and may help prevent cardiac deaths.

1. INTRODUCTION

According to the 2008 World Health Organization report, Japan is the country with the longest life expectancy. [1] The latest report from the Japanese Ministry of Health, Labor and Welfare stated that the life expectancy has reached 81.2 years in men and 87.3 years in women, with 438,000 people over 90 years of age. [2] Unfortunately, this extreme-aged group has an increased prevalence of aortic stenosis and is more likely to have co-morbid conditions, which poses a dilemma to cardiologists and cardiac surgeons when having to choose between conservative or interventional treatment.

Seven years ago, surgical aortic valve replacement (SAVR) was the only treatment for the clinical management of severe aortic stenosis in Japan. However, since 2013, transcatheter aortic valve implantation (TAVI) has been covered by Japanese national health insurance, making it a less invasive alternative to SAVR. [3,4] TAVI was subsequently rapidly adopted, as previously seen in Europeans countries. [5]

The widespread use of TAVI and the aging of the population in Japan have led to an increase in the number of TAVI procedures in elderly patients. Some Western studies have reported the outcomes of TAVI for nonagenarians. [6-8] However, there are few reports on TAVI for nonagenarians from Asian countries. The aim of this study was to clarify the outcomes of TAVI in nonagenarians with severe aortic stenosis in Japan.

2. MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Yamaguchi University Hospital (Study ID: H2019-071) with an opt-out consent process, and was conducted in accordance with the Declaration of Helsinki.

A total of 140 patients who were treated at our institution for severe aortic stenosis from April 2014 to July 2019 were included in the study. All patients were assessed by a multidisciplinary cardiac team that included cardiac surgeons, cardiologists, cardiac anesthesiologist, and physical therapists to determine the appropriate treatment strategy. We retrospectively assessed the early and mid-term clinical outcomes after TAVI in nonagenarians (group N; n=23) in comparison to those of younger patients (group Y; n=117).

2.1 Operative procedure

TAVI was performed under general anesthesia with endotracheal intubation. A temporary right ventricle pacing lead wire was inserted though the right jugular vein and used when needed. The approach to deployment of the transcatheter prosthetic valve was discussed by the cardiac team. The trans-femoral approach was considered as the initial choice. If a femoral approach was not feasible, a different approach was utilized. The type and size of the prosthetic valves used were determined according to the findings in the aortic valve complex on preoperative enhanced cardiac computed tomography. The Edwards Sapien XT and Sapien 3 (Edwards Lifesciences, Irvine, CA) were used as balloon-expandable valves. The Core Valve, Evolut R, and Evolut PRO (Medtronic Inc., Minneapolis, MN) were used as self-expandable valves.

2.2 Statistical analysis

Continuous data are expressed as the mean $\pm$ standard deviation and their differences were evaluated using Student's t -test. For categorical data, the differences were evaluated using the $\chi 2$ and Fisher exact tests. Time-to-event analyses were performed using Kaplan–Meier estimates and compared between groups using the log-rank test. Independent predictors of overall survival were determined using Cox regression analysis. The multivariable models included covariates with a p <0.10 in the univariate analyses. All statistical analyses were performed using StatView version 5.0 software (SAS Institute, Cary, NC). In each analysis, p <0.05 was regarded as significant.

RESULTS

3.1 Patient characteristics

Baseline patient characteristics are shown in Table 1. The mean age was 83.2±4.7 years in group Y and 92.1±1.9 years in group N (p <0.0001). Preoperative pacemaker implantation was slightly higher in group N than in group Y (17.3% vs. 5.9%). The other patient characteristics did not differ significantly between the two groups. The Society of Thoracic Surgery (STS) risk score was 7.7% in group Y and 8.4% in group N.

3.2 Operative parameters

Operative procedures and intraoperative findings are shown in Table 2. In this study, 75% of patients underwent TAVI through the trans-femoral approach, 19% through the trans-apical, 3%, through the trans-subclavian, and 2% through the ascending aorta. A balloon-expandable valve was implanted in 72% of patients, while a self-expandable valve was implanted in 28%. The interventional approach, type of prosthetic valve, procedure time, and blood transfusion rates were statistically equivalent between the two groups.

