Impact of High Body Mass Index on Vascular and Bleeding Complications After Transcatheter Aortic Valve Implantation

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Increased body mass index (BMI) is an established cardiovascular risk factor. The impact of high BMI on vascular and bleeding complications in patients undergoing transcatheter aortic valve implantation (TAVI) is not clarified. RISPEVA, a multicenter prospective database of patients undergoing TAVI stratified by BMI was used for this analysis. Patients were classified as normal or high BMI (obese and overweight) according to the World Health Organization criteria. A comparison of 30-day vascular and bleeding outcomes between groups was performed using propensity scores methods. A total of 3776 matched subjects for their baseline characteristics were included. Compared with normal BMI, high BMI patients had significantly 30-day greater risk of the composite of vascular or bleeding complications (11.1% vs 8.8%, OR: 1.28, 95% CI [1.02 to 1.61]; p = 0.03). Complications rates were higher in both obese (11.3%) and overweight (10.5%), as compared with normal weight patients (8.8%). By a landmark event analysis, the effect of high versus normal BMI on these complications appeared more pronounced within 7 days after the TAVI procedure. A significant linear association between increased BMI and vascular complications was observed at this time frame (p = 0.03). In conclusion, compared with normal BMI, both obese and overweight patients undergoing TAVI, experience increased rates of 30-day vascular and bleeding complications. These findings indicate that high BMI is an independent risk predictor of vascular and bleeding complications after TAVI. **© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)** **(Am J Cardiol 2021;155:86−95)**

Body mass index (BMI) is an established biometric measure of obesity commonly adopted to estimate cardiovascular risk.[1] Increased BMI values are associated with greater risk of cardiovascular morbidity and mortality.[2−5] Interestingly an obesity paradox has been demonstrated in coronary artery disease,[6,7] heart failure,[8] and after surgical aortic valve replacement.[9] Better outcomes of patients with high BMI are reported in the transcatheter aortic valve intervention (TAVI) field, as well.[10−12] However, besides this debated inverse relationship with BMI, a direct impact to vascular and bleeding complications after TAVI has not been well characterized. Within this framework, a relevant question arise as to whether high BMI affects the risk of vascular complications and

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See page 93 for disclosure information.

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bleeding associated with TAVI. We aimed to investigate the 30-day vascular and bleeding outcomes of patients with high versus normal BMI undergoing TAVI procedures.

Methods

The current project is a planned analysis of the RISPEVA registry. Details on the registry are reported elsewhere.[13] Briefly, RISPEVA is a prospective database addressing complications and outcomes after TAVI involving over 20 Italian centers performing TAVI. The study is registered online (clinicaltrials.gov ID: NCT02713932). Data were collected between March 2012 and July 2019. Centers contributing to this study have long-standing and high-volume experience in TAVI. Relevant baseline information, as well as vascular and bleeding outcomes at 30-days, were entered into prespecified electronic case report forms. This study received approval by the local ethics committee of all participating centers, and patients signed a written informed consent.

The primary endpoint was addressed at 30 days and was predefined as the composite of access-related vascular and bleeding complications. Patients were classified according to the World Health Organization criteria such as normal weight, overweight, or obese according to their BMI (18.5 to 24.9 kg/m2, 25.0 to 29.9 kg/m2, and ≥30.0 kg/m2, respectively). High BMI was defined as ≥25 kg/m2. Clinical events were classified according to the Valve Academic Research Consortium-2 criteria.[14] Information on follow-up events was site-reported and adjudicated by a trained physician-investigator. Secondary endpoints were the individual components included in the primary outcome.

All analyses have been performed in the propensity-matched population. Categorical variables are reported as n (%) and continuous variables as mean ± standard deviation. Categorical variables were compared by $\chi 2$ or Fisher's exact tests, as appropriate. Continuous data were analyzed by independent-samples t-test. An adjusted analysis based on propensity score (PS) was performed. PS is the probability that each individual patient is included in the high BMI or normal BMI group and was estimated via logistic regression based on the available baseline covariates.[15] Potential confounders were entered into the PS model on the basis of known clinical relevance or of associations ($p < 0.10$) observed at univariate analysis; final variable selection was performed by a logistic or Cox regression model with LASSO (Least Absolute Shrinkage and Selection Operator) penalty and a tuning parameter selected by cross-validation, which allows to minimize overfitting.[16] Variables that were used to construct the PS model are listed in Table S1. Missing data were imputed when present in less than 5% of inspected variables or the variable was excluded if had a higher percentage of missingness. Assuming that data were missing at random we used polytomous logistic regression, logistic regression and predictive mean matching as multiple imputation techniques to fill in missing values, using the R mice package. We imputed 5 different datasets and the same statistical analyses were performed on each of them. After that, Rubin's rule was used to derive pooled PS adjusted odds ratio (OR) estimates and confidence intervals (CIs) for each endpoint (primary and secondary), according to the matching method. A further sensitivity analysis using PS as covariate was used. Full matching was performed to minimize bias.[17] Weights using PS were included in the survival analysis to estimate 2 adjusted cumulative event curves (1 for high and low BMI). Log rank test was used to compare the curves. Covariate balancing was assessed exploring the standardized mean differences between unadjusted and adjusted populations and distribution of the PS. Standardized differences were estimated for all the baseline covariates before and after matching to assess pre-match imbalance and post-match balance. Standardized differences of less than 10.0% for a given covariate indicate a relatively small imbalance. A p value <0.05 was considered statistically significant for all analyses. For the subgroup analyses, p interaction was calculated and a value <0.10 was considered significant. The adjusted statistical analysis was performed using R 4.0 and some related packages, as mice, survival and matchthem packages.

