A Meta-Analysis on the Impact of High BMI in Patients Undergoing Transcatheter Aortic Valve Replacement

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Abstract: Background: A paradoxical association of obesity with lower risk of transcatheter aortic valve replacement (TAVR) outcomes has been reported. We aimed to systematically review the literature and compare TAVR-related morbidity and mortality among individuals with overweight or obesity and their peers with normal body mass index (BMI). Methods: PubMed and Embase databases were systematically searched for studies reporting TAVR outcomes in different BMI groups. Separate meta-analyses were conducted for studies reporting hazard ratios (HR) and odds ratios/relative risks. Short- and mid-/long-term outcomes were examined. Results: 26 studies with a total of 74,163 patients were included in our study. Overweight was associated with lower risk of short-term mortality (HR: 0.77; 95% CI: 0.60–0.98) and mid-/long-term mortality (HR: 0.79; 95% CI: 0.70–0.89). Obesity was associated with lower risk for mid-/long-term mortality (HR: 0.79; 95% CI: 0.73–0.86), but no difference was observed in short-term mortality, although a trend was noted (HR: 0.87; 95% CI: 0.74–1.01). Individuals with obesity demonstrated an association with higher odds of major vascular complications (OR: 1.33; 95% CI: 1.05–1.68). Both overweight (OR: 1.16; 95% CI: 1.03–1.30) and obesity (OR: 1.26; 95% CI: 1.06–1.50) were associated with higher likelihood for receiving permanent pacemakers after TAVR. Conclusion: Individuals with overweight and obesity were associated with lower mortality risk compared to those with normal BMI but with higher likelihood of major vascular complications and permanent pacemaker implantation after TAVR.

Keywords: high body mass index; obesity paradox; transcatheter aortic valve replacement

1. Introduction

Obesity is a major public health concern with a disease burden that has tripled over the last 40 years [1]. In 2016, 650 million adults, which is 13% of the adult population globally, were estimated to suffer from obesity (BMI ≥ 30 kg/m²), and two billion people were estimated to be overweight (BMI 25–29.9 kg/m²) [1]. Obesity is a well-established risk factor for developing cardiovascular disease and a precursor to significant cardiovascular morbidity and mortality [2]. However, the impact of obesity in individuals undergoing cardiovascular interventions such as transcatheter aortic valve replacement (TAVR) is unclear. Despite the prevalence of obesity reaching nearly 15% in patients undergoing TAVR [3] and the annual TAVR volume in the United States overwhelmingly exceeding all forms of surgical aortic valve replacements (SAVR) (72,991 TAVR in 2019 vs. 57,626 surgical
aortic valve replacement), the relationship between body mass index (BMI) and TAVR outcomes remains to be established [4].

Previously published reports evaluating the relationship between overweight or obesity and TAVR-associated mortality have reported conflicting results, wherein some studies paradoxically found individuals with obesity who underwent TAVR to have significantly better long-term survival rates compared to individuals with normal BMI and those who were underweight, an association commonly reported as the “obesity paradox” [5–10]. It has been hypothesized that this may be related to individuals with obesity being relatively younger and less frail and thus with a tendency to seek care early, be managed more intensively, and have lower comorbidity burden [5–7,11]. Conflicting data also exist in respect to short-term mortality and periprocedural complications. Some studies found an association between individuals with obesity and improved short-term survival after TAVR compared to their counterparts with normal BMI, while others found no significant difference [6,8–10,12]. Despite the lack of consensus in current literature, ascertaining the effect of overweight and obesity on TAVR outcomes is clinically relevant, as BMI can serve as a simple pre-procedural risk stratification tool during TAVR evaluation and potentially for other structural heart procedures. With this systematic review and meta-analysis, we aimed to evaluate the association of baseline overweight and obesity with periprocedural complications and with regards to short- and mid-/long-term mortality risk after TAVR.

2. Methods

This study was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [13]. The study protocol was registered in PROSPERO (CRD42022350427).

2.1. Database Search and Study Eligibility

PubMed and EMBASE databases were systematically searched for eligible studies published up to June 26, 2022, by two independent researchers (JS and WL). The following search algorithm was adopted: (“transcatheter aortic valve implantation” OR “transcatheter aortic valve replacement” OR TAVI OR TAVR) AND (“body mass index” OR “body weight” OR BMI OR obes* OR overweight OR “body-mass index”). Reference lists of selected articles were additionally reviewed to identify eligible studies potentially excluded from our search algorithm. Any disagreements between two researchers were resolved by consensus of all the authors.

