Age-Related Differences in the Effects of Initial Aortic Valve Replacement vs. Conservative Strategy on Long-Term Outcomes in Asymptomatic Patients With Severe Aortic Stenosis

Akihiro Kushiyama, MD; Tomohiko Taniguchi, MD; Takeshi Morimoto, MD; Hiroki Shiomi, MD; Kenji Ando, MD; Norio Kanamori, MD; Koichiro Murata, MD; Takeshi Kitai, MD; Yuichi Kawase, MD; Chisato Izumi, MD; Makoto Miyake, MD; Hirokazu Mitsuoka, MD; Masashi Kato, MD; Yutaka Hirano, MD; Shintaro Matsuda, MD; Tsukasa Inada, MD; Kazuya Nagao, MD; Hiroshi Mabuchi, MD; Yasuyo Takeuchi, MD; Keiichiro Yamane, MD; Mamoru Toyofuku, MD; Mitsuru Ishii, MD; Eri Minamino-Muta, MD; Takao Kato, MD; Moriaki Inoko, MD; Tomoyuki Ikeda, MD; Akihiro Komasa, MD; Katsuhisa Ishii, MD; Kozo Hotta, MD; Nobuya Higashitani, MD; Yosihiko Kato, MD; Yasutaka Inuzuka, MD; Toshikazu Jinnai, MD; Yuko Morikami, MD; Naritatsu Saito, MD; Kenji Minatoya, MD; Takeshi Kimura, MD on behalf of the CURRENT AS Registry Investigators

Background: This study aimed to evaluate the effect of the initial aortic valve replacement (AVR) strategy relative to a conservative strategy on long-term outcomes stratified by age among asymptomatic patients with severe aortic stenosis (AS).

Methods and Results: Among 1,808 asymptomatic severe AS patients in the CURRENT AS registry, there were 1,166 patients aged ≥75 years (initial AVR: n=124, and conservative: n=1,042), and 642 patients with age <75 years (initial AVR: n=167, and conservative: n=475). Median follow-up interval was 1,280 (interquartile range [IQR]: 1,012–1,611) days, and 1,461 (IQR: 1,132–1,886) days in patients aged ≥ and <75 years, respectively. The favorable effect of the initial AVR strategy relative to conservative strategy for heart failure (HF) hospitalization was seen regardless of the age stratum (≥75 years: adjusted hazard ratio [HR] 0.13, 95% confidence interval [CI] 0.05–0.34, and <75 years: HR 0.37, 95% CI 0.14–0.99, interaction P=0.35). However, the lower mortality risk of the initial AVR strategy relative to conservative strategy was significant in patients aged ≥75 years, but not in patients <75 years, with significant interaction (HR 0.35, 95% CI 0.20–0.61, and HR 0.69, 95% CI 0.41–1.16, interaction P=0.016).

Conclusions: The benefit of initial AVR in reducing HF hospitalization in asymptomatic patients with severe AS was consistently seen regardless of age. The magnitude of mortality benefit of initial AVR was greater in super-elder patients than in non-super-elder patients.

Key Words: Aortic stenosis; Aortic valve replacement; Outcomes; Valvular diseases

The current guidelines recommend watchful waiting for aortic valve replacement (AVR) until symptoms emerge in asymptomatic patients with severe aortic stenosis (AS), except for those patients with very severe AS, left ventricular systolic dysfunction, or need for other cardiac surgery.\(^1\)\(^-\)\(^3\) However, the recommendation was based on previous small, single-center studies that sought to evaluate symptoms and/or AVR, but not death, as the outcome measures.\(^4\)\(^-\)\(^7\) We recently reported that an initial AVR strategy in asymptomatic patients with severe AS...
was associated with lower long-term risk for all-cause death and heart failure (HF) hospitalization than a conservative strategy in the large multicenter observational CURRENT AS (Contemporary outcomes after sUrgery and medical tREatment in patients with severe Aortic Stenosis) registry. One of the major differences between the CURRENT AS registry and the previous observational studies was the age of the study patients. The CURRENT AS registry included a much larger proportion of super-elder patients as compared with the previous studies that reported good outcomes with a watchful waiting strategy. The clinical outcomes under the watchful waiting strategy might be different according to the age of the patients. Therefore, we sought to evaluate the effect of initial AVR strategy relative to conservative strategy on long-term outcomes stratified by age (super-elder and non-super-elder patients) in asymptomatic patients with severe AS in the CURRENT AS registry.