Results

From an initial cohort of 5856 patients, a total of 3776 subjects undergoing TAVI were matched with the full matching procedure and included in the present analysis (Figure 1). Demographic, clinical, and outcome data of patients with high BMI were compared with those of patients with normal BMI. All TAVI procedures were performed via femoral access with local anesthesia. Clinical, echocardiographic and procedural characteristics at presentation are reported in Table 1. The baseline characteristics were balanced in the matched population with no significant differences between the high versus normal BMI cohorts, as expressed by standardized differences and PS differences in frequency between active and control.

The incidence of the primary endpoint in the high BMI versus normal BMI is presented in Figure 2. At 30-days, compared with normal BMI, high BMI yielded a significantly greater risk of the composite primary endpoint (11.1% vs 8.8%, p = 0.03). This relationship remained significant after adjustment for clinical covariates comparing high BMI versus normal BMI (Figure 2).Vascular or bleeding complications rates were higher both in obese and overweight patients as compared with the normal BMI group (Figure 2).

An overall cumulative analysis of the primary endpoint at 30 days was conducted. The cumulative incidence of composite of vascular and bleeding complications was significantly greater in the high BMI group within the 30 day time frame (Figure 3). A landmark analysis of the cumulative event distribution at the 7 day landmark point displayed the statistically significant increased incidence within 7 days of periprocedural vascular or bleeding complications in the high versus normal BMI groups. This difference became numerical but not significant in the explored time window between 7 and 30 days (Figure 3).

The relation between increased BMI values and clinical events was confirmed using BMI as continuous measure, which identified a significant linear association with vascular complications at 30 days (Figure 4). The 30-day primary outcome was also explored in prespecified subgroups.

