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【 ORIGINAL ARTICLE 】

The Prognosis of Elderly Patients with Aortic Stenosis after Transcatheter Aortic Valve Replacement

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Abstract:
Objective Aortic stenosis (AS) is common among elderly patients. Since transcatheter aortic valve replacement (TAVR) is a less invasive procedure than surgical aortic valve replacement for symptomatic severe AS, super-elderly patients have tended to undergo TAVR. We retrospectively investigated the post-TAVR outcome in super-elderly patients with severe AS.
Methods This analysis included 433 patients who underwent TAVR in the University of Wisconsin Hospital and Clinics from 2012 to 2017. Post-TAVR mortality, complications in-hospital, rehospitalization, the New York Heart Association (NYHA) functional class and echocardiographic parameters were compared between patients <85 years old (n = 290) and ≥85 years old (n = 143).
Results The patients ≥85 years old less frequently had a history of coronary artery disease (73.1% vs. 62.2%, p=0.026) and hypertension (87.2% vs. 77.6%, p=0.012) than younger patients. Furthermore, the patients ≥85 years old had moderate-severe mitral regurgitation more frequently (19.3% vs. 28.7%, p=0.037) at baseline than younger patients. There was no significant difference in in-hospital outcomes between the age groups. The 30-day mortality was worse in patients ≥85 years old than in younger ones (0.7% vs. 3.5%, p=0.042). While there was no significant difference in the long-term mortality between the 2 groups, the estimated 1-year mortality from Kaplan-Meier curves were 9.6% in patients <85 years old and 14.9% in patients ≥85 years old. The rate of in-hospital complications, rehospitalization rate, improvement in the NYHA functional class and echocardiographic parameters were comparable between the two groups.
Conclusion The outcomes of super-elderly patients after TAVR were acceptable, suggesting that these patients could benefit from TAVR.

Key words: severe AS, TAVR

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Introduction

The elderly population is growing at an unprecedented rate, and access to minimally invasive treatment options is improving as well. In elderly adults, aortic stenosis (AS) is a common valvular disease with a prevalence of 3.9% at 70 to 79 years old and 9.8% at 80 to 89 years old (1). Consequently, the incidence of heart failure due to AS is also on the rise (2).

The natural history of untreated patients with symptomatic severe AS is poor. The mean survival after the onset of heart failure ranges from 0.5 to 2.8 years (3). AVR has been the standard therapy in patients with symptomatic severe AS, but surgical AVR is relatively invasive for elderly people with severe AS, and surgical AVR was reportedly denied in one-third of elderly patients (4). Since transcatheter aortic valve replacement (TAVR) is now an established low-invasive tool, the number of super-elderly patients receiving TAVR has been increasing (5-11). Some reports have even shown that super-elderly patients have a comparable short-term prognosis to younger patients after TAVR (12-14).

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Table 1. Baseline Characteristics.