**Methods**

**Study Population**

The CURRENT AS registry is a multicenter, retrospective registry enrolling consecutive patients with severe AS among 27 centers in Japan between January 2003 and December 2011. The institutional review boards in all 27 participating centers approved the protocol. Written informed consent from each patient was waived in this retrospective study, because we used clinical information obtained during routine clinical practice, and no patients refused to participate in the study when contacted for follow-up. The design and patient enrollment of the CURRENT AS registry have been described previously. Among 3,815 patients enrolled in the registry who met the definition of severe AS (peak aortic jet velocity \( V_{\text{max}} \) and the mean aortic pressure gradient \( PG \) were calculated using the simplified Bernoulli equation. \( V_{\text{max}} = 1.0 \text{cm}^2 \) for the first time during the study period, 1,808 patients were without symptoms related to AS at the time of the index echocardiography. We divided those 1,808 asymptomatic patients into 2 strata according to age (<75 and ≥75 years). The long-term clinical outcomes were compared according to the treatment strategy selected after the index echocardiography (initial AVR vs. conservative strategy) (Figure 1). The INITIAL AVR and conservative strategies were compared by the intention-to-treat principle regardless of the actual performance of AVR. Follow-up was commenced on the day of the index echocardiography.

**Data Collection and Definitions**

The collection of baseline clinical information was conducted through review of the hospital charts and databases. Angina, syncope, and HF symptoms, including both acute HF requiring hospitalization and chronic exertional dyspnea, were regarded as AS-related symptoms. All patients at each participating center underwent comprehensive 2D and Doppler echocardiographic evaluations. \( V_{\text{max}} \) and the mean aortic PG were calculated using the standard continuity equation. The follow-up data were mainly collected through a review of hospital charts or through contact with patients, their relatives, and/or the referring physicians asking questions on survival status, symptoms, and subsequent hospitalization. The primary outcome measures in the present analysis were all-cause death and HF hospitalization consistent with our previous report. We also evaluated cardiovascular death, AV-related death, sudden death, non-cardiovascular death, and the composite endpoint relatively specific for AS (a composite of AV-related death or HF hospitalization). The cause of death was classified according to the VARC (Valve Academic Research Consortium) definitions and was adjudicated by a clinical event committee (see Supplementary File).

**Statistical Analysis**

Categorical variables are presented as numbers and percentages, and were compared with the chi-square test or Fisher’s exact test. Continuous variables are expressed as the mean and standard deviation or median and interquartile range (IQR). Based on their distributions, continuous variables were compared using Student’s t-test or the Wilcoxon rank sum test. We used the Kaplan-Meier method to estimate the cumulative incidences of events comparing between initial AVR and conservative groups in the 2 age strata, and assessed the differences with the log-rank test. To adjust for the differences in baseline characteristics between the initial AVR and conservative strategy groups, we constructed multivariable Cox proportional hazard models incorporating the 21 clinically relevant risk-adjusting variables listed in Table 1 consistent with our previous report. The continuous variables were dichotomized by median values or clinically meaningful reference values except for age. Age was incorporated as the continuous variable in both the super-elder and non-super-elder age strata. Proportional hazard assumptions for the risk-adjusting variables, including the categorized age in quartiles, were assessed on the plots of log (time) vs. log \([-\log (\text{survival})]\) stratified by the variable, and were verified to be acceptable. Centers were incorporated as the stratification variable in the multivariable Cox models.
effects of initial AVR strategy relative to conservative strategy for the clinical endpoints were expressed as hazard ratios (HR) and their 95% confidence intervals (CI). We also conducted the formal interaction test between the age strata and the effects of initial AVR strategy relative to conservative strategy. We also divided the 1,808 asymptomatic patients into 2 groups according to mean aortic PG (high: Vmax >4.0 m/s or mean aortic PG >40 mmHg, and low: Vmax <4.0 m/s or mean aortic PG <40 mmHg, and AVA <1.0 cm²). We performed sensitivity analyses in 816 asymptomatic patients with high-gradient severe AS and 992 asymptomatic patients with low-gradient severe AS using a Cox proportional hazard models with the same risk-adjusting variables except for Vmax ≥4 m/s.