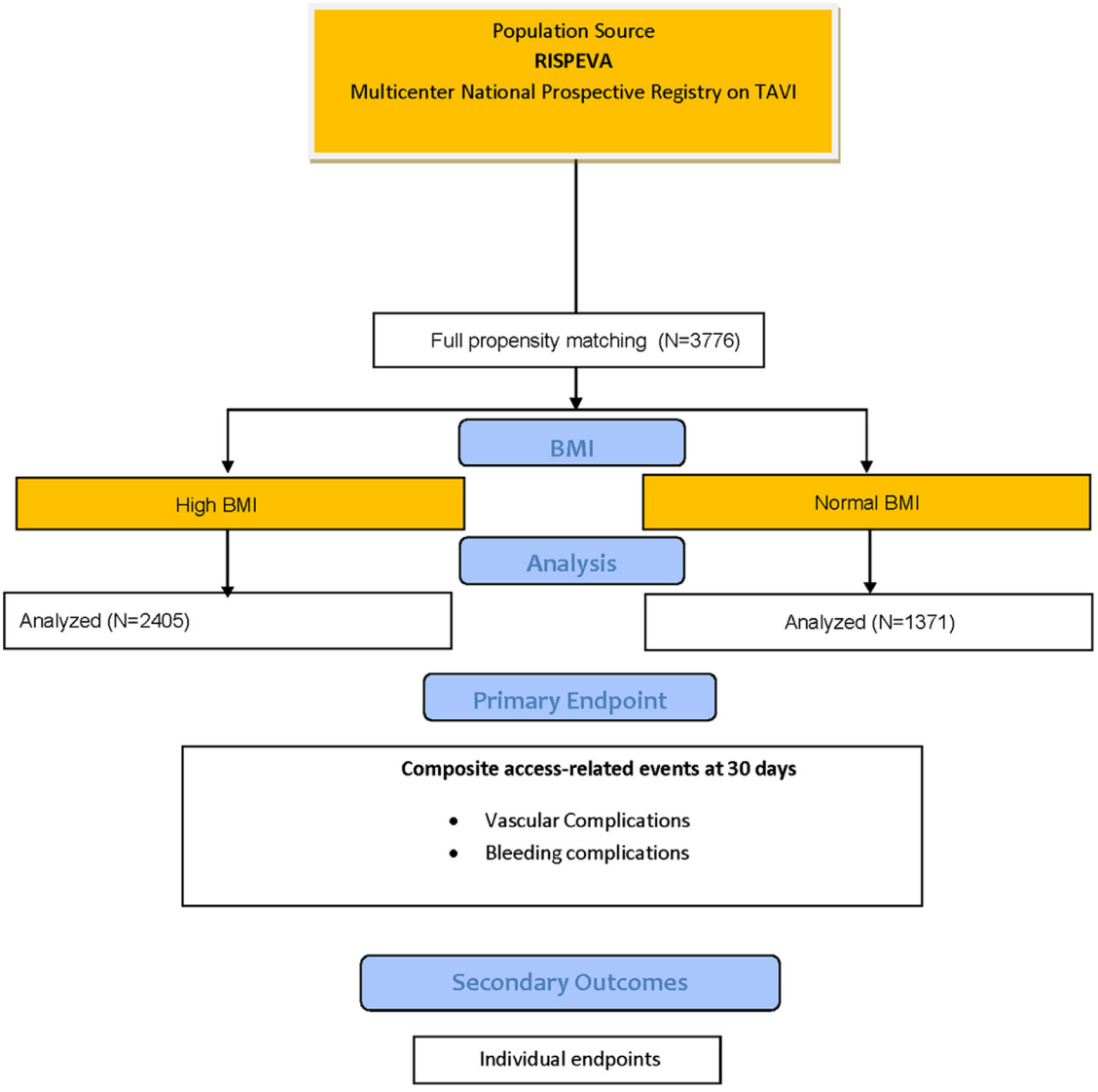

Figure 1. Flow chart of the study.

When compared with normal BMI, the risk of the primary endpoint remained greater in the high BMI group, regardless of diabetes, gender, chronic kidney disease, type of vascular closure device (VCD), sheath diameter size and degree of calcifications. A significant interaction with gender and VCD used was noted, with male patients having higher BMI than females and those treated with Prostar device being at the greatest risk of complications if BMI was high (Figure 5). By multivariate analysis, we tested whether changes in TAVR practice over time might have influenced the results by comparing the effect of high BMI in patients undergoing TAVI in the years 2013 to 2016 to that for 2017 to 2019. Results were comparable across time periods with a significant increase in the odds of bleeding in the high versus normal BMI for both time frames: OR 1.25 [95% CI 1.04 to 1.50], p = 0.01 for 2013 to 2016 and OR 1.21 [95% CI 1.02 to 1.43], p = 0.02 for 2017 to2019, without a significant p for interaction.

At 30-day follow-up a significantly cumulative increased risk of vascular complications in the high BMI cohort was found (9.8% vs 7.8%, p = 0.03) (Table 2). A significant increased risk of cumulative bleeding was also observed in the high BMI cohort (5.9% vs 4.4%, p = 0.03), which was nominally significant using propensity score as covariate. These bleeding estimates were driven by a markedly significant increase of minor bleeding (4.3% vs 2.5%, p = 0.005) (Table 2). The significant increase was confirmed by treating the propensity score estimates as a covariate.

Discussion

The salient findings of this large-scale analysis of 3776 propensity-matched patients are that: 1) as compared with normal BMI, high BMI values are associated with a greater 30-day risk of access-related vascular or bleeding complications; 2) the effect on these complications occurs more frequently earlier, within 7 days after procedure than afterwards; 3) a direct linear association is observed between BMI and the risk of vascular complications.

Table 1
Baseline clinical, echocardiographic and procedural characteristics of patients with high versus normal BMI