Studies were deemed eligible if (i) TAVR was performed in patients with aortic stenosis, (ii) the objective of the study was to report post-TAVR outcomes based on Valve Academic Research Consortium-2 definitions [14], (iii) comparative analysis based on their BMI was performed, and (iv) there were enough data reported to extract pertinent effect measures such as odds ratio (OR) or hazard ratio (HR).

Exclusion criteria were: (i) non-English language articles, (ii) duplicate patient population, (iii) lack of data on post-TAVR outcomes between different BMI groups, (iv) underweight population, and (v) surgical aortic valve replacement as the primary procedure performed. Case reports, editorials, reviews, conference abstracts and letters, guidelines, and study designs were excluded. There were no restrictions in terms of patient characteristics, sample size, or TAVR access approaches.

2.2. Data Extraction and Outcomes

Detailed information was extracted from each selected study by two independent reviewers (AK and AT) in a pre-defined data collection form. The following data were collected: (i) study characteristics (study design, location, study period, number of patients, BMI cutoff values, TAVI access approach, follow-up duration), (ii) patient baseline characteristics, (iii) primary outcomes, and (iv) secondary outcomes.

The primary outcomes were defined as short-term (30-day) mortality and mid-/long-term mortality (>1 year of follow up). The secondary outcomes included post-TAVI proce-
dural complications defined as major bleeding, vascular complications, cerebrovascular events, myocardial infarction, new-onset atrial fibrillation, permanent pacemaker implantation, post-operative delirium, hospital readmission, and acute kidney injury.

2.3. Quality of Evidence Assessment

The Newcastle–Ottawa Scale (NOS) was used by two independent researchers (JS and AT) to methodologically assess the quality of non-randomized studies included in the analysis [15]. The NOS score ranges from 0 to 9 and three dimensions contribute to the overall quality score: selection of studies, comparability, and exposure [16]. A score of $\geq 7$ denoted a high-quality study.

2.4. Statistical Analysis

Categorical variables were presented as frequencies or percentages, while continuous variables were listed in the form of means and standard deviations. The number of events, odds ratios (ORs), and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were collected for primary and secondary outcomes. Bland’s method [17] was used to estimate the mean and standard deviation from the sample size, median, and interquartile ranges. Meta-analyses were carried out to compare groups among normal body weight, overweight, and obesity groups. Different BMI cutoff values were utilized when defining each body weight group in selected studies. Analyses were performed based on the group category defined in each article. Adjusted multi-variate ORs or HRs were prioritized for the analysis when available, and if not, unadjusted ORs with 95% confidence intervals were pooled using data from the original studies. Different meta-analyses were conducted for studies reporting HRs vs. ORs/event rates. We used the random-effects model (DerSimonian–Laird) for effect size estimation [18]. Statistical significance was defined as $p < 0.05$. Between-study heterogeneity was assessed through Q-statistic and Higgins $I^2$ test, and high heterogeneity was indicated when $p < 0.05$ and $I^2 \geq 50\%$ [19]. Meta-regression analysis was performed to examine baseline variables with significant interaction with the outcomes. Funnel plots and Egger’s tests were used to assess publication bias, with $p < 0.05$ indicating significant bias [20,21]. All statistical analyses were performed using STATA IC 17.0 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Study Selection and Characteristics

Of the 1040 records identified, 26 studies were eligible, with a total of 74,163 patients included in our analysis [7,9,10,12,22–43]. The PRISMA flow diagram is presented in Figure 1. All studies were retrospective observational studies published between 2013 and 2022, and follow-up duration ranged from 6 months to 5 years. The definitions of different weight groups were variable. Thirteen studies [7,9,22–24,29,32,36,37,39,41–43] categorized patients’ BMI (kg/m$^2$) according to World Health Organization definitions [44]: underweight (BMI < 18.5 kg/m$^2$), normal (BMI $\geq 18.5$ kg/m$^2$ and <25 kg/m$^2$), overweight (BMI $\geq 25$ kg/m$^2$ and < 30 kg/m$^2$), obesity (BMI $\geq 30$ kg/m$^2$). Overweight and obesity groups were younger with lower logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgeons (STS) score but had higher comorbidity (coronary artery disease, chronic obstructive pulmonary disease, diabetes mellitus, dyslipidemia, hypertension) rates compared to normal BMI group. Details of included studies and patient characteristics are summarized in Tables 1 and 2, respectively.
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process.
Table 1. Summary of the included studies.

