Long-Term Outcomes Stratified by Body Mass Index in Patients Undergoing Transcatheter Aortic Valve Implantation

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Transcatheter aortic valve implantation (TAVI) is emerging as the default strategy for older patients with severe, symptomatic, and trileaflet aortic stenosis. Increased body-mass index (BMI) is associated with a protective effect in patients undergoing percutaneous coronary intervention. We assessed whether elevated BMI was associated with a similar association in TAVI. We evaluated prospectively collected data from 634 patients who underwent TAVI at 2 centers from August 2008 to April 2019. Patients were stratified as normal weight (BMI 18.5 to 24.9 kg/m^2, n = 214), overweight (25 to 29.9 kg/m^2, n = 234), and obese (>30 kg/m^2, n = 185). Outcomes were reported according to VARC-2 criteria. Mortality was assessed using Cox proportional hazards regression analysis (median follow-up 2 years). Kaplan-Meier analysis was used to estimate cumulative mortality. Baseline differences were seen in age (85 vs 84 vs 82, p <0.001), STS-PROM score (4.3 vs 3.4 vs 3.6, p <0.001), sex (50% vs 36% vs 55% female, p <0.001), clinical frailty score (p = 0.02), diabetes (21% vs 29% vs 40%, p <0.001), and presence of chronic obstructive pulmonary disease (COPD) (13% vs 13% vs 23%, p = 0.009). On multivariable analysis there was no mortality difference between normal and obese patients (hazard ratio [HR] 0.70, confidence interval [CI] 0.46 to 1.1 p = 0.11), however overweight patients had significantly lower mortality (HR 0.56 CI 0.38 to 0.85, p = 0.006). Variables independently associated with increased mortality were increasing age, male sex, COPD, previous balloon valvuloplasty, and higher STS-PROM. In conclusion, overweight patients have lower long-term mortality when compared with normal weight and obese patients undergoing TAVI. **(Am J Cardiol 2020;137:77−82)**

Transcatheter aortic valve implantation (TAVI) has become an important treatment for severe aortic stenosis. Recent studies comparing surgical aortic valve replacement and TAVI[1−4] have suggested that preintervention assessment should focus less on predicted mortality and more on patient-related and anatomical factors to determine which treatment is most appropriate for individual patients. Increased body mass index (BMI) has long been associated with increased all-cause and cardiovascular mortality.[5] However, an "obesity paradox" has been observed in patients undergoing percutaneous coronary intervention.[6−8] Furthermore, increased BMI in the elderly, the predominant population undergoing TAVI, has been associated with reduced mortality.[9] Indeed, studies show the obesity paradox may extend to patients undergoing TAVI.[10−12] Frailty scores are of increasing interest in patients undergoing TAVI as a way to better stratify those at increased procedural risk.[13,14] Older adults with low-normal BMI[9] have elevated baseline mortality and frailty may act as a confounder in this group. This study aimed to investigate long-term outcomes according to BMI from a multicenter TAVI registry, and sought to elicit whether increased BMI is associated with improved outcomes following TAVI. Furthermore, we sought to establish whether the presence of frailty in patients with normal or low-normal BMI could, in part, contribute to this phenomenon.

Methods

Between August 2008 and April 2019, 634 consecutive patients undergoing TAVI for severe, symptomatic aortic stenosis were included in a prospective multicenter registry. All patients who underwent TAVI for severe, symptomatic AS in 2 experienced centers in Melbourne, Australia with the CoreValve and Evolut R/PRO (Medtronic Inc., MN), Edwards Sapien XT, Sapien 3 and Centera (Edwards Lifesciences, CA) or Portico (Abbott, IL) bioprostheses were included in the registry. Access was via the femoral, subclavian, apical or direct aortic route as determined by

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preprocedural computed tomography, angiography, and transthoracic and/or transesophageal echocardiography. The study was approved by the local ethics committee.

AS was considered severe by at least 1 out of 2 criteria assessed by transthoracic echocardiogram (TTE): Aortic valve area <1 cm^2 or aortic valve mean pressure gradient (MPG) >40 mm Hg. Symptoms of dyspnea were graded using the New York Heart Association classification. All patients were reviewed by the multidisciplinary “Heart Team” to decide on final suitability for TAVI. Consideration was also given to the STS-PROM score, co-morbidities, frailty indices and results of anatomical assessment, including angiography and CT.

