Relation of Body Mass Index to Risk of Death or Stroke in Patients Who Underwent Transcatheter Aortic Valve Implantation

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Obesity and overweight have been associated with better clinical outcomes in different populations with a diverse spectrum of cardiovascular disease (obesity paradox). However, conflicting data exist about the relation between body mass index (BMI) and outcomes after transcatheter aortic valve implantation (TAVI). The aim of this study is to evaluate the association of body mass index with clinical outcomes in patients with severe aortic stenosis (AS) who underwent TAVI. The study cohort included 379 consecutive patients with symptomatic severe AS who underwent TAVI between March 2010 and February 2017 in 3 centers in East Asia. Patients were grouped into tertiles of baseline BMI (first tertile: ≤22.3 kg/m^2, second tertile: 22.4 to 24.8 kg/m^2, and third tertile: ≥24.9 kg/m^2). The primary outcome was a composite of death from any causes or stroke at 1 year. The median (interquartile range) BMI was 23.5 (21.8 to 26.1) kg/m^2. During the median follow-up of 18.4 months, there were 69 deaths and 23 strokes. At 1 year, the primary outcome occurred in 21.9% in the first tertile, 18.7% in the second tertile, and 7.8% in the third tertile, respectively (p = 0.009). After adjustment for confounding variables, an inverse relation was observed between BMI and primary outcome: with the third BMI tertile as the reference category, the adjusted hazard ratios were 2.51 (95% confidence interval, 1.20 to 5.26) for the second BMI tertile and 2.61 (95% confidence interval, 1.20 to 5.66) for the first BMI tertile. In conclusion, in patients with severe AS who underwent TAVI, an inverse association between BMI and the risk of death or stroke was observed. **(Am J Cardiol 2019;123:638−643)**

Transcatheter aortic valve implantation (TAVI) has developed from a novel therapeutic technique to an established therapy for high-risk patients with symptomatic severe aortic stenosis (AS).[1,2] Recently, its application is rapidly expanding to intermediate-risk[3] and low-risk populations.[4] With the wide expansion of TAVI indications, the evaluation of risk factors more accurately stratifying patients into higher- or lower-risk categories for TAVI procedures would be of great clinical value for risk prediction and more aggressive preventive or therapeutic measures.[5] Excess adiposity is a well-established risk factor for cardiovascular disease,[6,7] and overweight or obesity are associated with higher risks of mortality and cardiovascular morbidity in the general population.[8−10] However, a so-called obesity paradox has been reported in a diverse spectrum of patients with cardiovascular disease.[11−15] This pattern was also reported in patients with severe AS who underwent surgical aortic valve replacement (SAVR).[16] There are limited data about the relation of BMI with mortality and outcomes in patients with AS who underwent TAVI.[17,18] Therefore, we evaluated the association between BMI and the risk of death and stroke in patients with symptomatic severe AS who underwent TAVI, using multicenter prospective registry data.

Methods

The study population consisted of consecutive patients with symptomatic severe AS who underwent successful TAVI procedures and had a valid BMI measurement at baseline between March 2010 and February 2017 in 3 centers in East Asia. For the screening process for TAVI, each patient underwent a clinical evaluation thoroughly. All data were prospectively collected and maintained at the Clinical Research Center of Asan Medical Center, Seoul, South Korea. The weight and height of all patients were collected at admission before the TAVI procedure for the calculation of BMI. For the current analysis, patients were stratified into tertiles based on their baseline BMI (≤22.3 kg/m^2, 22.4 to 24.8 kg/m^2, and ≥24.9 kg/m^2). This study was approved by the institutional review board of each participating center, and all

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patients provided written informed consent. The decision of indicating the TAVI procedure was made through discussions with a local multidisciplinary heart team, and the TAVI procedure was performed using standard methods under general anesthesia or monitored anesthesia care. The types of access routes were preferentially based on the transfemoral approach and were determined in consideration of the size, level of calcification, and tortuosity of the aortoiliofemoral artery. The type (balloon-expandable devices [Sapien XT and Sapien 3; Edwards Lifesciences] or self-expandable devices [CoreValve and Evolut R; Medtronic or Lotus; Boston Scientific]) and size of devices were determined before the procedure based on assessment using 3-dimensional, multidetector CT and transesophageal echocardiography. After the TAVI procedure, the patients were prescribed dual antiplatelet therapy with aspirin (100 mg once daily) and clopidogrel (75 mg once daily) for at least 6 months.[19]