Variables	Age<85 (n=290)	Age ≥85 (n=143)	p value
Age: years	77 (70-81)	88 (86-90)	<0.001
Male: No (%)	178 (61.4)	74 (51.7)	0.062
Race: No (%)			
White	281 (96.9)	141 (98.6)	0.352
Black	7 (2.4)	1 (0.7)	0.280
Asian	1 (0.3)	1 (0.7)	0.552
American Indian/Alaskan Native	1 (0.3)	0 (0.0)	1.000
Body mass index (kg/m²)	27.9 (24.3-33.2)	28.9 (24.3-34.4)	0.599
Past medical history: No (%)			
Coronary artery disease	212 (73.1)	89 (62.2)	0.026
Percutaneous coronary intervention	115 (39.7)	41 (28.7)	0.026
Coronary artery bypass grafting	86 (29.7)	28 (19.6)	0.028
Myocardial infarction	52 (17.9)	29 (20.3)	0.601
Aortic valve replacement	13 (4.5)	10 (7.0)	0.396
Stroke	25 (8.6)	15 (10.5)	0.597
Peripheral artery disease	48 (16.6)	25 (17.5)	0.787
Moderate-severe chronic lung disease	74 (25.7)	30 (21.6)	0.400
Dialysis	9 (3.1)	7 (4.9)	0.418
Atrial fibrillation or flutter	118 (40.7)	48 (33.6)	0.172
Hypertension	253 (87.2)	111 (77.6)	0.012
Diabetes mellitus	111 (38.3)	47 (32.9)	0.414
NYHA functional class III-IV: No (%)	228 (80.0)	119 (84.4)	0.292
KCCQ-12 overall score	50.0 (31.3-67.7)	44.8 (26.6-67.5)	0.202
STS score	6.5 (4.1-9.5)	7.3 (4.1-10.7)	0.334
Echocardiographic parameters			
Left ventricular ejection fraction (%)	60.0 (45.0-65.0)	60.0 (50.0-68.0)	0.071
Left ventricular end-diastolic diameter (mm)	47.0 (40.3-52.0)	46.0 (40.8-51.0)	0.565
Stroke volume index (mL/m²)	35.0 (29.1-44.4)	36.8 (30.1-46.7)	0.280
Mean aortic pressure gradient (mmHg)	41.0 (34.0-51.0)	44.0 (35.0-52.0)	0.142
Aortic valve area (cm²)	0.70 (0.60-0.90)	0.70 (0.60-0.90)	0.948
Moderate-severe mitral regurgitation: No (%)	56 (19.3)	41 (28.7)	0.037
Moderate-severe tricuspid regurgitation: No (%)	52 (17.9)	24 (16.8)	0.893

Data are presented as median (25th–75th percentile) or number (%). Mann-Whitney test or Fisher's exact test, respectively.

Therefore, we retrospectively compared the short- and long-term mortality, rehospitalization rate, in-hospital complications and New York Heart Association (NYHA) functional class between patients <85 and ≥85 years old who underwent TAVR.

Materials and Methods

Patients

From January 2012 to December 2017, a total of 543 patients underwent TAVR at the University of Wisconsin Hospital and Clinics. We excluded 110 patients from the analysis because they were not serially followed within our hospital system. We therefore analyzed the remaining 433 patients retrospectively. The Institutional Review Board approved this study, IRB# 2015-1050.

Definition of endpoints

Procedural and in-hospital complications, cardiovascular and non-cardiovascular mortality, and stroke were defined by Valve Academic Research Consortium-2 (VARC-2) (15). The endpoints were all-cause mortality, rehospitalization for valve-related symptoms or worsening congestive heart failure and NYHA functional class III or IV.

Echocardiography

The left ventricular ejection fraction (LVEF) was determined with the biplane Simpson's method and eyeball assessment. Doppler velocity measurements of the left ventricular outflow tract flow and transvalvular flow were measured, and the stroke volume and aortic valve area were calculated with the continuity equation. The mean transaortic pressure gradient (MPG) was obtained with Bernoulli's equation. The stroke volume index (SVI) was calculated with the body surface area (BSA) determined by the Du Bois method (16, 17).

Survival curve of the general population

The survival curve of the 85- or 90-year-old general

Table 2. Procedural Characteristics and In-hospital Outcomes.