Study end-points were defined according to Valve Academic Research Consortium 2 (VARC-2) criteria[15] whereas in-hospital, after 30-days, 1-year, and then annually. These included myocardial infarction, cerebrovascular event (stroke or transient ischemic attack), major bleeding (3a, 3b or 5 according to the Bleeding Academic Research Consortium classification[16]), acute kidney injury stage 2 or 3, vascular complications (major and minor), as well as major adverse cardiovascular events, aortic valve failure requiring reintervention, device success, and mortality. Baseline variables were chosen based on previous studies and available data. Clinical and echocardiographic data were entered prospectively. Echocardiographic data was obtained from preprocedural visits, TAVI work up, procedural reports, and 30-day follow-up. Patients were stratified according to BMI as normal weight (BMI 18.5 to 24.9 kg/m^2, n = 214), overweight (25 to 29.9 kg/m^2, n = 234), and obese (>30 kg/m^2, n = 185). Patients with BMI <18.5 kg/m^2 were excluded due to small sample size (n = 15).

Comparison between the 3 BMI categories was performed using Pearson chi-square test for categorical variables and analysis of variance for continuous variables. Categorical variables are presented as number (percent), continuous variables are represented as mean ± standard deviation, or median with interquartile range as appropriate. Kaplan-Meier survival analysis with log-rank test was used to estimate cumulative mortality. Multivariable Cox proportional hazards regression analysis was performed to investigate the relationship between BMI category and long-term mortality. Proportional Hazards assumption was checked for each covariate using both Schoenfeld residuals and inclusion of interaction with time. Variables were included in the multivariable model if found to have a p value of <0.20 on univariable analysis. Variables included in the final multivariable model included: BMI category, age, sex, hypertension, chronic obstructive pulmonary disease (COPD), preprocedure balloon aortic valvuloplasty, and STS-PROM score. All statistical analyses were performed using Stata 15.0 (Stata-Corp LP, College Station, Texas) and R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided p-value of <0.05 was considered statistically significant.

Results

We evaluated data from 632 patients who underwent TAVI and had baseline BMI data available from August 2008 to November 2019. Mean age of the cohort was 82.7 ± 6.7 years and 46% (292) of patients were female. Median STS-PROM score was 3.6 (IQR 2.7 to 5.6) and mean BMI was 27.5 ± 5.0 kg/m^2. Baseline clinical characteristics according to BMI are shown in Table 1. When stratified by BMI, 214 (34%) patients were normal weight, 234 (37%) overweight and 185 (29%) obese. Compared with those with normal BMI, overweight and obese patients were on average 1 to 3 years younger (p <0.001) and tended to have lower STS-PROM scores (p <0.002). Overweight patients were more likely be male whilst obese patients were more likely to be female (p = 0.005). With regard to premorbid conditions, both diabetes (p <0.001) and COPD (p = 0.009) were more prevalent with increased BMI. Proportions of patients with previous coronary artery disease or coronary intervention did not differ, nor did rates of stroke, hypertension, or atrial fibrillation. Median frailty score, as measured by the clinical frailty scale, was higher in obese patients (p = 0.02). Medtronic Evolut R (42%) and Medtronic CoreValve ‘Classic’ (25%) valves were the most commonly used valves. There was no difference in valve type used across BMI groups. Access was predominantly transfemoral (95%) with no differences in access site seen between groups.

Preprocedural echocardiographic measures differed marginally. Normal BMI patients were more likely to have moderate or severe aortic regurgitation (p = 0.02) and a smaller aortic valve area (p = 0.003), however there was no difference in mean pressure gradient or left ventricular ejection fraction (Table 1).

There was no difference in in-hospital and 30-day procedural complications of bleeding or vascular access between groups (Table 2). There was no difference in early postprocedural rates of death, myocardial infarction, stroke, or need for permanent pacemaker insertion.

Aortic valve MPG was the only echocardiographic measure to differ postprocedurally between BMI groups. Overweight and obese patients had higher MPGs at both 1- (p <0.001) and 2-years (p = 0.003) following TAVI (Table 3). There was no difference in the proportion of patients with moderate or severe paravalvular aortic regurgitation between the groups at either 1- or 2-year postprocedure.