All statistical analyses were conducted by 2 physicians (A. Kushiyama and T. Taniguchi) and a statistician (T. Morimoto) using JMP 10.0.2 (SAS Institute Inc., Cary, NC, USA) or SAS 9.4 (SAS Institute Inc.). All reported P values were 2-tailed, and P<0.05 was considered statistically significant.

**Results**

**Baseline Characteristics**

There were 1,166 patients in the super-elder stratum (age ≥75 years; initial AVR: n=124, conservative: n=1,042), and 642 patients in the non-super-elder stratum (age <75 years; initial AVR: n=167, conservative: n=475). Mean age was 66.8±7.1 years and 82.3±5.4 years in the non-super-elder and super-elder strata, respectively. The clinical and echocardiographic characteristics were different in several aspects between groups, including higher prevalence of women, hypertension, prior symptomatic stroke, coronary artery disease, and anemia and lower prevalence of hemodialysis and congenital etiology of AS in patients aged ≥75 years than in patients aged <75 years (Table 1, Supplementary Table 1). Median STS (Society of Thoracic Surgeons) score was higher in patients aged ≥75 years than in patients aged <75 (3.9, IQR: 2.7–5.8, and 1.9, IQR: 1.3–3.3) (Supplementary Table 1).

Baseline clinical characteristics were significantly different between the initial AVR and conservative strategy groups, and the differences were generally consistent in the 2 age strata (Table 1). Patients in the conservative group more often had prior myocardial infarction, prior percutaneous coronary intervention (PCI), and prior open-heart surgery, and had higher serum creatinine levels than patients in the initial AVR group. In patients aged ≥75 years, patients in the conservative group were older, had smaller body mass index (BMI), and more often undergone prior coronary artery bypass grafting (CABG) than those in the initial AVR group. In patients aged <75 years, patients in the conservative group had higher BMI, and more often had diabetes, atrial fibrillation, and serum creatinine level >2 mg/dL. Regarding the echocardiographic variables, patients in the initial AVR group had greater AS severity than those in the conservative group. Surgical risk scores such as the Logistic European System for Cardiac Operation Risk Evaluation score, European System for Cardiac Operative Risk Evaluation II score, and STS score were significantly higher in the conservative group than in the initial AVR group (Table 1).

**Clinical Outcomes**

Median follow-up interval was 1,280 (IQR: 1,012–1,611) days, and 1,461 (IQR: 1,132–1,886) days in patients aged ≥ and <75 years, respectively. Among 167 patients aged <75 and 124 patients aged ≥75 years referred for AVR

---

**Figure 1.** Study patient flow. AS, aortic stenosis; AVR, aortic valve replacement.
Age-Related Differences in Asymptomatic Patients With Severe AS

Table 1. Baseline Clinical and Echocardiographic Characteristics Compared Between Initial AVR and Conservative Groups Stratified by Age