The primary outcome of the present study was the composite of death from any causes or stroke at 1 year of follow-up. Secondary outcomes included all-cause death, a composite of death from cardiovascular causes or stroke, bleeding events, vascular complications, acute kidney injury, and permanent pacemaker implantation. All study outcomes were defined according to the Valve Academic Research Consortium-2 definition.[20]

The baseline characteristics were examined across BMI categories. Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]), depending on variable distribution. Categorical variables were presented as numbers and percentages. Group comparisons according to BMI categories were analyzed using analysis of variance or its nonparametric equivalent, Kruskal-Wallis test for continuous variables, and chi-square test or Fisher's exact test for categorical variables. Cumulative rates of clinical events were calculated using Kaplan-Meier survival analysis, and the log-rank test was used for comparisons across the groups. The entire follow-up was used to analyze time-to-event outcomes, and patients were censored at the time of clinical events or last available follow-up. A univariate Cox proportional hazard regression model was used to evaluate potential predictors of the primary composite outcome of all-cause death or stroke. The proportional hazard assumption was checked for all screened covariates, and no relevant violations were found. Then, to assess the independent relation of BMI to the primary composite outcome, multivariate analysis was performed using important clinical covariates, including clinically relevant variables and statistically significant variables with a p value of <0.05 in univariate analysis. Using the third tertile of BMI as the reference category, we estimated hazard ratios and 95% confidence intervals for the first and second tertiles of BMI. All statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY). A p value of <0.05 was considered statistically significant.

Results

Between March 2010 and February 2017, a total of 379 patients with severe AS who underwent TAVI and had baseline BMI data were included in the final analysis for evaluating the association between BMI and outcomes. Overall, the median (IQR) BMI for the study population was 23.5 kg/m^2 (21.8 to 26.1 kg/m^2). The baseline clinical characteristics and echocardiographic data of the study population according to the BMI tertile (first tertile: ≤22.3 kg/m^2, second tertile: 22.4 to 24.8 kg/m^2, and third tertile: ≥24.9 kg/m^2) are summarized in Table 1. Patients in the first tertile were relatively older and more likely to be male. In addition, patients in the first tertile had a higher logistic European system for cardiac operative risk evaluation score (EuroSCORE) and Society of Thoracic Surgeons (STS) score, and had higher incidences of prior congestive heart failure and renal insufficiency. Baseline CT and procedural data are shown in Table 2. There were no significant differences in all CT parameters and device type or procedural features according to the BMI tertile.

The median follow-up was 18.4 months (IQR, 7.3 to 37.2 months). During the entire follow-up period, there were 69 deaths and 23 strokes. The primary composite outcome of death from any cause or stroke at 12 months occurred in 21.9% patients of the first tertile group, 18.7% patients of the second tertile group, and 7.8% patients in the third tertile group (p = 0.009; Table 3 and Figure 1). The cumulative incidence of primary composite outcome over time showed an initial steep increase, followed by a continuous separation of the curves, with a significantly higher rate of events in the lower BMI groups. In analyses of secondary outcomes, the 1-year rate of all-cause mortality was significantly higher in the first tertile group compared with the second and third tertile groups (On-line Figure 1), and the 1-year rate of cardiovascular death or stroke proportionally increased with decreasing levels of BMI (On-line Figure 2). However, there was no difference in the rates of periprocedural and postprocedural bleeding, vascular complications, acute kidney injury, and permanent pacemaker implantation according to BMI tertile. And, additional analysis was performed to evaluate the relation of body weight to outcomes by tertiles of body weight. The baseline characteristics were summarized in On-line Table 1 and 2. There were no significant differences in clinical outcomes according to tertiles of body weight (On-line Table 3 and On-line Figure 3, 4, and 5).