3.3 Early outcomes

No inpatient deaths occurred in both the groups. The hospital stay was significantly longer in group N than in group Y (19±32.1 days vs. 12.1±9.3 days, p=0.04). However, the incidence of any complication, including the need for pacemaker implantation, paravalvular leakage, cerebral infarction, and acute type B dissection, was equivalent in the two groups (Table 3).

We assessed postoperative cardiac function using transthoracic echocardiography (Supplemental Figure 1). The aortic valve area was significantly increased in both groups. Peak systolic velocity and mean pressure gra-

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dient were significantly decreased in both groups. There were no significant differences in echocardiographic findings between the two groups.

3.4 Mid-term outcomes

The overall 5-year survival rate was 35.1% across the entire cohort; 51.1% in group N, and 29.5% in group Y (log-rank test, group N vs. group Y, p=0.26; Figure 1A). The 5-year freedom from cardiac events rate was 66.7% across the entire cohort; 69.5% in group N, and 66.0% in group Y (log-rank test, group N vs. group Y, p=0.68; Figure 1B). In terms of 5-year freedom from cardiac death, the rate was 88.7% across the entire cohort; 100% in group N, and 84.6% in group Y (Figure 1C).

In total, 36 remote deaths occurred across the entire cohort, with 7 in group N and 29 in group Y. The causes of remote death in group N were pneumonia in 3 patients, other infectious disease in 3, and malignancy in 1, with no cardiac deaths. On the other hand, the major causes in group Y were cardiac death in 8 patients, pneumonia in 8, cerebrovascular disease in 3, malignancy in 2, and other causes in 8.

3.5 Predictors of mortality after TAVI

We used Cox proportional hazard models to analyze the predictors of mortality after TAVI, as shown in Table 4. The univariate analysis revealed that preoperative serum albumin and hemoglobin were associated with mortality. In the multivariate analysis, only preoperative serum albumin showed a tendency towards predicting mortality, however the association did not reach statistical significance (hazard ratio: 0.54, 95% confidence interval CI: 0.65–1.03, p=0.08).

DISCUSSION

Life expectancy varies from country to country and in addition, the healthcare systems of each country are unique in themselves. In Japan, where health insurance is a requirement, the healthcare delivery environment is different as compared to other countries where health insurance is not a requirement. There are several reports on the outcomes of TAVI for nonagenarians in Western countries.[6-8] However, to our knowledge, this is the first report to investigate outcomes in the Japanese population. Takeji et al. reported that the current hospital mortality rate of TAVI in Japan is 1.3%, suggesting that it has a high success rate and is being performed safely with very low mortality. [3] This study revealed that TAVI in nonagenarians have excellent early- and mid-term outcomes. The in-hospital mortality rate of our nonagenarian cohort was 0%, which was statistically equivalent to the younger patients' cohort (0%). Although hospital stays were longer in the nonagenarian cohort, the other early outcomes were comparable, indicating that TAVI can be safely performed even in very elderly populations. Investigators from Western countries have shown that TAVI in nonagenarians can achieve acceptable in-hospital outcomes and that age alone should not exclude patients from treatment, [6-8] a viewpoint that is supported by our findings.

A decade ago, SAVR was the only effective therapy for aortic valve stenosis. The development of TAVI has dramatically changed the surgical treatment of aortic valve stenosis. Previous studies with nonagenarian cohorts showed that early mortality after SAVR ranged from 11% to 17%.[9,10] In contrast, the in-hospital or 30-day mortality rates after TAVI in nonagenarians has been reported as 0%–8.7% in recent observational studies, showing a distinct advantage.[6,7] In fact, there were no in-hospital or 30-day mortalities in our nonagenarian cohort. Although the long-term results of TAVI remain unclear, it is a useful therapeutic option and a reasonable alternative to SAVR in nonagenarians based on their relatively short life expectancy.