Variable	BMI (kg/m^2)		p value
	≥25 (n = 2405)	18.5-24.9 (n = 1371)	
Age (years)	82.2 ± 79	81 ± 52	0.86
Women	1386 (57.6%)	816(59.5%)	0.91
Body mass index (kg/m2)	29.06 ± 3.64	22.42 ± 1.97	<0.001
Coronary artery Disease	826 (34.3%)	469 (34.2%)	0.93
Diabetes mellitus	716 (29.8%)	391(28.5%)	0.41
Smoker	220 (9.1%)	127 (9.3%)	0.90
Dyslipidemia	1354 (56.3%)	754 (55.0%)	0.43
Arterial Hypertension	2031 (84.4%)	1160 (84,6%)	0.89
Chronic kidney disease	686 (28.5%)	395 (28.8%)	0.85
STS score	6.1 ± 5.7	6.2 ± 6.0	0.86
Euroscore (logistic)	17.4 ± 12.9	18.9 ± 13.0	0.36
Frailty score	3.73 ± 4.1	3.78 ± 4.6	0.72
NYHA class			0.74
I	57 (2.4%)	26 (1.9%)	
II	719 (29.9%)	400 (29.2%)	
III	1462 (60.8%)	850 (62%)	
IV	167 (6.9%)	95 (6.9%)	
Hemoglobin (g/dl)	12.0 ± 1.6	12.0 ± 1.6	0.86
Platelet count (x10^3/μl)	208.6 ± 71.2	209.4 ± 76.6	0.74
Echocardiographic data			
Left ventricular end-diastolic diameter (mm)	50.6 ± 12.9	49.5 ± 12.9	0.72
Left ventricular end-systolic diameter (mm)	33.4 ± 10.1	33.3 ± 9.6	0.81
Left ventricular ejection fraction (%)	53.06 ± 10.6	52.7 ± 11.3	0.36
Peak gradient (mm Hg)	77.4 ± 23	76.9 ± 22.4	0.52
Mean gradient (mm Hg)	48.9 ± 17.5	48.1 ± 14.8	0.16
Annular area (mm^2)	401.2 ± 137.8	402.3 ± 138.9	0.80
Computed tomography vascular data			
Tortuosity			0.67
Mild	2216 (92.1%)	1258 (91.8%)	
Moderate and severe	189 (7.9%)	113 (8.2%)	
Calcium (access site)			0.18
Mild	2138 (88.9%)	1199 (87.5%)	
Moderate and severe	267 (11.1%)	172 (12.5%)	
Porcelain aorta	243 (10.1%)	164 (12.0%)	0.07
Procedural characteristics			
ProGlide vascular closure device	1279 (53.2%)	736 (53.7%)	0.76
Prosthesis type			0.76
Sapien	882 (36.7%)	492 (35.9%)	
Corevalve	807 (33.6%)	506 (36.9%)	
Portico	304 (12.6%)	142 (10.4%)	
Other	412 (17.1%)	231 (16.8%)	
Contrast media (ml)	169.5 ± 97.2	169.6 ± 105.3	0.97
Fluoroscopy time (min)	24.7 ± 36.3	25.1 ± 17.4	0.76

Data given as mean ± SD, or n (%). BMI= body mass index; Calcium grading = mild ≤ 1 cm, ≤180°, moderate > 1 cm, ≤180), severe > 180°; Frailty was assessed using the Hospital Frailty Risk Score (HFRS).

NYHA= New York Heart Association; SD = standard deviation; STS score = Society of Thoracic Surgeons 30-day mortality score.

The prognostic role of high BMI and obesity in the TAVI field has been subject of intense debate. Several studies have shown that obesity might be regarded as a protective factor in TAVI, leading to an "*obesity paradox*" phenomenon.[10,12,18–20] They reported lower rates of adverse outcomes after TAVI in overweight and obese compared with normal weight or underweight patients at follow-up. Another recent study reported neutral effect of high BMI on mortality and worst outcomes in patients with BMI < 20 kg/m^2.[21] The increased mortality in the low-BMI groups could be explained by frail characteristics of this population and the smaller peripheral access site sizes.[22,23]

According to these previous findings, high BMI could be considered to exert a protective role and favorably affects the outcomes over time. However, this observation could lead to the misleading interpretation of a universal beneficial effect of high BMI on TAVI outcomes regardless of the timing after the TAVI procedure.

Within this framework, the early impact of high BMI on procedural vascular access-related complications and