One- and 2-year mortality differed significantly between groups, with those in the overweight BMI group having the lowest mortality compared with normal BMI and obese BMI groups (p = 0.03 and 0.02 respectively) (Table 2). Kaplan-Meier survival analysis demonstrated early separation of curves (Figure 1) which was maintained out to 24 months (log rank p = 0.02).

On multivariable analysis, obese patients had similar long-term mortality to those with normal BMI. Whereas overweight BMI was independently associated with significantly lower long-term mortality (hazard ratio [HR] 0.56 95% confidence interval [CI] 0.38 to 0.85, p = 0.006) as compared with normal BMI, with a median follow up of 2 years (Table 4). Other variables independently associated with increased mortality on multivariable analysis included increasing age, male sex, co-morbid COPD, previous balloon aortic valvuloplasty, and increasing STS-PROM score. Frailty was not significantly associated with mortality in the univariate analysis so was not included in the multivariate model.

Table 1
Baseline characteristics for patients by BMI category; represented as mean (± standard deviation), median (IQR) or number (percentage)

	Body mass index (kg/m^2)			
Variable	18.5−24.9 (n = 214)	25.0−29.9 (n = 234)	>30.0 (n = 185)	p Value
Age (years)	84.0 (± 7.6)	82.7 (± 6.2)	81.3 (± 6.1)	<0.001
STS-PROM	4.3% (3.0-6.0)	3.4% (2.4-4.8)	3.6% (2.5-5.5)	<0.002
Women	106 (49.5%)	85 (36.3%)	101 (54.6%)	0.005
BMI (kg/m^2)	22.5 (± 1.6)	27.2 (± 1.4)	33.8 (± 3.5)	<0.001
Coronary artery disease	93 (43.4%)	116 (49.8%)	88 (47.8%)	0.40
Prior coronary procedure				0.32
- Bypass surgery	31(14.5%)	51 (21.9%)	36 (19.6%)	
- Percutaneous intervention	35 (16.4%)	40 (17.2%)	32 (17.4%)	
Prior balloon aortic valvuloplasty	45 (21.7%)	43 (19.2%)	42 (23.7%)	0.54
Atrial fibrillation	70 (32.7%)	74 (31.6%)	61 (33.2%)	0.94
Cerebrovascular disease	25 (11.7%)	42 (17.9%)	26 (14.1%)	0.17
Hypertension	138 (64.5%)	166 (70.9%)	136 (73.5%)	0.12
Diabetes mellitus	45 (21.0%)	68 (29.1%)	74 (40.0%)	<0.001
Peripheral vascular disease	33 (15.6%)	37 (15.9%)	29 (16%)	0.99
Chronic obstructive pulmonary disease	28 (13.4%)	29 (12.7%)	41 (23%)	0.009
Estimated glomerular filtration rate (ml/min/1.73m^2)	59.1 (± 20.8)	60.0 (± 18.7)	57.5 (±19.6)	0.421
Frailty score	4 (3-4)	4 (3-4)	4 (4-5)	0.02
Aortic regurgitation				0.018
- Moderate	24 (12.2%)	17 (7.8%)	6 (3.7%)	
- Severe	2 (1.01%)	1 (0.5%)	1 (0.6%)	
Mean pressure gradient (mm Hg)	47.4 (±16)	47.1 (±13.8)	45.9 (±12.3)	0.559
Aortic valve area (cm^2)	0.71 (±0.2)	0.77 (±0.2)	0.77 (±0.2)	0.003
Left ventricular ejection fraction (%)	56.8 (±11.7)	57.4 (±11.1)	57.8 (±10.2)	0.66
Vascular access route				
- Transfemoral	200 (93.9%)	223 (95.3%)	175 (95.1%)	
- Subclavian	9 (4.2%)	4 (1.7%)	3 (1.6%)	
- Direct aortic	3 (1.4%)	2 (0.9%)	5 (2.7%)	
- Transapical	0 (0%)	2 (0.9%)	0 (0%)	
- Subclavian and transfemoral	1 (0.5%)	3 (1.3%)	1 (0.5%)	0.31
Valve type				0.22
- Corevalve	53 (25%)	56 (23.9%)	51 (28%)	
- Evolut R	84 (39.6%)	106 (45.3%)	71 (39%)	
- Evolut Pro	14 (6.6%)	5 (2.1%)	4 (2.2%)	
- Sapien 3	36 (17%)	48 (20.5%)	35 (19.2%)	
- Sapien XT	12 (5.7%)	11 (4.7%)	13 (7.1%)	
- Portico	13 (6.1%)	8 (3.4%)	8 (4.4%)	
Year of implantation				0.67
2008-2010	16 (7.5%)	16 (6.8%)	13 (7.0%)	
2011-2013	25 (11.7%)	29 (12.4%)	16 (8.6%)	
2014-2016	60 (28.2%)	57 (24.4%)	59 (31.9%)	
2017-2019	112 (52.6%)	132 (56.4%)	97 (52.4%)	