Variables	Age<85 (n=290)	Age ≥85 (n=143)	p value
Access site			
Transfemoral	229 (79.0)	112 (78.3)	0.901
Transapical	37 (12.8)	21 (14.7)	0.653
Transaortic	16 (5.5)	9 (6.3)	0.827
Transsubclavian	6 (2.1)	0 (0.0)	0.184
Transaxillary	1 (0.3)	0 (0.0)	1.000
Device			
Sapien	49 (16.9)	23 (16.1)	0.891
Sapien XT	48 (16.6)	31 (21.7)	0.234
Sapien 3	144 (49.7)	68 (47.6)	0.684
CoreValve	15 (5.2)	4 (2.8)	0.324
Evolute	32 (11.0)	16 (11.2)	1.000
In-hospital complications			
Death	1 (0.3)	3 (2.1)	0.107
Cerebral vascular disease	7 (2.4)	3 (2.1)	1.000
New-onset atrial fibrillation	11 (3.8)	4 (2.8)	0.782
New permanent pacemaker	15 (5.2)	10 (7.0)	0.512
Major vascular complication	6 (2.1)	3 (2.1)	1.000
Life-thretening or major bleeding	28 (9.7)	23 (16.1)	0.058
Myocardial infarction	1 (0.3)	2 (1.4)	0.255
Cardiac arrest	10 (3.4)	4 (2.8)	1.000
Acute kidney injury	24 (8.3)	14 (10.1)	0.588
New requirement for dialysis	3 (1.0)	2 (1.4)	0.667
ICU Hours	19.7 (2.0-28.5)	21.0 (2.0-38.0)	0.348
Moderate-sever paravalvular leak	8 (2.8)	5 (3.7)	0.764
Post-TAVR mean aortic pressure gradient (mmHg)	5.0 (3.0-10.0)	4.5 (3.0-9.0)	0.336
Post-TAVR aortic valve area (cm^2)	1.65 (1.30-2.10)	1.60 (1.30-2.00)	0.774

Data are presented as median (25th–75th percentile) or number (%). Mann-Whitney test or Chi-Square test, respectively.

population in 2010 was created based on actual life tables made available by the United States Social Security Administration.

Statistical analyses

The analyses were performed using the SPSS software program, version 26 (IBM, Armonk, USA). Categorical variables were compared with the chi-square test. Continuous variables were expressed as the median with the corresponding 25th and 75th quartiles and were compared with the Mann-Whitney U-test. The survival was analyzed with Kaplan-Meier curves, a generalized Wilcoxon test and a Cox regression analysis. p<0.05 was considered significant.

Results

Baseline characteristics

The clinical characteristics are shown in Table 1. There was no significant difference in sex ratios between the groups (p=0.062). Patients <85 years old more frequently had a history of coronary artery disease, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) than older ones (p=0.026, 0.026 and 0.028, respectively). In addition, a history of hypertension was also more frequent in patients <85 years old than in older ones. There were no marked differences between groups in the NYHA functional class III-IV symptoms or the Kansas City Cardiomyopathy Questionnaire (KCCQ)-12 overall score. Regarding the baseline echocardiographic parameters, moderate-severe mitral regurgitation was less frequent in patients <85 years old than in those ≥85 years old (p=0.037).

Procedural characteristics and in-hospital complications

Procedural characteristics and in-hospital outcomes are shown in Table 2. The access sites and device types were similar in the two groups. There were no significant differences in hospital complications or valve-related dysfunction between the two groups.

Mortality

The survival curves are shown in Figure. The observation periods were 461 (339-781) days in patients <85 years old and 395 (263-777) days in patients ≥85 years old (p=0.239). Neither the all-cause nor cardiovascular mortality rates were significantly different between the groups (p=0.120 and 0.149, respectively; Figure A, B). We also performed Cox