Our results showed that nonagenarian patients required longer hospital stays. Prolonged hospitalization can cause postoperative muscle weakness and deterioration of activities of daily living (ADL). Stehli et al. reported that deterioration of ADL after TAVI is more frequent in older patients and that 25% of nonagenarians transition to aged-care facilities within 1 year after TAVI. [7] We believe that this points to a particular disadvantage of TAVI in very elderly patients. In this cohort, only 15 of 23 nonagenarians had frailty assessment data available as these assessments were not routinely performed during the early period of our series. Although the sample size is limited, we could not find any deterioration in frailty status in the early phase after TAVI (Supplemental table1). However, the data is insufficient for assessing the possible

future changes in ADL and quality of life. Unconscious scaling back of physical activity in patients with cardiac disease is a well-characterized phenomenon. Gradual improvement in activity may be possible after recovery of cardiac function (Supplemental Figure1). Further investigations into long-term ADL outcomes are required.

The freedom from cardiac events rates in each group were almost equivalent in this study. Interestingly no late cardiac deaths occurred in the nonagenarian cohort. The Japanese Ministry of Health, Labor and Welfare reported that the top 5 causes of mortality in nonagenarians are cardiac disease, pneumonia, senility, cerebrovascular disease, and malignancy. [11] In our nonagenarian cohort, the causes of late mortality were pneumonia in 3 patients, other infectious disease in 3, and malignancy in 1, but there were no cardiac deaths. Thus, TAVI may contribute to the avoidance of cardiac death in nonagenarians.

The wide-spread adoption of TAVI and the aging of the population have led to an increase in the number of procedures performed worldwide. The identification of prognostic factors is thus essential for patient selection and stratification in the TAVI era. Various predictors of prognosis after TAVI have been reported; for example, anemia, intra- or post-operative blood transfusion, psoas muscle area, and appetite immediately before discharge were associated with postprocedural mortality. [12-15] In this study, lower preoperative serum albumin seemed to be associated with poor long-term outcomes, but the results were not statistically significant (p=0.08). Serum albumin is a known frailty marker and may be a potential predictor of TAVI outcomes. In this study, age was not a predictor of prognosis despite generally being a significant factor in all procedures. Older patients have more co-morbidities and are at a higher operative risk. In fact, major operative risk scores, including the STS risk score, EuroSCORE, and JapanSCORE, identified older age as independent operative risk factor. [16-18] We believe that our results could be explained by the equivalent risk scores in the nonagenarian and the younger age groups (Table 1). This indicates that the nonagenarian patients may have been selected to some degree and be in relatively better condition as compared to the younger group, which would affect the assessment of age as a prognostic indicator.

This study has several limitations. Since this was a retrospective, observational study, selection bias may be present. The sample size was limited because our hospital is not a high-volume center. Furthermore, data regarding outcomes of conservative medical therapy in nonagenarian aortic stenosis patients were not available.

CONCLUSIONS

The early and mid-term clinical outcomes of TAVI in selected nonagenarians were comparable to those in younger patients and TAVI may contribute to the prevention of cardiac death in nonagenarians. These findings indicate that TAVI may be an effective treatment for aortic stenosis, even in nonagenarian patients.

Author Contributions

Hiroshi Kurazumi: Data analysis, Drafting article,

Akihito Mikamo, Takayuki Okamura: Concept/design

Ryo Suzuki, Bungo Shirasawa, Yosuke Miyazaki, Hiroki Tateishi, Tetsuro Oda: Data collection

Masafumi Yano, Kimikazu Hamano: Approval of article

Disclosure statement

The authors declare no conflict of interest.

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Figure Legends

Figure 1. Mid-term outcomes

(A) Cumulative survival, (B) freedom from cardiac events, (C) and freedom from cardiac death curves. The survival curve of the overall cohort is presented as a dashed black line, that of the nonagenarian group (N) is presented as a solid black line, and that of the younger group (Y) is presented as a solid gray line.