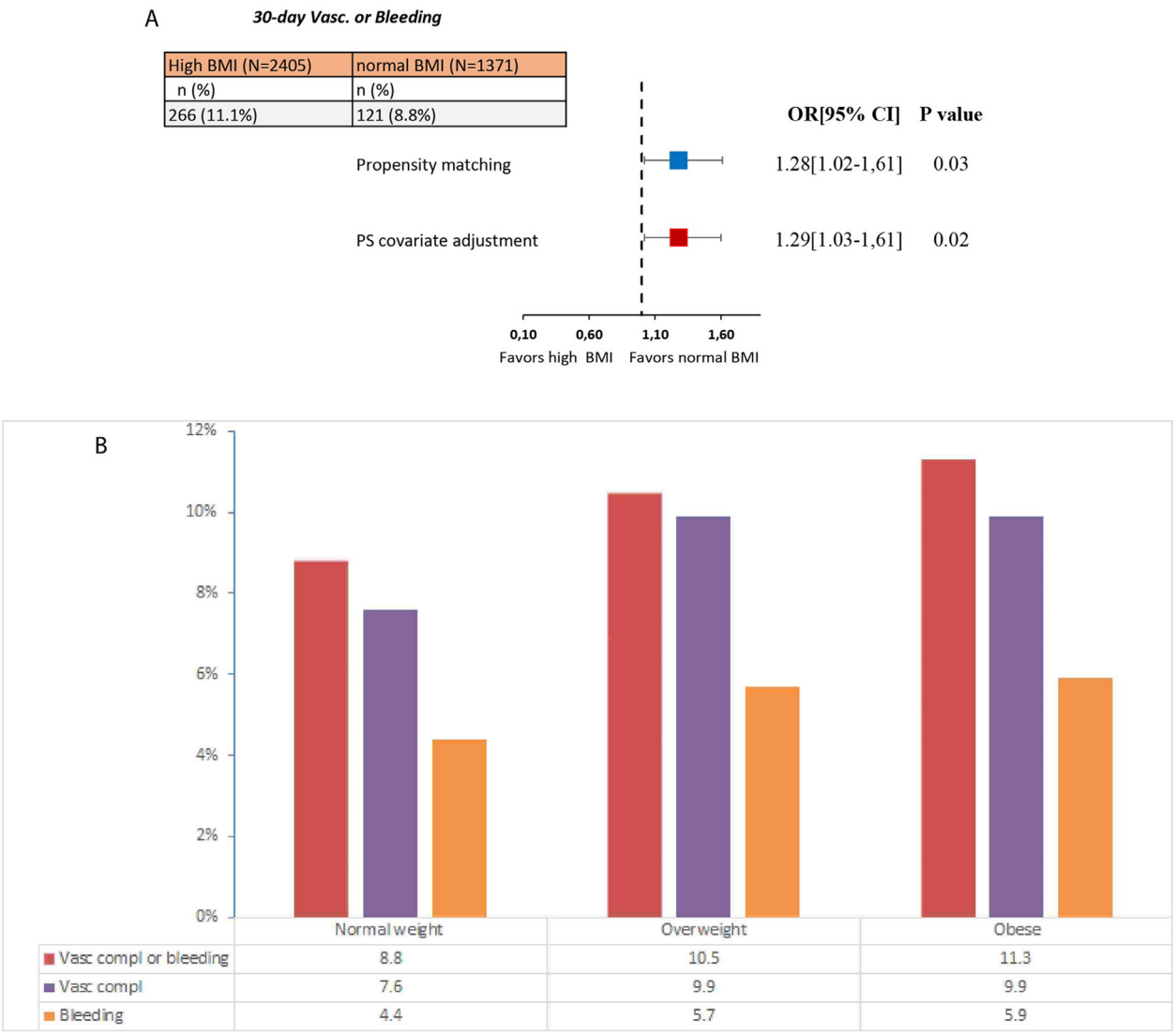

Figure 2. (A) Propensity score adjusted analysis of the primary endpoint (composite of vascular complications or bleeding) risk at 30-day follow-up in patients with high versus normal BMI. OR= odds ratio. (B) Rates of the primary endpoint (composite of vascular complications or bleeding) risk at 30-day follow-up in the matched population of normal weight, overweight and obese patients. CI = confidence interval; n = clinical events in the high and normal BMI cohorts; OR= odds ratio; PS = propensity score; vasc = vascular.

bleeding has not been clarified. Although major technical improvements have led to a progressive downsizing of the sheath introducers and TAVI prostheses, vascular and bleeding complications continue to occur in a consistent number of patients undergoing TAVI.[24–29] Therefore, identifying procedural or patient-related factors that can contribute to increase the risk of vascular complications is a pivotal procedural step when planning TAVI.

Increased BMIs could pose major challenges in gaining and closure of vascular access.[30] Excess weight contributes to changes in patients' anatomy and physiology in ways that render more challenging the invasive procedure.[31] Failure in gaining femoral access due the fat panniculus associated with higher BMI has already been reported in patients undergoing coronary revascularization and in need for intraortic balloon counterpulsation, and is determined by the inability to advance the sheath and secure the deep access to the femoral artery.[32] A high BMI has been associated with image quality impairment during fluoroscopy-based procedures, increased radiation dose and prolonged fluoroscopy times.[25]

A major finding of this study conducted in a propensity matched population of 3776 subjects undergoing TAVI is the prognostic role of higher BMI to drive an excess of access-related vascular and bleeding complications. The analysis of the cumulative event distribution offered a better understanding of the mechanistic underpinnings for the increase of vascular and bleeding complications in patients with high BMI undergoing TAVI. In aggregate, 30-day clinical events were more frequently observed in patients with high versus normal BMI. The analysis of the event distribution at the landmark time of 7 days has further contributed to identify 2 temporal stages after TAVI differently sensitive to BMI: an early time frame within 7 days after the index procedure and later stages.

Based on this landmark analysis, during the early time frames high BMI values pose increased interventional challenges to the operator. In contrast, the BMI