| Study                      | Year | Country    | Study Characteristic | Study Population (n) | Follow-Up Duration (months) | BMI Classification (kg/m²) | Vascular Access |
|----------------------------|------|------------|----------------------|-----------------------|-----------------------------|-----------------------------|-----------------|
| Abawi et al. [24]          | 2017 | Netherlands | retrospective single center | 562                   | 12                          | WHO definition              | Tf, Ta, Tao     |
| Abramowitz et al. [9]      | 2016 | USA        | retrospective single center | 805                   | 33                          | WHO definition              | Tf, Ta, Tao, S  |
| Ahmad et al. [25]          | 2019 | USA        | retrospective single center | 269                   | N/A                         | Underweight < 25            | N/A             |
|                           |      |            |                      |                       |                             | Normal 25 –< 30             | N/A             |
|                           |      |            |                      |                       |                             | Overweight 30 –< 35         | N/A             |
|                           |      |            |                      |                       |                             | Obesity ≥ 35                | N/A             |
| Berti et al. [22]          | 2021 | Italy      | retrospective single center | 3776                  | N/A                         | WHO definition              | N/A             |
| Boukhris et al. [12]       | 2021 | Canada     | retrospective single center | 412                   | 12                          | Underweight < 20            | Tf              |
|                           |      |            |                      |                       |                             | Normal 20 –< 25             |                 |
|                           |      |            |                      |                       |                             | Overweight 25 –< 30         |                 |
|                           |      |            |                      |                       |                             | Obesity ≥ 30                |                 |
| Corcione et al. [23]       | 2021 | Italy      | retrospective single center | 3075                  | (mean): 9.8–11.8           | WHO definition              | N/A             |
| DeMarzo et al. [26]        | 2021 | Italy      | retrospective single center | 645                   | 12                          | Low to normal < 25          | Tf, Ta, S       |
|                           |      |            |                      |                       |                             | Overweight 25 –< 30         |                 |
|                           |      |            |                      |                       |                             | Obesity ≥ 30                |                 |
| DePalma et al. [27]        | 2018 | Sweden     | retrospective single center | 493                   | 36                          | Underweight < 18            | Tf, S, Ta, O    |
|                           |      |            |                      |                       |                             | Normal 18–25                |                 |
|                           |      |            |                      |                       |                             | Overweight 25.1 –< 30       |                 |
|                           |      |            |                      |                       |                             | Obesity ≥ 30                |                 |
| Gonska et al. [28]         | 2021 | Germany    | retrospective single center | 611                   | N/A                         | BMI ≥ 25                    | Tf              |
| Gonzalez-Ferreiro et al. [29] | 2017 | Spain      | retrospective multi-center | 770                   | 36                          | WHO definition              | Tf, Tax          |
| Kische et al. [30]         | 2016 | Germany    | retrospective         | 172                   | 12                          | Non-obesity BMI < 30        | Tf              |
|                           |      |            |                      |                       |                             | Obesity BMI ≥ 30             |                 |
| Koifman et al. [31]        | 2016 | USA        | retrospective single center | 448                   | 12                          | Low <20                     | Tf              |
|                           |      |            |                      |                       |                             | Normal 20–24.9              |                 |
|                           |      |            |                      |                       |                             | Overweight 25–30            |                 |
|                           |      |            |                      |                       |                             | Obesity > 30                |                 |
| Konigstein et al. [32]     | 2015 | Israel     | retrospective single center | 409                   | 2                           | WHO definition              | Tf              |
| Lung et al. [33]           | 2014 | France     | retrospective multi-center | 2552                  | 1                           | Low < 18.5                  | Tf, Ta, S, O    |
|                           |      |            |                      |                       |                             | Normal 18.5–29.9            |                 |
|                           |      |            |                      |                       |                             | Overweight BMI ≥ 30         |                 |
Table 1. Cont.