Table 2
Short-term outcomes according to BMI, represented as number (percentage)

	Body mass index (kg/m^2)			
Outcome	18.5−24.9 (n = 214)	25.0−29.9 (n = 234)	>30.0 (n = 185)	p Value
Vascular access complication	15 (7.9%)	15 (7.2%)	16 (9.7%)	0.67
Bleeding complication	6 (3.2%)	9 (4.3%)	3 (1.9%)	0.43
Myocardial infarction at 30 days	3 (1.5%)	1 (0.5%)	2 (1.2%)	0.59
Stroke at 30 days	3 (1.5%)	4 (1.7%)	4 (2.2%)	0.54
New pacemaker insertion at 30 days	44 (21.4%)	43 (18.9%)	40 (22.6%)	0.76
All-cause mortality 30 days	4 (2.1%)	2 (0.9%)	2 (1.2%)	0.656
All-cause mortality 1 year	15 (9.8%)	5 (3%)	6 (4.7%)	0.029
All-cause mortality 2 years	23 (19.3%)	9 (7.2%)	16 (15.2%)	0.019

Table 3
Post-TAVI echocardiographic measures at 1 and 2 years, represented as mean (± standard deviation) or number (percentage)

	Body mass index (kg/m^2)			
Variable	18.5−24.9 (n = 214)	25.0−29.9 (n = 234)	>30.0 (n = 185)	*p* Value
1-year post-TAVI				
Paravalvular aortic regurgitation				0.67
- Moderate	6 (4.8%)	6 (4.2%)	2 (1.8%)	
- Severe	0 (0%)	0 (0%)	0 (0%)	
Mean pressure gradient (mm Hg)	8.92 (±4.6)	10.9 (±4.8)	11.0 (±4.5)	<0.001
Aortic valve area (cm^2)	1.66 (±0.4)	1.79 (±0.5)	1.63 (±0.5)	0.16
2-years post-TAVI				
Paravalvular aortic regurgitation				0.36
- Moderate	1 (1.2%)	5 (5.8%)	3 (3.5%)	
- Severe	0 (0%)	0 (0%)	1 (1.2%)	
Mean pressure gradient (mm Hg)	8.9 (±3.7)	11.1 (±4.3)	10.8 (±4.6)	0.003
Aortic valve area (cm^2)	1.68 (±0.41)	1.60 (±0.29)	1.60 (±0.61)	0.73