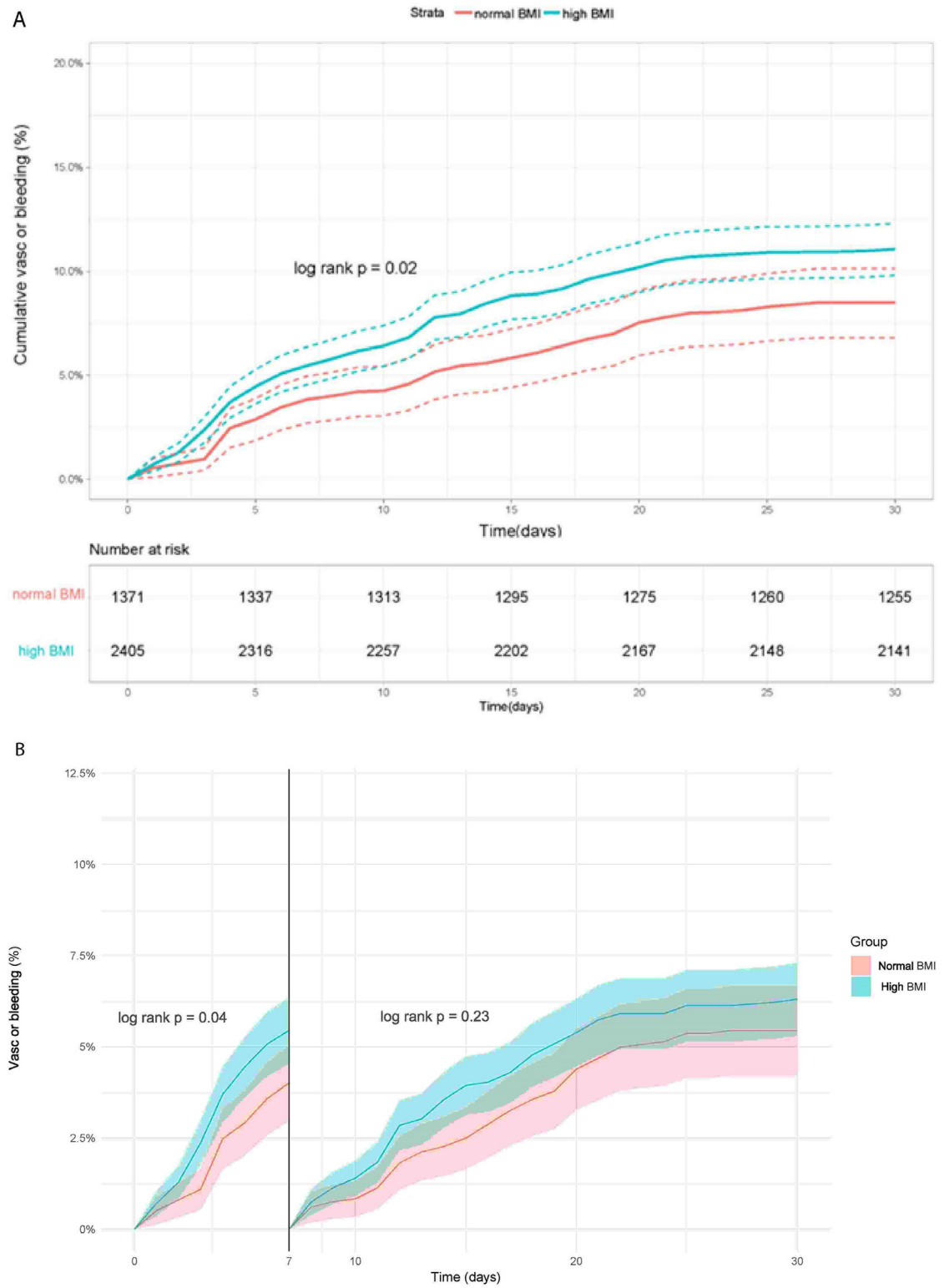

Figure 3. (A) Propensity score adjusted cumulative rates of the composite vascular or bleeding complications at 30 days in patients with high versus normal BMI. Dashed lines denote the 95% confidence intervals. (B) Landmark analysis at the 7 day landmark time point of the 30-day composite vascular or bleeding complications in patients with high versus normal BMI. Colored bands are the 95% confidence intervals.

effect appears more tempered during later stages after 7 days, that are less sensitive to the procedural impediments caused by operating on patients with BMI above normal ranges.

Another relevant aspect of this analysis is that the increased risk in subjects with a high BMI was not limited to obese but affected also overweight patients. Based on this finding, the entire population of patients with high BMI values, and not