| Clinical characteristics | Age <75 years | Age ≥75 years | P value | Age <75 years | Age ≥75 years | P value |
|--------------------------|---------------|---------------|---------|---------------|---------------|---------|
| Age, years*              | 66.2±7.4      | 67.1±7.0      | 0.16    | 79.0±3.3      | 82.7±5.4      | <0.0001 |
| Men*                     | 76 (46%)      | 231 (49%)     | 0.49    | 50 (40%)      | 373 (36%)     | 0.32    |
| BMI*                     | 21.7±3.4      | 22.5±3.7      | 0.01    | 22.6±3.0      | 21.6±4.0      | 0.007   |
| BMI <22*                 | 94 (56%)      | 237 (50%)     | 0.16    | 52 (42%)      | 674 (65%)     | <0.0001 |
| BSA, m²                  | 1.52±0.17     | 1.54±0.18     | 0.15    | 1.50±0.16     | 1.42±0.16     | <0.0001 |
| Hypertension*            | 98 (59%)      | 288 (61%)     | 0.66    | 90 (73%)      | 772 (74%)     | 0.72    |
| Current smoking*         | 13 (8%)       | 37 (8%)       | 1.00    | 9 (7%)        | 36 (3%)       | 0.047   |
| History of smoking       | 40 (24%)      | 129 (27%)     | 0.42    | 34 (27%)      | 199 (19%)     | 0.03    |
| Dystipidemia             | 58 (35%)      | 170 (36%)     | 0.81    | 58 (47%)      | 362 (35%)     | 0.008   |
| On statin therapy        | 32 (19%)      | 123 (26%)     | 0.08    | 40 (32%)      | 269 (26%)     | 0.12    |
| Diabetes mellitus        | 23 (14%)      | 126 (27%)     | 0.0008  | 36 (29%)      | 249 (24%)     | 0.21    |
| On insulin therapy*      | 7 (4%)        | 26 (5%)       | 0.52    | 4 (3%)        | 54 (5%)       | 0.34    |
| Coronary artery disease* | 28 (17%)      | 107 (23%)     | 0.12    | 33 (27%)      | 320 (31%)     | 0.35    |
| Prior myocardial infarction* | 3 (2%) | 1 (7%) | 0.02 | 2 (2%) | 115 (11%) | 0.001 |
| Prior PCI                | 9 (5%)        | 60 (13%)      | 0.009   | 12 (10%)      | 205 (20%)     | 0.007   |
| Prior CAGB               | 5 (3%)        | 27 (6%)       | 0.17    | 2 (2%)        | 64 (6%)       | 0.04    |
| Prior open-heart surgery | 9 (5%)        | 64 (13%)      | 0.005   | 4 (3%)        | 88 (8%)       | 0.04    |
| Prior symptomatic stroke*| 11 (7%)       | 56 (12%)      | 0.06    | 14 (11%)      | 172 (17%)     | 0.13    |
| Atrial fibrillation or flutter* | 21 (13%) | 107 (23%) | 0.006  | 18 (15%)      | 192 (18%)     | 0.28    |
| Aortic/peripheral vascular disease* | 13 (8%) | 51 (11%) | 0.27  | 10 (8%) | 97 (9%) | 0.65 |
| Serum creatinine, mg/dL* | 0.8 (0.6–1.0) | 0.9 (0.7–1.4) | 0.002 | 0.8 (0.6–0.9) | 0.9 (0.7–1.2) | 0.002 |
| Creatinine >2mg/dL       | 23 (14%)      | 101 (21%)     | 0.03    | 11 (9%)       | 114 (11%)     | 0.48    |
| Hemodialysis*            | 22 (13%)      | 94 (20%)      | 0.06    | 10 (8%)       | 81 (8%)       | 0.91    |
| Anemia*                  | 62 (37%)      | 173 (36%)     | 0.87    | 68 (55%)      | 559 (54%)     | 0.80    |
| Liver cirrhosis (Child-Pugh B or C)* | 0 (0%) | 3 (1%) | 0.57 | 1 (1%) | 7 (1%) | 0.59 |
| Malignancy               | 15 (9%)       | 70 (15%)      | 0.06    | 19 (15%)      | 172 (17%)     | 0.74    |
| Malignancy currently under treatment* | 4 (2%) | 20 (4%) | 0.29 | 3 (2%) | 67 (6%) | 0.08 |
| Chest wall irradiation   | 1 (1%)        | 5 (1%)        | 1.0     | 0 (0%)        | 6 (1%)        | 1.0     |
| Immunosuppressive therapy| 2 (1%)        | 27 (6%)       | 0.02    | 2 (2%)        | 29 (3%)       | 0.77    |
| Chronic lung disease     | 20 (12%)      | 49 (10%)      | 0.55    | 7 (6%)        | 85 (8%)       | 0.33    |
| Chronic lung disease (moderate or severe)* | 2 (1%) | 15 (3%) | 0.26  | 0 (0%) | 26 (3%) | 0.1 |
| Logistic EuroSCORE, %    | 4.0 (2.9–5.9) | 4.8 (3.1–7.4) | 0.02 | 7.9 (5.8–11.4) | 11.3 (7.9–17.1) | <0.0001 |
| EuroSCORE II, %          | 1.2 (0.9–1.7) | 1.5 (1.0–2.2) | 0.001 | 2.1 (1.4–2.7) | 3 (2.2–4.2) | <0.0001 |
| STS score (PROM), %      | 1.6 (1.3–2.2) | 2.0 (1.3–3.7) | 0.0004 | 2.9 (2.2–4.0) | 4.0 (2.9–6.2) | <0.0001 |
| Etiology of AS           |              |              |         |              |              | <0.0001 |
| Degenerative             | 111 (66%)     | 379 (80%)     | <0.0001 | 109 (88%)     | 988 (95%)     | <0.0001 |
| Congenital               | 44 (26%)      | 64 (13%)      | 9 (7%)  | 22 (2%)       |              |         |
| Rheumatic                | 8 (5%)        | 30 (6%)       | 1 (1%)  | 27 (3%)       |              |         |
| Infective endocarditis   | 3 (2%)        | 0 (0%)        | 0 (0%)  | 1 (0.1%)      |              |         |
| Other                    | 1 (1%)        | 2 (0.4%)      | 5 (4%)  | 4 (0.4%)      |              |         |