| Study                        | Year | Country        | Study Characteristic      | Study Population (n) | Follow-Up Duration (months) | BMI Classification (kg/m²)                                      | Vascular Access |
|------------------------------|------|----------------|---------------------------|----------------------|----------------------------|----------------------------------------------------------------|-----------------|
| Luo et al. [34]              | 2022 | China          | retrospective single center | 109                  | 35                         | Low < 21.9<br>Middle 21.9–27.0<br>High > 27.0                      | Tf, Ta          |
| McInerney et al. [10]        | 2021 | Europe, USA    | retrospective multi-center | 3174                 | 24                         | Non-obesity 18.5–29.9<br>Morbidly obesity ≥40 or ≥35 with obesity-related comorbidities | Tf, non-Tf      |
| Om et al. [35]               | 2019 | Korea          | retrospective multi-center | 379                  | (median): 18.4 (IQR 7.3 to 37.2) | First tertile ≤ 22.3<br>Second tertile 22.4–24.8<br>Third tertile ≥ 24.9 | Tf, Ta, Tao     |
| Owais et al. [36]            | 2020 | Germany        | retrospective single center | 1609                 | 12                         | WHO definition                                                    | Tf              |
| Quine et al. [37]            | 2020 | Australia      | retrospective multi-center | 634                  | (median): 24               | WHO definition                                                    | Tf, S, Ta, O    |
| Saji et al. [38]             | 2022 | Japan          | retrospective multi-center | 14472                | 12                         | Underweight < 20<br>Normal 20–25<br>Overweight ≥ 25<br>Obesity ≥ 30 | Tf, non-Tf      |
| Salizzoni et al. [39]        | 2016 | Italy          | retrospective multi-center | 1904                 | (median): 25.7 (IQR 15.6 to 37.5) | WHO definition                                                    | Tf, Ta, Tao, Tax|
| Sgura et al. [40]            | 2022 | Italy          | retrospective multi-center | 794                  | (median): 26.4             | underweight < 20<br>Normal 20–24.9<br>Overweight/Obesity ≥ 25    | Tf, Ta          |
| Sharma et al. [41]           | 2020 | USA            | retrospective multi-center | 31929                | 12                         | WHO definition                                                    | Tf, Ta, Tao, S, O|
| Tokarek et al. [7]           | 2019 | Poland         | retrospective single center | 148                  | (median): 15.3 (IQR 6 to 34.7) | WHO definition                                                    | Tf, Ta, Tao, S  |
| Van der Boon et al. [42]     | 2013 | Europe         | retrospective multi-center | 940                  | (median): 12 (IQR 6 to 18) | WHO definition                                                    | Tf, Ta, S, O    |
| Yamamoto et al. [43]         | 2013 | France         | retrospective multi-center | 3072                 | (median): 4.1 (IQR 1 to 8.3) | WHO definition                                                    | Tf, Ta, S, O    |

BMI: body mass index; S: subclavian; Tao: transaortic; Ta: transapical; Tf: transfemoral; Tax: trans-axillary; O: others; IQR: interquartile range; WHO definition of BMI (kg/m²): underweight: (BMI < 18.5), normal: (BMI ≥ 18.5 and <25), overweight: (BMI ≥ 25 and <30), obesity: (BMI ≥ 30).
Table 2. Basic characteristics of normal, overweight, and obesity BMI patients.