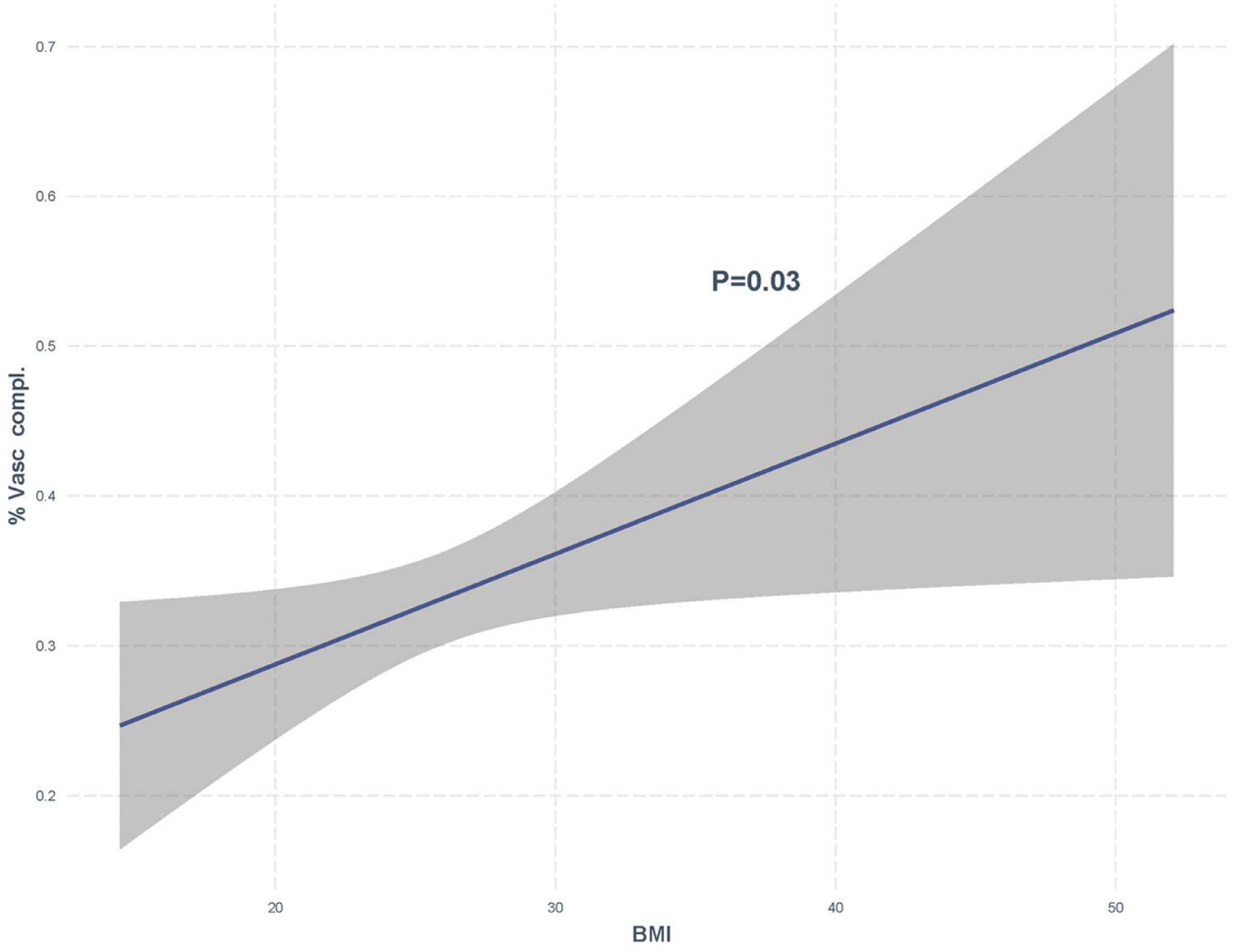

Figure 4. Linear relationship between BMI and increased risk of vascular complications. Event rates are predicted based on the linear regression equation.