Echocardiographic variables

| LV end-diastolic diameter, mm | 46.0±6.1 | 46.5±6.2 | 0.46 | 43.7±5.1 | 43.9±5.8 | 0.75 |
| LV end-systolic diameter, mm | 28.6±6.2 | 29.4±6.5 | 0.17 | 27.2±5.6 | 28.0±6.2 | 0.17 |
| LVEF, %*                    | 66.6±9.7  | 66.3±10.6 | 0.75 | 67.2±10.1 | 65.5±11.3 | 0.11 |
| LVEF <40%                   | 2 (1%)    | 15 (3%)   | 0.26 | 2 (2%)    | 38 (4%)   | 0.31 |
| LVEF <50%                   | 12 (7%)   | 33 (7%)   | 0.92 | 7 (6%)    | 90 (9%)   | 0.25 |
| IVST in diastole, mm        | 11.8±2.4  | 11.0±2.1  | <0.0001 | 12.1±2.2 | 10.9±2.1 | <0.0001 |
| PWT in diastole, mm         | 11.6±2.4  | 10.8±1.9  | <0.0001 | 11.6±1.9 | 10.4±1.9 | <0.0001 |
| Peak aortic jet velocity, m/s | 4.7±0.8 | 3.9±0.7  | <0.0001 | 4.8±0.9 | 3.7±0.7 | <0.0001 |
| Peak aortic pressure gradient, mmHg | 93±31 | 62±23 | <0.0001 | 94±34 | 58±23 | <0.0001 |

(Table 1 continued the next page.)
were 1 and no cases of active infective endocarditis. In the initial AVR group, surgical AVR was actually performed in 122 (98%) and 165 (98%) patients with a median interval of 41 and 49 days from the index echocardiography in patients aged ≥ and <75 years, respectively (Figure 2). In the conservative group, surgical AVR or transcatheter aortic valve implantation (TAVI) during follow-up was more
despite absence of symptoms related to AS, 103 (62%) and 81 (65%), respectively, had ≥1 formal indications for AVR; 68 and 50 patients had very severe AS (Vmax ≥5.0 m/s or mean aortic PG ≥60 mmHg); 12 and 7 patients had LV dysfunction (defined as LVEF <50%); 12 and 12 patients were candidates for other cardiac surgery; 16 and 16 patients had rapid hemodynamic progression; and there

Figure 2. Cumulative incidence of surgical AVR or TAVI compared between initial AVR and conservative groups stratified by age: (A) <75 years, and (B) ≥75 years. AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation.
Age-Related Differences in Asymptomatic Patients With Severe AS

The main findings of the present study were as follows. (1) Initial AVR as compared with a conservative strategy was associated with significantly lower risk for HF hospitalization regardless of age in asymptomatic patients with severe AS. (2) The lower mortality risk of initial AVR relative to a conservative strategy was significant in patients aged ≥75 years, but not in patients aged <75 years, with significant interaction. 

**Discussion**

The main findings of the present study were as follows. (1) Initial AVR as compared with a conservative strategy was associated with significantly lower risk for HF hospitalization regardless of age in asymptomatic patients with severe AS. (2) The lower mortality risk of initial AVR relative to a conservative strategy was significant in patients aged ≥75 years, but not in patients aged <75 years, with significant interaction.