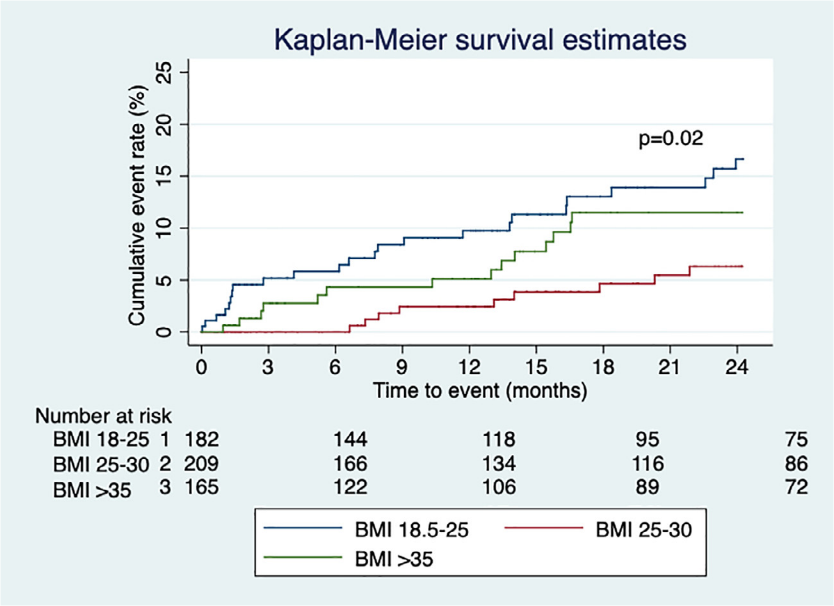

Figure 1. Cumulative all-cause mortality over 2 years stratified by body-mass index.

Discussion

From this multicenter registry, we have demonstrated that patients who are overweight (BMI 25 to 29.9 kg/m^2) have reduced long-term mortality compared with patients with normal BMI. This was confirmed by demonstrating that being overweight was independently associated with lower long-term mortality on multivariable analysis.

The present study reported a "J-shaped" curve which has been previously found in a study by González-Ferreiro et al.[12] They reported similar baseline characteristics in a cohort of 770 Spanish patients undergoing TAVI with a CoreValve prosthesis. When compared with normal weight, overweight BMI was independently associated with reduced mortality (HR 0.64 CI 0.42 to 0.99, p = 0.048) whilst obese weight was not (HR 0.76 CI 0.49 to 1.17, p = 0.211). When stratified by BMI group there was a difference in baseline brain natriuretic peptide levels. The investigators noted this may represent a higher proportion of end-stage heart failure and therefore cardiac cachexia among normal weight patients. However, the proportion of patients with ejection fraction less than 50% also differed which stands in contrast to the present study where mean ejection fraction was not different between groups.

Table 4
Multivariate analysis of factors affecting all-cause mortality, median follow-up 2 years; represented as hazard ratios (confidence interval)

Variable	Hazard ratio	Confidence interval	p Value
BMI Category (kg/m^2)			
18.5−24.9	1.00		
25.0−29.9	0.56	0.38−0.85	0.006
>30	0.71	0.46−1.08	0.11
Age	1.03	1.01−1.07	0.009
Men	1.68	1.17−2.42	0.005
STS-PROM	1.07	1.02−1.12	0.006
Chronic obstructive pulmonary disease	1.50	1.01−2.24	0.04
Prior balloon aortic valvuloplasty	2.00	1.38−2.91	<0.001

BMI = Body mass index (kg/m^2).

Previous studies have supported the finding of an obesity paradox in TAVI[11,17,18] and indeed in cardiovascular procedures more broadly.[6−8] The largest of these studies reported on the outcomes of 32,000 patients in the STS/ACC TVT registry. They were stratified into normal weight, overweight, and obesity classes I (BMI, 30.0 to 34.9 kg/m^2), II (BMI, 35.0 to 39.9 kg/m^2), and III (BMI, >40 kg/m^2). The proportions of patients in each weight category were similar to the present study reflecting the societal parallels between Australia and the United States. Baseline characteristics such as age, sex and STS-PROM score were comparable to the present study. Sharma et al found class I and II obesity were independently associated with decreased mortality in addition to overweight BMI when compared with normal weight; however, class III obesity was associated with increased mortality at 1 year.

Contrary to our hypothesis, obese patients were more frail than overweight and normal weight patients as determined by the clinical frailty score. Rogers et al examined the relationship between frailty and outcomes following TAVI and found no difference in mean BMI when groups were dichotomized into frail and nonfrail.[13] The STS/ACC TVT registry data did not report an overall frailty score but found that 5-meter walk times were longer in obese patients, suggesting increased frailty in the higher BMI cohort. In that study, improved outcomes were attributed to earlier onset of symptoms, increased muscular strength and higher metabolic reserve.