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TABLES

Table 1. Preoperative patients' characteristics

	Entire cohort (n=140)	N group (n=23)	Y group (n=117)	p value
Age (years)	84.6±5.4	92.1±1.9	83.2±4.7	<0.0001
[range]	[69-97]	[90–97]	[69–89]	
Male	47 (33.5%)	5 (21.7%)	42 (35.8%)	0.18
Hypertension	126 (90.0%)	22 (95.6%)	104 (88.8%)	0.32
Dyslipidemia	77 (55%)	12 (52.1%)	65 (55.5%)	0.76
DM	38 (27.1%)	4 (17.3%)	34 (29.0%)	0.25
IHD	55 (39.2%)	4 (17.3%)	51 (43.5%)	0.13
CVD	36 (25.7%)	4 (17.3%)	32 (27.3%)	0.30
COPD	6 (4.2%)	0	6 (5.1%)	0.58
Smoking	9 (6.4%)	0	9 (7.6%)	0.35
Chronic AF	21 (15.0%)	4 (17.3%)	17 (14.5%)	0.72
PMI	11 (7.8%)	4 (17.3%)	7 (5.9%)	0.09
Malignancy	7 (5.0%)	1 (4.3%)	6 (5.1%)	0.98
Previous cardiac surgery	11 (7.8%)	1 (4.3%)	10 (8.5%)	0.49
Serum creatinine (mg/dl)	1.01±0.31	0.98±0.29	1.02±0.29	0.60
Serum albumin (g/dl)	3.66±0.40	3.74±0.38	3.64±0.40	0.27
Hemoglobin (g/dl)	10.80±1.68	10.34±1.53	10.89±1.70	0.15
Oral administration				
β-blocker	22 (15.7%)	5 (21.7%)	41 (35.0%)	0.26
Ca^{2+} blocker	67 (47.8%)	13 (56.5%)	54 (46.1%)	0.36
ACE-I	34 (24.2%)	5 (21.7%)	29 (24.7%)	0.75
ARB	57 (40.7%)	13 (56.5%)	44 (37.6%)	0.09
Statins	62 (44.2%)	10 (43.4%)	52 (44.4%)	0.93
Risk score				
STS risk score	7.9±4.6	8.4±4.6	7.7±4.8	0.50
EuroSCORE II	5.1±4.7	5.4±3.3	5.0±4.9	0.72
JapanSCORE	7.2±6.2	5.1±4.7	7.6±6.8	0.09

ACE-I: angiotensin converting enzyme inhibitor, AF: atrial fibrillation, ARB: angiotensin II receptor blocker, COPD: chronic obstructive pulmonary disease, CVD: cerebral vascular disease, DM: diabetes mellitus, IHD: ischemic heart disease, PMI: pace maker implantation, .

Table 2. Operative procedures and parameters

	Entire cohort (n=140)	N group (n=23)	Y group (n=117)	p value
Approach				
Femoral	105 (75.0%)	17 (73.9%)	88 (75.2%)	1.00
Apical	27 (19.3%)	4 (17.3%)	23 (19.7%)	1.00
Subclavian	5 (3.6%)	1 (4.4%)	4 (3.4%)	1.00

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	Entire cohort (n=140)	N group (n=23)	Y group (n=117)	p value
Aorta Prosthetic valves	3 (2.1%)	1 (4.4%)	2 (1.7%)	0.41
Balloon-expandable	101 (72.2%)	16 (69.6%)	85 (72.6%)	
Size (mm) 20/23/26/29	5/70/25/1	3/12/1/0	2/58/24/1	0.80
Self-expandable	39 (27.8%)	7 (30.4%)	32 (27.4%)	[Balloon vs. Self-expandable]
Size (mm) 23/26/29	2/23/14	0/6/1	2/17/13	
Operation time (min)	149±40	159±40	147±40	0.20
Blood transfusion	47 (33.5%)	9 (39.1%)	38 (32.4%)	0.80

Table 3. Early clinical outcomes

	Entire cohort (n=140)	N group (n=23)	Y group (n=117)	p value
In-hospital death	0	0	0	1.00
ICU stay (days)	1.9±1.1	2.0±1.1	1.9±1.1	0.76
Hospital stay (days)	13.3±15.6	19.1±15.6	12.1±15.	0.04
Newly required PMI	11 (7.8%)	3 (13.0%)	8 (8.5%)	0.34
PVL	14 (10.0%)	2 (8.6%)	12 (10.2%)	1.00
Cerebral infarction	5 (3.5%)	1 (4.3%)	4 (3.4%)	0.82
Disabling cerebral infarction	3 (2.1%)	1 (4.3%)	2 (1.7%)	0.41
Acute type B aortic dissection	2 (1.4%)	1 (4.3%)	1 (0.8%)	0.30
Annulus rupture	1 (0.7%)	1 (4.3%)	0	0.16
Coronary occlusion	1 (0.7%)	1 (4.3%)	0	0.16
Cardiac tamponade	1 (0.7%)	0	1 (0.8%)	1.00
Esophageal perforation	1 (0.7%)	0	1 (0.8%)	1.00