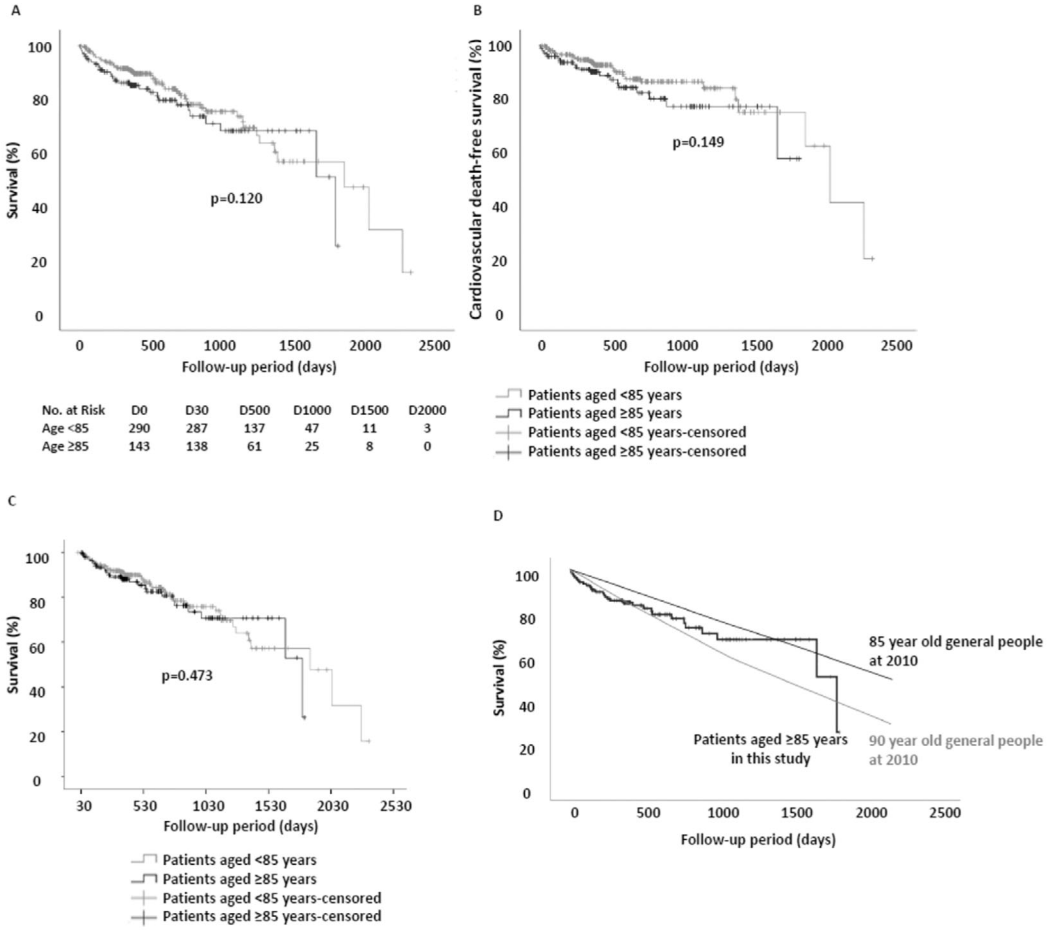

Figure. **Kaplan-Meier curves of the cumulative survival. (A) The rate of survival from any cause. (B) The rate of survival from cardiovascular causes. (C) Landmark analyses after day 30 post-TAVR. (D) A comparison of the survival curves of patients ≥85 years old in our study and the 85- or 90-year-old general population in 2010. The survival curve of the 85- or 90-year-old general population in 2010 was created based on the actual life tables made available by the United States Social Security Administration.**

regression analyses (Table 3). However, the 30-day mortality was worse in patients ≥85 years old than in younger ones (0.7% vs. 3.5%, respectively, p=0.042) as shown in Table 4. There was no marked difference between the groups in the all-cause mortality after day 30 post-TAVR (Figure C).

Rehospitalization and stroke

As shown in Table 5, there was no marked difference in the rehospitalization rate for valve-related symptoms or worsening congestive heart failure or stroke between the two groups.

Improvement of NYHA functional class

The NYHA functional class values at one month and one year post-TAVR are shown in Table 6. The NYHA functional class improved in both groups after TAVR. There was no marked difference in the improvement of the NYHA functional class.

Echocardiographic data after TAVR

One month after TAVR, the LVEF was significantly better in patients ≥85 years old than in younger ones: 60.0% (50.0-65.0%) vs. 65.0% (55.0-70.0%), p=0.003. There were no marked differences in the SVI, MPG or frequency of aortic and mitral regurgitation between the older and younger groups: SVI, 36.4 (28.5-44.1) vs. 37.5 (30.2-43.1) mL/m^2; MPG, 10.0 (8.0-14.0) vs. 11.4 (8.0-15.0) mmHg; mild-severe aortic regurgitation, 43.9% vs. 44.7%; moderate-severe mitral regurgitation, 9.4% vs. 12.7%.