To determine the independent association of BMI categories on the primary composite outcome of death or stroke, a multivariate Cox regression analysis was performed with adjustment for clinically relevant covariates. After adjustment for a wide range of confounding factors, BMI tertile and STS score remained as the independent predictors of the primary composite outcome. As compared with the third tertile of BMI as the reference category, the adjusted risks for death or stroke were higher in patients in the lower BMI categories (by a factor of 2.51 for the second tertile and 2.61 for the first tertile). In an additional multivariate model including brain natriuretic peptide levels, although the results were not statistically significant,

Table 1
Baseline clinical characteristics and echocardiographic data according to categories of body mass index

Variables	Body mass index (kg/m^2)			P value
	≤22.3 (n = 128)	22.4−24.8 (n = 123)	≥24.9 (n = 128)	
Age (years)	81.0 (76.5−85.0)	79.0 (76.0−84.0)	78.0 (75.0−82.0)	0.03
Men	74 (58%)	66 (54%)	52 (41%)	0.02
Body mass index* (kg/m^2)	21.0 (19.1−21.8)	23.5 (22.9−24.2)	27.1 (26.1−28.6)	<0.001
Logistic EuroSCORE (%)	17.8 (11.4−27.6)	12.6 (9.1−20.8)	14.9 (9.2−23.3)	0.009
Society of thoracic surgery score (%)	4.9 (3.3−7.8)	3.4 (2.4−5.2)	2.8 (1.9−4.6)	<0.001
Hypertension	100 (78%)	106 (86%)	113 (88%)	0.06
Diabetes mellitus	34 (27%)	38 (31%)	51 (40%)	0.07
Hyperlipidemia	66 (52%)	79 (64%)	91 (71%)	0.005
Current or ex-smoker	24 (19%)	14 (11%)	13 (10%)	0.09
Atrial fibrillation	22 (17%)	12 (10%)	18 (14%)	0.23
Prior congestive heart failure	59 (46%)	30 (24%)	34 (27%)	<0.001
Coronary artery disease†	63 (49%)	50 (41%)	55 (43%)	0.37
Prior cerebrovascular accident	13 (10%)	16 (13%)	8 (6%)	0.19
Renal insufficiency‡	60 (47%)	43 (35%)	42 (33%)	0.045
Estimated glomerular filtration rate (ml/min/1.73 m^2)	61.8 ± 26.5	68.7 ± 27.1	68.2 ±22.0	0.04
Chronic lung disease	21 (17%)	8 (7%)	25 (20%)	0.009
Prior coronary bypass surgery	10 (8%)	9 (7%)	8 (6%)	0.88
Hemoglobin (g/dL)	11.3 (10.3−12.5)	11.9 (10.7−12.9)	12.4 (11.3−13.3)	<0.001
Platelet ($\times 10^3/\mu$L)	187 (149−230)	193 (159−236)	186 (156−234)	0.52
Creatinine (mg/dL)	1.1 (0.8−1.4)	0.9 (0.7−1.3)	0.9 (0.7−1.1)	0.01
Brain natriuretic peptide (pg/mL)	364 (158−905)	194 (90−477)	146 (53−339)	<0.001
Echocardiographic data				
Etiology of aortic stenosis				
Degenerative	124 (97%)	116 (94%)	123 (96%)	0.59
Rheumatic	5 (4%)	9 (7%)	4 (3%)	0.25
Congenital	13 (10%)	8 (7%)	10 (8%)	0.56
Peak jet velocity (m/s)	4.8 ± 0.8	5.0 ± 0.8	4.9 ± 0.8	0.52
Mean gradient (mmHg)	53.5 (42.0−66.5)	57.5 (44.0−74.0)	53.0 (45.0−68.0)	0.26
Aortic valve area (cm^2)	0.6 (0.5−0.8)	0.6 (0.5−0.7)	0.6 (0.5−0.8)	0.68
Pulmonary hypertension§	46 (37%)	24 (21%)	29 (25%)	0.01
Left ventricular ejection fraction (%)	59.0 (49.5−65.0)	62.0 (56.0−66.0)	61.0 (57.0−65.0)	0.14

Data are expressed as number (%), mean ± standard deviation, or median (interquartile range), depending on variable distribution.
* Body mass index is the weight in kilograms divided by the square of the height in meters.
† Coronary artery disease was defined as stenosis more than 50% as evidenced by coronary angiography or computed tomography.
‡ Renal insufficiency was defined as eGFR <60 ml/min/1.73 m^2.
§ Pulmonary hypertension indicates pulmonary artery systolic pressure ≥50 mm Hg.

the trends for risk according to tertiles of BMI were similar (On-line Table 4).