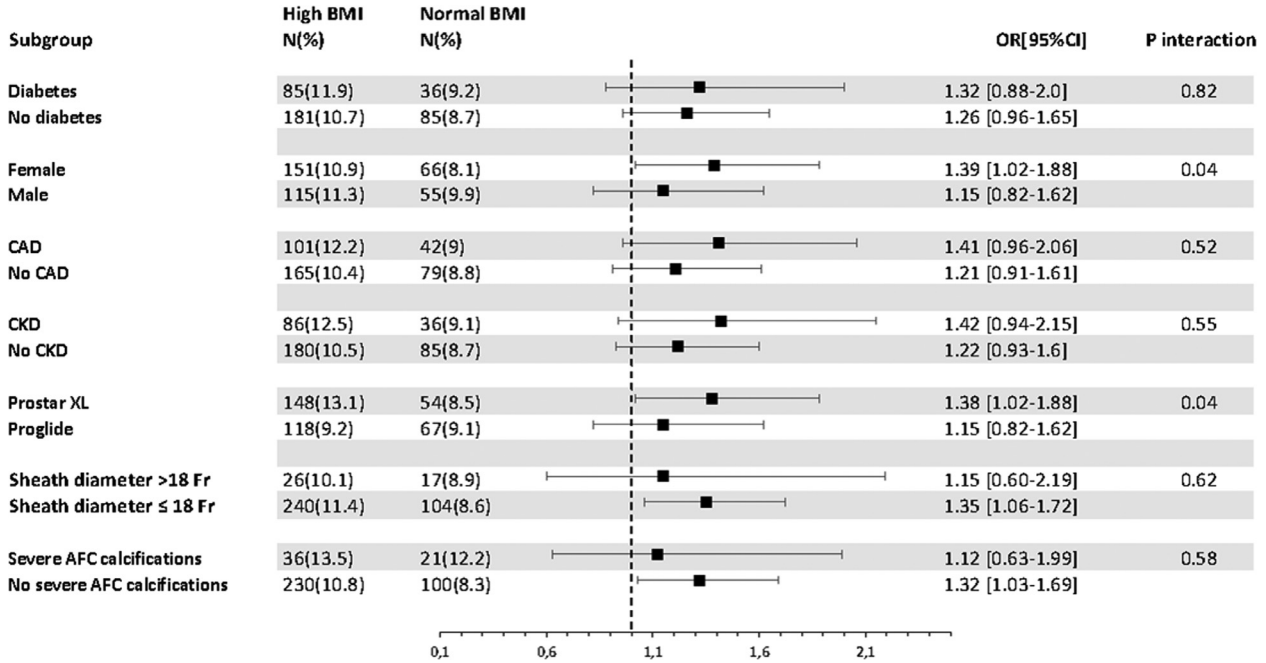

Figure 5. Vascular complications or bleeding risk at 30-day follow-up with high versus normal BMI in prespecified subgroups. CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; Fr = French; N = number of events in each group; OR = odds ratio.

Table 2
Individual outcomes at 30 days in subjects with high versus normal BMI undergoing TAVI

Variable	High BMI (n = 2405)	Normal BMI (n = 1371)	Propensity matching adjusted OR [95% CI]	p value	Propensity score covariate adjusted OR [95% CI]	p value
Any vascular complication	239 (9.8%)	107 (7.8%)	1.29 [1.02-1.64]	0.03	1.29 [1.12-1.49]	<0.001
Major vascular complications	87 (3.6%)	36 (2.6%)	1.39 [0.93-2.06]	0.10	1.40 [0.94-2.07]	0.09
Minor vascular complications	149 (6.2%)	71 (5.2%)	1.20 [0.90-1.61]	0.20	1.90 [0.94-1.61]	0.20
Any bleeding	141(5.9%)	61 (4.4%)	1.39 [1.01-1.92]	0.03	1.33 [0.98-1.81]	0.06
Life threatening or major bleeding	38 (1.6%)	27 (2.0%)	0.79 [0.48-1.31]	0.37	0.88 [0.51-1.51]	0.60
Minor bleeding	103 (4.3%)	34 (2.5%)	1.75 [1.18-2.60]	0.005	1.79 [1.20-2.67]	<0.001

BMI = body mass index; CI = confidence interval; OR = odds ratio.

just the obese, should be referred to as a continuum group at increased risk. The significant linear relation observed between BMI and predicted risk of vascular complications corroborates this hypothesis. Although the guidewire protection of the contralateral vessel to the access-site for the TAVI procedure was applied in most patients undergoing TAVR procedures in our registry the rate of vascular complications was not reduced in the high-BMI patients. Another aspect worth nothing is that a significant interaction with gender and VCD used was noted, with female patients and those treated with Prostar device being at the greatest risk of complications if BMI was high. These results align with the findings of a recent analysis in which as compared with Prostar XL, ProGlide use reduced composite adverse outcomes driven by a reduction in bleeding complications at 30-days.[29] Similarly, Manta, a VCD based on collagen-based technology has been associated with reduced vascular complications as compared to Prostar XL.[33] No significant differences have been found between MANTA and ProGlide in small observational studies.[34] However, powered head-to-head studies comparing these devices will clarify the optimal VCD in this setting.

Taken together, the findings of the current study call for further investigations to identify and compare interventional techniques and devices that can improve outcomes in these patients. Accordingly, a systematic implementation of the ultrasound-guided puncture and VCD may further reduce the access-related complications in these high-risk groups.

The RISPEVA study is observational by design, presenting the limitations common to all non-randomized studies which are prone to unmeasured confounders. On the other hand, the optimal group balancing obtained with 2 propensity score adjustment methods and the prospective data collection in electronic case report forms support the final hypothesis of the current analysis. The scope of the current analysis was to compare patients with high versus normal BMI as no inference has been done for underweight individuals. Thus, future studies are needed to compare the early effect after TAVI of lower BMI values versus normal BMI ranges.

In conclusion, as compared with normal BMI, patients with high BMI values undergoing TAVI have higher risk for vascular and bleeding complications. These findings suggest that BMI may be regarded as a potential risk predictor of access-related vascular and bleeding complications in the early period after TAVI.

Disclosures

Dr Berti was a proctor for Abbott. Dr Sherwood declares honoraria from Medtronic and Boston scientific. Dr Giordano was a proctor for Abbott. The remaining authors have no disclosures to report. Dr Navarese reports consulting fees/honoraria from Abbott, Astra-Zeneca, Amgen, Bayer, and Sanofi-Aventis; and grants from Abbott, and Amgen, outside the submitted work.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Berti Sergio reports a relationship with Abbott Vascular that includes: consulting or advisory. Matthew W. Sherwood reports a relationship with Medtronic Coronary and Structural Heart Disease Management that includes: speaking and lecture fees. Eliano P. Navarese reports a relationship with Abbott Vascular that includes: speaking and lecture fees.

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EPN and SB conceived the rationale and wrote the first draft. EPN conducted the statistical analysis. All co-authors have contributed providing important intellectual content and a critical revision of the manuscript.

Supplementary materials

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