Discussion

Our study showed that the 30-day mortality was worse in patients ≥85 years old than in younger ones. Their mortality was 3.5%, which is equivalent to that in previous studies (7.7% in the study by Buellesfeld et al.; 4.3% in the study by Havakuk et al.) (12, 14). In addition, in the PARTNER trial, the 30-day mortality was 5.3% in inoperable patients

Table 3. Cox Regression Analyses of Factors Associated with All-cause Mortality.

	Hazard ratio	95.0% CI		p value
		Lower	Upper	
Age ≥85	0.751	0.479	1.178	0.212
Sex	0.774	0.492	1.217	0.268
Coronary artery disease	0.932	0.559	1.553	0.787

	Hazard ratio	95.0% CI		p value
		Lower	Upper	
Age ≥85	0.815	0.518	1.282	0.376
Sex	0.897	0.568	1.416	0.641
Serum creatinine	1.259	1.136	1.394	0.000

	Hazard ratio	95.0% CI		p value
		Lower	Upper	
Age ≥85	0.770	0.491	1.209	0.257
Sex	0.757	0.485	1.181	0.219
Stroke	0.684	0.361	1.297	0.245

	Hazard ratio	95.0% CI		p value
		Lower	Upper	
Age ≥85	0.793	0.502	1.251	0.318
Sex	0.771	0.492	1.210	0.258
NYHA functional class ≥3	0.557	0.278	1.116	0.099

	Hazard ratio	95.0% CI		p value
		Lower	Upper	
Age ≥85	0.814	0.492	1.344	0.421
Sex	0.736	0.451	1.200	0.219
Stroke volume index	0.975	0.955	0.996	0.018

	Hazard ratio	95.0% CI		p value
		Lower	Upper	
Age ≥85	0.747	0.477	1.171	0.204
Sex	0.781	0.499	1.222	0.280
Left ventricular ejection fraction	0.995	0.981	1.009	0.482

receiving standard therapy without balloon aortic valvuloplasty (18). However, the rate of rehospitalization, rate of in-hospital complications and improvement in the NYHA functional class were similar between patients <85 and ≥85 years old, as previous studies have shown (12-14).

Patients ≥85 years old had a worse short-term mortality than younger patients in our study. However, differences in age are expected to be associated with mortality. The 30-day mortality in patients ≥75/<85 years (median age 80.0 years old) was 1.2%, and that in patients <75 years (median age 69.0 years) was 0%. There was no significant difference in the 30-day mortality between patients ≥75/<85 years and patients ≥85 years old. Havakuk et al. compared outcomes between patients ≤85 and >85 years old. In the younger group, with a mean age 80.5±4 years old, the 30-day mortality was 1.5%, and in the older group, with a mean age of 88.8±2.5 years old, the 30-day mortality was 4.3% (14). Buellesfeld et al. also compared the 30-day mortality among 4 groups, noting no marked differences among them: group A, mean age 73.4±4.5 years old, 30-day mortality 8.4%; group B, 80.6±1.1 years old, 8.3%; group C, 84.5±1.1 years old, 8.9%; and group D, 88.9±2.2 years old, 7.7% (12). In addition, the proportion of women among the patients ≥85 years old was 49.3%, and there was no significant difference between the 2 groups in this study; of note, this value was lower than that in previous studies, in which approximately 70% were women, and significant sex ratio differences were detected between younger and older cohorts in the previous studies (12, 14). Generally, super-elderly patients would not tolerate well any type of complications and one complication could be a life-threatening issue for them. This could be one of the reasons why our super-elderly patients had higher

Table 4. Thirty-day Mortality and Characteristics of Deceased Patients.