Discussion

This study aimed to evaluate the relation of BMI with major clinical events of death or stroke in "real-world" patients with severe AS who underwent TAVI. The main findings of our study can be summarized as follows: First, patients with lower BMI had a significantly higher rate of all-cause death or stroke after TAVI than patients with higher BMI. Second, the rates of all-cause mortality and the composite of cardiovascular death or stroke were also higher in the lowest BMI tertile than in the other BMI groups. Third, after adjusting for potential confounding factors, an inverse association between BMI and the risk of death or stroke was observed. In the general population, obesity has been associated with adverse clinical outcomes, especially increased all-cause mortality, in several prior studies.[8,21,22] Obesity is closely related to excessive secretion of proinflammatory adipokines leading to low-grade systemic inflammation, elevated levels of free fatty acids, insulin resistance, and long-term overactivity of the sympathetic nervous system, all of which increase the risk of cardiovascular disease.[23] However, in contrast to these mechanisms induced by obesity, a number of studies have reported that overweight or obese patients have better clinical outcomes compared with the patients with normal or low BMI in certain subgroups, such as patients with established cardiac disease and those who underwent PCI or cardiac surgery.[11,16,24] This relation between increasing BMI and decreasing clinical events, known as the "obesity paradox," was also reported in some previous studies for patients with AS who underwent SAVR or TAVI.[18,25,26]

Our findings are in line with previous reports demonstrating an inverse relation between BMI and adverse events after TAVI. Although we cannot fully clarify the exact mechanism of the inverse association of BMI and clinical outcomes, some plausible explanations can be suggested for this phenomenon. First, excess body weight in an elderly population may increase the metabolic and physical reserve and counteract the negative effects of acute

Table 2
Computed tomography and procedural data according to categories of body mass index

Variables	Body mass index (kg/m^2)			P value
	≤22.3 (n = 128)	22.4−24.8 (n = 123)	≥24.9 (n = 128)	
Aortic annulus maximal diameter (mm)	26.7 ± 2.8	26.3 ± 2.5	26.2 ± 3.0	0.23
Aortic annulus minimal diameter (mm)	21.2 ± 2.5	20.7 ± 2.4	21.3 ± 2.3	0.74
Aortic annulus area (mm^2)	446.0 ± 85.2	433.7 ± 73.6	437.4 ± 76.4	0.47
Aortic annulus perimeter (mm)	76.2 ± 7.1	74.7 ± 6.6	75.5 ± 7.1	0.48
Access site				0.66
Transfemoral	122 (95%)	119 (97%)	123 (96%)	
Transapical	4 (3%)	3 (2%)	5 (4%)	
Transaortic	2 (2%)	1 (1%)	0 (0%)	
Type of device				0.24
Balloon expandable	61 (48%)	59 (48%)	73 (57%)	
Self-expandable	67 (52%)	64 (52%)	55 (43%)	
Device size (mm)				0.44
23	29 (23%)	26 (21%)	38 (30%)	
25	2 (2%)	4 (3%)	1 (1%)	
26	50 (39%)	57 (47%)	54 (42%)	
27	0 (0%)	1 (1%)	0 (0%)	
29	40 (31%)	30 (25%)	30 (24%)	
31	7 (5%)	4 (3%)	4 (3%)	

Data are expressed as number (%) or mean ± standard deviation.

Table 3
Clinical outcomes at 1 year according to the categories of body mass index

Outcomes at 1 Year	Body mass index (kg/m^2)			P value
	≤22.3 (n = 128)	22.4−24.8 (n = 123)	≥24.9 (n = 128)	
Primary outcome				
Death from any causes or stroke	28 (22%)	23 (19%)	10 (8%)	0.009
Secondary endpoint				
Death from any causes	24 (19%)	12 (10%)	8 (6%)	0.006
Death from cardiovascular causes or stroke	24 (19%)	16 (13%)	8 (6%)	0.01
Bleeding events				
Any bleeding	48 (38%)	49 (40%)	42 (33%)	0.50
Major bleeding	35 (27%)	37 (30%)	33 (26%)	0.74
Vascular complications	9 (7%)	7 (6%)	5 (4%)	0.55
Acute kidney injury	12 (9%)	16 (13%)	13 (10%)	0.62
Permanent pacemaker implantation	8 (6%)	10 (8%)	11 (9%)	0.76