Attention should be paid to the utility of BMI in older populations compared with young- or middle-aged adults. Meta-analyses have shown that increased BMI is associated with reduced mortality in the elderly.[9,19] Winter et al found that mortality increased at a BMI less than 23 kg/m^2 with an ideal weight range for those older than 65 being between 24.0 kg/m^2 and 39.0 kg/m^2. It should be noted that BMI, whilst a useful and accessible measure of body mass, is relatively crude and does not assess body composition. Waist-hip ratio has been studied as an adjunct to BMI in coronary disease.[20] Patients with normal BMI and increased waist-to-hip ratio had the highest mortality in a large cohort of patients with coronary artery disease when compared with those of high BMI without elevated waist-hip ratio. Similar results have been seen in the general elderly population. A large UK study demonstrated that waist-hip ratio positively correlates with all-cause and circulatory-specific mortality whereas increased BMI showed a negative association with circulatory mortality in women and no association in men.[21] Given that TAVI is predominantly carried out in the elderly, the findings of the present study may simply be reflective of overall population trends. As such, the notion of a paradox should be re-examined. The underlying mechanisms of these findings remain controversial, but it is clear that patient context is important to the interpretation of BMI. Traditional negative views of increased BMI in cardiovascular medicine may need some readjustment in the both the elderly and the periprocedural populations.

There are some important limitations to the current study. Given this study was performed across 2 centers with a majority Caucasian population, we cannot assume generalizability to other ethnic groups. The Clinical Frailty Score is an easy-to-use clinical assessment, however does not include physiological measures of frailty such as walk speed and grip strength. Our study did not measure any alternate measures of body composition such as body fat percentage or waist-hip ratio. We do not collect data on comorbid rheumatologic conditions or steroid use. These factors have been shown to influence bleeding risk and may confound our findings. The observational nature of this study means it may be influenced by other unmeasured confounders. Finally, studies observing the influence of a single risk factor in a population with a particular disease are at risk of a type of systematic bias known as collider stratification. This occurs where a single causative risk factor for a disease is analyzed according to outcomes. It may reveal that the subsequent disease phenotype associated with this risk factor is less malignant and therefore appears to demonstrate improved outcomes associated with the risk factor.

Our study details a multicenter Australian experience of TAVI assessing outcomes by BMI. The results are consistent with previous international data on this subject demonstrating that patients who are overweight (BMI 25 to 29.9 kg/m^2) have reduced long-term mortality compared with patients with normal BMI. Furthermore, this adds to the developing weight of evidence relating to improved outcomes in overweight and obese patients in numerous aspects of cardiovascular medicine and suggests clinicians need to remain open-minded to the impact of BMI given its traditional association with increased cardiovascular risk.

Credit Author Statement

Edward J Quine: Conceptualization, methodology, formal analysis, data curation, writing − original draft, visualization. Misha Dagan: Methodology, formal analysis, data curation, writing − review and editing. Jeremy William: Formal analysis, writing − review and editing. Shane Nanayakkara: Validation, formal analysis, writing − review and editing, visualization. Luke P Dawson: Data curation. Stephen J Duffy: Methodology, investigation, resources, writing − review and editing, supervision. Julia Stehli: Resources, data curation, writing − review and editing. Ron J Dick: Investigation, resources. Nay M Htun: Investigation, resources, writing − review and editing. Dion Stub: Conceptualization, investigation, resources, writing − review and editing, supervision. Antony S Walton: Investigation, resources, writing − review and editing, supervision, project administration.