---

**Table 2**

Cumulative incidence of all-cause death compared between initial AVR and conservative groups stratified by age: (A) <75 years, and (B) ≥75 years. AVR, aortic valve replacement.

| Interval     | Conservative group | Initial AVR group |
|--------------|--------------------|-------------------|
| N of patients with event | 4 | 19 |
| N of patients at risk | 475 | 1042 |
| Cumulative incidence | 0.9% | 1.8% |

| Interval     | Conservative group | Initial AVR group |
|--------------|--------------------|-------------------|
| N of patients with event | 1 | 0 |
| N of patients at risk | 167 | 124 |
| Cumulative incidence | 0.6% | 0% |

![Figure 3](image_url) Cumulative incidence of all-cause death compared between initial AVR and conservative groups stratified by age: (A) <75 years, and (B) ≥75 years. AVR, aortic valve replacement.
incidence of all-cause death was relatively higher compared with that of HF hospitalization in the non-super-elder age stratum. Among 642 patients aged <75 years, 132 (initial AVR group: 25 patients; conservative group: 107 patients) died during the follow-up period. In patients aged <75 years, the rate of HF hospitalization was very low once they underwent AVR, although the mortality rate was substantial even after AVR because the patients in the initial AVR group often had severe comorbidities such as hemodialysis (20% of patients) despite younger age. The causes of death in the initial AVR group aged <75 years were cardiovascular death (17 patients) and non-cardiovascular death (8 patients). The details of cardiovascular death were AV procedure-related death (5 patients), infective endocarditis (3 patients), myocardial infarction (1 patient), sudden death after AVR (3 patients), sudden death before AVR/TAVI (2 patients), HF (1 patient), and unknown (2 patients). In the conservative group aged <75 years, the rate of HF hospitalization was substantial, but the mortality rate was much higher than the rate of HF hospitalization. The causes of death in the conservative group aged <75 years were cardiovascular death (17 patients) and non-cardiovascular death (8 patients). The details of cardiovascular death were AV procedure-related death (5 patients), infective endocarditis (3 patients), myocardial infarction (1 patient), sudden death after AVR (3 patients), sudden death before AVR/TAVI (2 patients), HF (1 patient), and unknown (2 patients). In the conservative group aged <75 years, the rate of HF hospitalization was substantial, but the mortality rate was much higher than the rate of HF hospitalization. The causes of death in the initial AVR group aged <75 years were cardiovascular death (17 patients) and non-cardiovascular death (8 patients). The details of cardiovascular death were AV procedure-related death (5 patients), infective endocarditis (3 patients), myocardial infarction (1 patient), sudden death after AVR (3 patients), sudden death before AVR/TAVI (2 patients), HF (1 patient), and unknown (2 patients). The causes of death in the conservative group aged <75 years were cardiovascular death (17 patients) and non-cardiovascular death (8 patients). The details of cardiovascular death were AV procedure-related death (5 patients), infective endocarditis (3 patients), myocardial infarction (1 patient), sudden death after AVR (3 patients), sudden death before AVR/TAVI (2 patients), HF (1 patient), and unknown (2 patients).

Figure 4. Cumulative incidence of HF hospitalization compared between initial AVR and conservative groups stratified by age: (A) <75 years, and (B) ≥75 years. AVR, aortic valve replacement; HF, heart failure.
Table 2. Clinical Outcomes: Initial AVR vs. Conservative Strategies Stratified by Age