	Age<85 (n=290)	Age ≥85 (n=143)	p value
30-day mortality	2 (0.7)	5 (3.5)	0.042
Deceased cases	(n=2)	(n=5)	
Cardiovascular death	1 (50)	4 (80)	
Perioperative factors			
Male	1 (50)	4 (80)	
STS score ≥15	1 (50)	3 (60)	
Coronary artery disease	2 (100)	4 (80)	
Atrial fibrillation/flutter	1 (50)	2 (50)	
LVEF<50%	1 (50)	2 (40)	
In-hospital complications			
New permanent pacemaker	1 (50)	0 (0)	
Major vascular complication	0 (0)	1 (20)	
Life-threatening or major bleeding	0 (0)	3 (60)	
Myocardial infarction	0 (0)	1 (20)	
Cardiac arrest	1 (50)	1 (20)	
Acute kidney injury	1 (50)	2 (40)	
New requirement for dialysis	0 (0)	2 (40)	

Data are presented as number (%). Fisher's exact test.

Table 5. Rehospitalization and Stroke after TAVR.

	Age<85 (n=290)	Age ≥85 (n=143)	p value
Rehospitalization for all cause	128 (44.8)	65 (45.8)	0.918
Rehospitalization for valve-related symptoms or worsening congestive heart failure	39 (13.5)	23 (16.1)	0.469
All stroke	13 (4.5)	5 (3.5)	0.800

Data are presented as number (%). Fisher's exact test.

Table 6. NYHA Functional Class after TAVR.

Variables	Age<85	Age ≥85	p value
NYHA functional class III-IV after 1 month: No (%)	41 (14.6)	24 (17.8)	0.471
Improvement of NYHA functional class after 1 month: No (%)	222 (79.3)	110 (82.1)	0.598
NYHA functional class III-IV after 1 year: No (%)	20 (10.8)	10 (11.6)	0.837
Improvement of NYHA functional class after 1 year: No (%)	156 (89.3)	73 (85.9)	0.721

Data are presented as number (%). Fisher's exact test.

30-day mortality than the younger patients although there were no differences in the in-hospital complications between the groups.

Patients ≥85 years old had similar rehospitalization rates and symptomatic improvement to younger patients. Notably, a history of coronary artery disease was significantly less frequent in patients ≥85 years old than in younger ones in the present study, which is important, given that coexisting coronary artery disease influences the 1-year mortality in patients undergoing TAVR (19). In addition, hypertension was also less frequent in the older group than in the younger group. These factors may explain the comparable rates of rehospitalization for valve-related symptoms or worsening congestive heart failure and symptomatic improvement and the superior LVEF after TAVR in the older group compared with the younger group. As noted in previous studies, younger patients undergoing TAVR frequently have significant comorbidities compared to older patients, including coronary artery disease, diabetes, chronic lung disease and renal dysfunction, implying an inherent selection bias (12, 14).

The estimated 1-year mortality from the Kaplan-Meier curve in patients ≥85 years old was 14.9%. According to the National Vital Statistics Report from the Centers for Disease Control and Prevention, the probabilities of dying within 1 year for 85- and 90-year-old were 8.3% and 14.4%, respectively, in 2017 (20). In the PARTNER Trial, the 1-year mortality was 50.7% for inoperable symptomatic severe AS patients assigned to standard therapy (21). The life expectancy in the general Caucasian population in the US is 6.5

years for 85-year-old and 4.5 years for 90-year-old (20). Therefore, TAVR may be beneficial for super-elderly patients, and the prognosis of super-elderly severe AS patients after TAVR is reasonable compared to that in the general population in the US (Figure D).

We noted no marked cost-effectiveness, although it is generally considered that TAVR may be superior to surgical aortic valve replacement (SAVR) in cost-effectiveness in inoperable or high-risk patients (22). While super-elderly patients are often inoperable or high-risk, the cost-effectiveness in super-elderly patients might be reduced because of their relatively short life expectancy.

Several limitations associated with the present study warrant mention. This study was a retrospective analysis with a significant number of excluded or censored cases. Consequently, there is the inherent possibility of selection bias. In addition, we did not directly compare the short- and long-term mortality between TAVR and maximal medical management. Thus, it is difficult to say that TAVR is beneficial for super-elderly patients with absolute certainty, although these data should aid in decision-making for clinical practice.

Conclusion

In summary, the outcomes of super-elderly patients after TAVR were acceptable, and this patient population may reasonably be expected to benefit from TAVR.

The authors state that they have no Conflict of Interest (COI).

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