Disclosures

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1. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *New Engl J Med* 2016;374:1609–1620.
2. Reardon MJ, Mieghem NM van, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PWJC, Kappetein AP. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *New Engl J Med* 2017;376:1321–1331.
3. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL, Forrest JK, Tchétché D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ, Investigators ELRT. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *New Engl J Med* 2019;380:1706–1715.
4. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Généreux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR. Investigators P 3. Investigators the P 3. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *New Engl J Med* 2019;380:1695–1705.
5. Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373:1083–1096.
6. Lancefield T, Clark DJ, Andrianopoulos N, Brennan AL, Reid CM, Johns J, Freeman M, Charter K, Duffy SJ, Ajani AE, Proietto J, Farouque O, Registry M (Melbourne IG. Is there an obesity paradox after percutaneous coronary intervention in the contemporary era? An Analysis from a multicenter Australian registry. *JACC Cardiovasc Interv* 2010;3:660–668.
7. Hastie CE, Padmanabhan S, Slack R, Pell ACH, Oldroyd KG, Flapan AD, Jennings KP, Irving J, Eteiba H, Dominiczak AF, Pell JP. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. *Eur Heart J* 2010;31:222–226.
8. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, Ahmed LM, Kent KM, Pichard AD, Suddath WO, Satler LF, Lindsay J. The impact of obesity on the short-term andlong-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol* 2002;39:578–584.
9. Winter JE, MacInnis RJ, Wattanapenpaiboon N, Nowson CA. BMI and all-cause mortality in older adults: a meta-analysis. *Am J Clin Nutrition* 2014;99:875–890.
10. Yamamoto M, Mouillet G, Oguri A, Gilard M, Laskar M, Eltchaninoff H, Fajadet J, Iung B, Donzeau-Gouge P, Leprince P, Leuguerrier A, Prat A, Lievre M, Chevreul K, Dubois-Rande J-L, Teiger E, FRANCE 2 Registry Investigators. Effect of body mass index on 30- and 365-day complication and survival rates of transcatheter aortic valve implantation (from the FRench Aortic National CoreValve and Edwards 2 [FRANCE 2] registry). *Am J Cardiol* 2013;112:1932–1937.
11. Om SY, Ko E, Ahn J, Kang D, Lee K, Kwon O, Lee PH, Lee S, Kim HJ, Kim JB, Choo SJ, Park D, Park S. Relation of body mass index to risk of death or stroke in patients who underwent transcatheter aortic valve implantation. *Am J Cardiol* 2019;123:638–643.
12. González-Ferreiro R, Muñoz-García AJ, López-Otero D, Avanzas P, Pascual I, Alonso-Briales JH, Trillo-Nouche R, Pun F, Jiménez-Navarro MF, Hernández-García JM, Morís C, Juanatey JRG. Prognostic value of body mass index in transcatheter aortic valve implantation: a "J"-shaped curve. *Int J Cardiol* 2017;232:342–347.
13. Rogers T, Alraies MC, Pacha HM, Bond E, Buchanan KD, Steinvil A, Gai J, Torguson R, Ben-Dor I, Satler LF, Waksman R. Clinical frailty as an outcome predictor after transcatheter aortic valve implantation. *Am J Cardiol* 2018;121:850–855.
14. Schoenenberger AW, Moser A, Bertschi D, Wenaweser P, Windecker S, Carrel T, Stuck AE, Stortecky S. Improvement of risk prediction after transcatheter aortic valve replacement by combining frailty with conventional risk scores. *JACC Cardiovasc Interv* 2018;11:395–403.
15. Kappetein AP, Head SJ, Généreux P, Piazza N, Mieghem NM van, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, Es G-A van, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document†. *Eur Heart J* 2012;33:2403–2418.
16. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials. *Circulation* 2011;123:2736–2747.
17. Sharma A, Lavie CJ, Elmariah S, Borer JS, Sharma SK, Vemulapalli S, Yerokun BA, Li Z, Matsouaka RA, Marmur JD. Relationship of body mass index with outcomes after transcatheter aortic valve replacement: results from the national cardiovascular data−STS/ACC TVT registry. *Mayo Clin Proc* 2020;95:57–68.
18. van der Boon RMA, Chieffo A, Dumonteil N, Tchetche D, Van Meighem NM, Buchanan GL, Vahdat O, Marcheix B, Serruys PW, Fajadet J, Colombo A, Carrié D, van Domburg RT, de Jaegere PPT, PRAGMATIC-Plus Researchers. Effect of body mass index on short- and long-term outcomes after transcatheter aortic valve implantation. *Am J Cardiol* 2013;111:231–236.
19. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obes Rev* 2007;8:41–59.
20. Coutinho T, Goel K, Corrêa de Sá D, Carter RE, Hodge DO, Kragelund C, Kanaya AM, Zeller M, Park JS, Kober L, Torp-Pedersen C, Cottin Y, Lorgis L, Lee S-H, Kim Y-J, Thomas R, Roger VL, Somers VK, Lopez-Jimenez F. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease role of "normal weight central obesity. *J Am Coll Cardiol* 2013;61:553–560.
21. Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE. Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. *Am J Clin Nutrition* 2006;84:449–460.