PMI: pace maker implantation, PVL: paravalvular leakage

Table 4. Predictors of mortality after transcatheter aortic valve implantation

	Univariate analysis	Univariate analysis	Univariate analysis	Multivariate analysis	
	Hazard ratio	(95% Confidence interval)	p value	Hazard ratio	(
Age	0.98	(0.93-1.04)	0.59		
Female gender	0.59	(0.30-1.14)	0.11		

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	Univariate analysis	Univariate analysis	Univariate analysis	Multivariate analysis	M
STS risk score	0.96	(0.88-1.05)	0.45		
EuroSCORE II	0.92	(0.81-1.04)	0.20		
JapanSCORE	0.95	(0.87-1.03)	0.25		
Previous cardiac surgery	0.59	(0.14-2.49)	0.48		
Preoperative creatinine	1.31	(0.46-3.40)	0.60		
Preoperative albumin	0.37	(0.15-0.89)	0.02	0.54	(
Preoperative BNP	1.00	(1.00-1.01)	0.38		
Preoperative hemoglobin	0.77	(0.63-0.95)	0.01	0.83	(
Preoperative EF	1.02	(0.98-1.05)	0.14		
Blood transfusion	1.77	(0.89-9.49)	0.11		

BNP: Brain Natriuretic Peptide, EF: Ejection fraction

Supplemental Figure and Table legends

Supplemental Figure 1. Preoperative and postoperative cardiac function evaluated by transthoracic echocardiography

The data of the nonagenarian (N) group are presented in black, and those of the younger (Y) group in gray. PG: pressure gradient

Supplemental Table 1. Frailty assessment of nonagenarian patients (n=15)
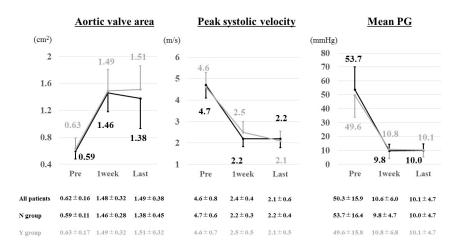
P value was determined by comparing to preoperative state.

% Grip strength was calculated from frailty borderline (men: 26 kg, women: 18kg at the dominant arm).

Knee extensor strength is presented as the average of the right and left knees.

The latest assessment was performed at 4.1±2.6 months after TAVI.

Supplemental Figure 1

	Aortic valve area (cm²) Pre 1week Last	Peak systolic velocity (m/s) Pre 1week Last	Mean PG (mmHg) Pre 1week Last
All patients	0.62±0.16 1.48±0.32 1.49±0.38	4.6±0.8 2.4±0.4 2.1±0.6	50.3±15.9 10.6±6.0 10.1±4.7
N group	0.59±0.11 1.46±0.28 1.38±0.45	4.7±0.6 2.2±0.3 2.2±0.4	53.7±16.4 9.8±4.7 10.0±4.7
Y group	0.63±0.17 1.49±0.32 1.51±0.32	4.6±0.7 2.5±0.5 2.1±0.5	49.6±15.8 10.8±6.8 10.1±4.7

Supplemental Table 1. Frailty assessment of nonagenarian patients (n=15)

	Preoperative state	At discharge [+]	Latest assessment[+, ¶]
5-meter walk test (sec)	7.2±2.4	8.2±3.1 (p=0.24)	8.7±5.2 (p=0.23)
% Grip strength (%)[++]	74.0±19.7	73.1±19.6 (p=0.82)	74.2±22.6 (p=0.94)
Knee extensor strength (N) [§]	145.8±63.4	144.5±61.9 (p=0.90)	127.8±59.1 (p=0.21)

[+]P value was determined by comparing to preoperative state.

[++]% Grip strength was calculated from frailty borderline (male: 26 kg, female: 18kg at the dominant arm).

[SS]Knee extensor strength is presented as the average of the right and left knees.

[P]The latest assessment was performed at 4.1+-2.6 months after TAVI.

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