|                              | Initial AVR group | Conservative group |
|------------------------------|-------------------|--------------------|
|                              | Patients at risk  | No. of patients with event (cumulative 5-year incidence) | Patients at risk  | No. of patients with event (cumulative 5-year incidence) |
| All-cause death              |                   |                    |                   |                    |
| Age <75 years                | n=167             | 25 (15.3%)         | n=475             | 107 (23.7%)        |
| Age ≥75 years                | n=124             | 15 (15.6%)         | n=1,042           | 435 (51.2%)        |
| HF hospitalization           |                   |                    |                   |                    |
| Age <75 years                | n=167             | 5 (2.9%)           | n=475             | 53 (12.5%)         |
| Age ≥75 years                | n=124             | 5 (5.1%)           | n=1,042           | 231 (33.0%)        |
| Composite of aortic valve-related death or HF hospitalization |                   |                    |                   |                    |
| Age <75 years                | n=167             | 15 (10.0%)         | n=475             | 85 (19.5%)         |
| Age ≥75 years                | n=124             | 8 (7.4%)           | n=1,042           | 283 (39.0%)        |
| Cardiovascular death         |                   |                    |                   |                    |
| Age <75 years                | n=167             | 17 (10.2%)         | n=475             | 78 (18.3%)         |
| Age ≥75 years                | n=124             | 8 (9.9%)           | n=1,042           | 245 (34.5%)        |
| Aortic valve-related death   |                   |                    |                   |                    |
| Age <75 years                | n=167             | 10 (7.3%)          | n=475             | 45 (11.1%)         |
| Age ≥75 years                | n=124             | 3 (2.5%)           | n=1,042           | 152 (25.4%)        |
| Sudden death                 |                   |                    |                   |                    |
| Age <75 years                | n=167             | 5 (2.6%)           | n=475             | 26 (6.0%)          |
| Age ≥75 years                | n=124             | 3 (2.5%)           | n=1,042           | 56 (8.1%)          |
| Non-cardiovascular death     |                   |                    |                   |                    |
| Age <75 years                | n=167             | 8 (5.6%)           | n=475             | 29 (6.6%)          |
| Age ≥75 years                | n=124             | 7 (6.4%)           | n=1,042           | 190 (25.5%)        |

The number of patients with at least 1 event was counted through the entire follow-up period, while the cumulative incidence was truncated at 5 years. Any death during the hospitalization for AVR or TAVI was regarded as aortic procedure-related death. Aortic valve-related death included aortic procedure-related death, sudden death, and death from HF. HF hospitalization was defined as hospitalization for worsening HF requiring intravenous drug therapy. AVR, aortic valve replacement; CI, confidence interval; HF, heart failure; HR, hazard ratio; TAVI, transcatheter aortic valve implantation.
did not undergo AVR died before presenting as HF.

On the other hand, the lower risk of initial AVR relative to conservative strategy for all-cause death was significant in super-elder patients, but not in non-super-elder patients, with significant interaction. Surgical AVR or TAVI was more often performed during follow-up in non-super-elder patients than in super-elder patients, suggesting that surgical AVR or TAVI during follow-up might have had a salvage effect on mortality in non-super-elder patients. Furthermore, surgical AVR or TAVI during follow-up was more often performed after HF hospitalization in super-elder patients than in non-super-elder patients. The biggest limitation of our previous report suggesting large mortality benefit of early AVR was the fact that the conservative group had inevitably included patients ineligible for surgical AVR who were deemed to have very poor prognosis, although we conducted an extensive multivariable adjustment. Ineligibility for surgical AVR is generally because of advanced age and comorbidities. In the present report, comorbidities precluding surgical AVR are much less prevalent in the non-super-elder population than in the super-elder population. Indeed, the lower risk of initial AVR relative to conservative strategy for non-cardiovascular death was seen in super-elder patients, but not in non-super-elder patients.

Study Limitations
First and most importantly, we did not collect the data on ineligibility for AVR. Therefore, we cannot deny the presence of selection bias and residual confounding even in the non-super-elder patients, although it was certainly much less prevalent than in the super-elder patients. Second, we did not conduct propensity score-matching because the results from the Cox multivariable models in the entire cohort were consistent with the results from the propensity score-matching in our previous report comparing the initial AVR and conservative strategies. Third, the cutoff value of 75 years of age was arbitrary, although it would be clinically relevant. Fourth, the number of patients aged <75 years was limited, leaving the possibility of type II error in the analysis of non-super-elder patients. Indeed, there was 31% risk reduction for mortality by early AVR in the non-super-elder stratum, although it was statistically insignificant. Therefore, the mortality benefit of early AVR was inconclusive in the present study. Fifth, we could not exclude the possibility of ascertainment bias for symptoms related to AS at baseline, even though we included only those without symptoms based on chart review. Sixth, in the present study, very few patients underwent TAVI, which has already drastically transformed the treatment of severe AS in super-elder patients. Much larger proportion of super-elder patients under watchful waiting would have had been treated with TAVI during follow-up, if it was available, which might have led to a reduction of mortality in the conservative group. Seventh, in the low-gradient AS patients aged <75 or ≥75 years, there were few AVR patients compared with the high-gradient AS patients aged <75 or ≥75 years, so sensitivity analyses of the patients with low-gradient AS might have resulted in a shortage of statistical power. Further studies are necessary to draw conclusions regarding patients with low-gradient AS. Finally, definitive conclusions on the role of early AVR in asymptomatic patients with severe AS should be based on ongoing randomized trials.