Event rates were calculated using Kaplan-Meier estimates, and presented as number (%).

morbidities. In the recent FRAILTY-AVR Study, frailty was associated with increased risks of death and disability after SAVR and TAVI.[27] In the factors determining frailty are muscle strength and amount of skeletal muscle mass. It is likely that patients with higher BMI had more muscle mass and lower frailty score, which are associated with better clinical outcomes. Second, it is possible that patients with higher BMI were treated more aggressively with cardioprotective drugs that may be related to a better prognosis. Patients with higher BMI tend to have more cardiovascular risk factors, including hypertension, diabetes mellitus, or dyslipidemia. It was demonstrated that patients with high BMI were more likely to be adherent to guideline-recommended medical treatment.[28] Third, excess fat stores have biologic advantages during periods of illness. This can be due to better access to food or a more robust appetite or more metabolic reserve. In addition, body fat may decrease oxidative stress and inflammation, and improve secretion of amino acids and adipokines, potentially improving survival in obese individuals. Hormones and cytokines such as leptin and tumor necrosis factor-alpha (TNF-α) have been suggested as possible moderators of the relation between obesity and mortality.[29,30] Lastly, as compared with patients with higher BMI, those with lower BMI represent a sicker population and a low BMI is a marker of being sicker. Even after multivariable adjustment of potentially relevant covariates, confounding by frailty- or disease-related sickness might possibly underestimate the association between BMI and mortality.

This study has several potential limitations. First, our study evaluated nonrandomized, observational data. The study results are possibly affected by unknown confounders; thus, the overall findings should be considered hypothesis-generating only. Second, BMI has a limitation in reflecting exact information about the amount of muscle mass or central obesity as a surrogate marker of body

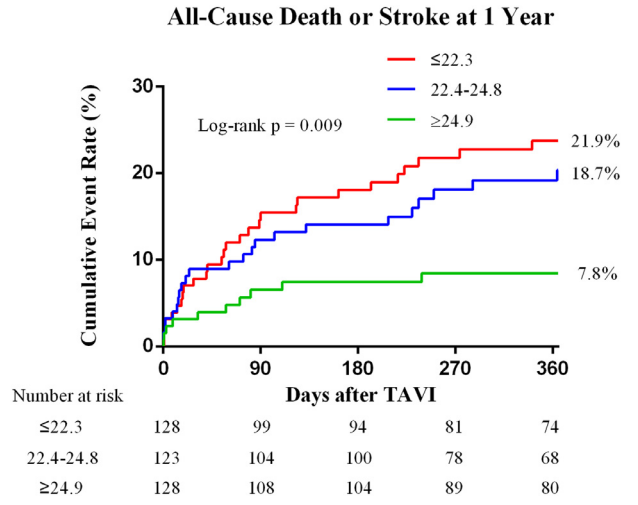

Figure 1. Time-to-event curves for the primary composite outcome of 1-year death from any cause or stroke according to body mass index categories.

Cumulative incidence curves are shown for the risk of death from any cause or stroke according to BMI tertiles. Abbreviations: BMI, body mass index; TAVI, transcatheter aortic valve implantation.

weight and composition. We did not assess the risk of death in relation to abdominal obesity, which may be a particularly important factor in Asian populations. Combining BMI with the measurements of other parameters, such as waist circumference or waist-to-hip ratio, would be more helpful in predicting obesity-related outcomes. Third, there were imbalances in the EuroSCORE and STS scores according to BMI tertile. However, despite the unbalanced baseline covariates, the BMI category was shown to be the independent predictor of death or stroke. Finally, we did not measure the BMI trends before and after TAVI. Weight loss before or after TAVR is a measure of frailty and can be predictive of a worse outcome. It warrants further investigations.

In patients with severe AS who underwent TAVI, the low BMI group had a significantly higher incidence of all-cause death or stroke, compared with the higher BMI groups. Furthermore, BMI was an independent predictor of death or stroke after the TAVI procedure. However, before presumably drawing the conclusion that obesity is protective against or does not increase the risk of cardiovascular events in patients who underwent TAVI, more reliable surrogate markers differentiating excess body fat and muscle mass are needed for future risk stratification, and additional clinical studies are needed to test different methods reflecting adiposity.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.015.

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