Conclusions
The benefit of initial AVR in reducing HF hospitalization in asymptomatic patients with severe AS was consistently seen regardless of age. The magnitude of mortality benefit of initial AVR was greater in super-elder patients than in non-super-elder patients, although we could not deny the significant effect of selection bias for initial AVR in super-elder patients who often have comorbidities precluding surgical AVR.

Acknowledgment
We appreciate the assistance of our co-investigators at the CURRENT AS registry.

Disclosures
The authors reported no conflicts of interest.

References
1. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012; 33: 2451–2496.
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol 2014; 63: 2438–2488.
3. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. Circulation 1997; 95: 2262–2270.
4. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000; 343: 611–617.
5. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005; 111: 3290–3295.
6. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. J Am Coll Cardiol 1990; 15: 1012–1017.
7. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kamamori N, Murata K, et al. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. J Am Coll Cardiol 2015; 66: 2827–2838.
8. Amato MCM. Treatment decision in asymptomatic aortic valve stenosis: Role of exercise testing. Heart 2001; 86: 381–386.
9. Nassimih D, Aronow WS, Ahn C, Goldman ME. Rate of progression of valvular aortic stenosis in patients > or =60 years of age. Am J Cardiol 2001; 87: 807–809.
10. Kume T, Kawamoto T, Okura H, Watanabe N, Toyota E, Neishi Y, et al. Rapid progression of mild to moderate aortic stenosis in patients older than 80 years. J Am Soc Echocardiogr 2007; 20: 1243–1246.
11. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation. J Am Coll Cardiol 2012; 60: 1438–1454.
12. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials. J Am Coll Cardiol 2011; 57: 253–269.
13. Banovic M, Iung B, Bartunek J, Asanin M, Beleslin B, Biocina B, et al. Rationale and design of the Aortic Valve replacement versus conservative treatment in Asymptomatic severe aortic stenosis (AVATAR) trial: A randomized multicenter controlled event-driven trial. Am Heart J 2016; 174: 147–153.
out surgery. Ann Thorac Surg 2019; 108: 74–79.
16. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, et al. High-versus low-gradient severe aortic stenosis. Circ Cardiovasc Interv 2017; 10: e004796.
17. Taniguchi T, Morimoto T, Sakata R, Kimura T. Reply: Is it time for a new paradigm in asymptomatic severe aortic stenosis? Asymptomatic severe aortic stenosis: Oxymoron? A randomized trial in patients with asymptomatic severe aortic stenosis: A future has begun! Might outcome of patients with asymptomatic severe AS be improved by an initial surgical strategy? J Am Coll Cardiol 2016; 67: 1972–1973.
18. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. Lancet 2012; 380: 37–43.
19. Singh M, Stewart R, White H. Importance of frailty in patients with cardiovascular disease. Eur Heart J 2014; 35: 1726–1731.
20. Schymik G, Varsami C, Bramlage P, Conzelmann LO, Würth A, Luik A, et al. Two-year outcomes of transcatheter compared with surgical aortic valve replacement in “minimal-risk” patients lacking EuroSCORE co-morbidities (from the TAVIK Registry). Am J Cardiol 2018; 122: 149–155.
21. Schoenenberger AW, Stortecky S, Neumann S, Moser A, Jüni P, Carrel T, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). Eur Heart J 2013; 34: 684–692.

Supplementary Files

Please find supplementary file(s):
http://dx.doi.org/10.1253/circj.CJ-19-0431