|                     | Normal       | Overweight   | Obesity       |
|---------------------|--------------|--------------|---------------|
| Age (years)         | 71.0 ± 24.3  | 65.9 ± 37.8  | 67.6 ± 19.1   |
| Male n (%)          | 9198/19,032  | 10,187/18,919| 4425/9571 (46.2)|
| BMI (kg/m²)         | 22.8 ± 2.6   | 27.6 ± 3.3   | 34.5 ± 5.9    |
| AF n (%)            | 1191/3536 (33.7)| 869/2947 (29.5)| 776/2390 (32.5)|
| CAD n (%)           | 10,256/17,154| 10,562/17,171| 5433/8627 (63)|
| CKD n (%)           | 623/2847 (21.9) | 898/3595 (25) | 93/688 (13.5)|
| COPD n (%)          | 1306/6286 (20.8) | 1140/5377 (21.2) | 1021/3601 (28.4)|
| DM n (%)            | 2058/8277 (24.9) | 2471/8228 (30) | 1770/3989 (44.4)|
| Dyslipidemia n (%)  | 2780/5133 (54.2) | 3283/5523 (59.4) | 1668/2486 (67.1)|
| HTN n (%)           | 14,450/17,389 (83.1) | 15,229/17,544 (86.8) | 7994/8933 (89.5)|
| GFR (mL/min/m²)     | 57.1 ± 71.8  | 57.1 ± 71.0  | 53.1 ± 58.1   |
| logistic EuroSCORE  | 18.0 ± 12.6  | 17.7 ± 11.9  | 14.5 ± 10.7   |
| STS score           | 6.1 ± 3.7    | 5.3 ± 3.5    | 4.8 ± 2.6     |

Categorical variables are presented as frequencies and percentages, while continuous variables are listed in the form of means and standard deviations. BMI: body mass index; AF: atrial fibrillation; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive disease; DM: diabetes mellitus; HTN: hypertension; GFR: glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; STS: Society of Thoracic Surgeons; SD: standard deviation.

3.2. Study Quality Assessment

The quality of all included studies was assessed using the Newcastle–Ottawa Scale (NOS), with a mean score of 7.9 (supplemental Table S1), suggesting that the included studies were of high quality.

3.3. Primary outcomes

3.3.1. Short-Term Mortality

HR as a measure of short-term mortality comparing patients with overweight vs. patients with normal BMI was available in four studies [24,40,41,43]. The analysis showed an association between overweight status and lower 30-day mortality risk (adjusted HR: 0.77; 95% CI: 0.60–0.98), but significant heterogeneity and publication bias existed (I² = 57.1%, Egger test p = 0.0082) (Figure 2A). No difference was seen when we compared patients with obesity vs. patients with normal BMI [24,41,43] (adjusted HR: 0.87; 95% CI: 0.74–1.01, I² = 0.0%) (Figure 2B). No significant differences were found between normal BMI versus overweight groups and obesity groups among studies reporting unadjusted ORs (Figure 2C,D).

3.3.2. Mid-/Long-Term Mortality

Eleven and ten studies compared the overweight and obesity groups, respectively, and provided adjusted HR for the comparison with normal BMI with regards to mid-/long-term mortality. Both the overweight (adjusted HR: 0.79; 95% CI: 0.70–0.89, I² = 44.47%) and the obesity group (adjusted HR: 0.79; 95% CI: 0.73–0.86, I² = 0.0%) had a significantly lower mid-/long-term mortality risk when compared to patients with normal BMI (Figure 3A,B). Pooled analysis of unadjusted ORs in five studies [12,23,26,35,37] confirmed this association for obesity (OR: 0.62; 95% CI: 0.40–0.95, I² = 40.83%), but no difference was found with regards to the overweight group (OR: 0.89; 95% CI: 0.63–1.27, I² = 42.73%) (Figure 3C,D). Only one-year mortality outcomes were pulled for unadjusted ORs, except for the Corcione [23] study, with a mean follow-up ranging 9.8 to 11.8 months.
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3.4. Secondary Outcomes

Patients with overweight had a higher likelihood of needing a permanent pacemaker implantation (OR: 1.16; 95% CI: 1.03–1.30, I² = 0%) [7,9,12,23–26,29,31,32,34–37,43] (Figure 4F) as compared to patients with normal BMI. No significant differences were found in terms of major and life-threatening bleeding (Figure 4A), major vascular complications (Figure 4B), cerebrovascular events (Figure 4C), myocardial infarction (Figure 4D), atrial fibrillation (Figure 4G), and acute kidney injury (Figure 4E) in the overweight group. Patients with obesity were associated with significantly higher odds of major vascular complications (OR: 1.33; 95% CI: 1.05–1.68, I² = 40.85%) [9,10,12,23,24,26,29,31,32,34–37,42,43] (Figure 5B) and need for permanent pacemaker insertion (OR: 1.26; 95% CI: 1.06–1.50, I² = 37.33%) [7,9,10,12,23–26,29–32,34–37,43] (Figure 5F) compared to patients with normal BMI. No statistically significant differences were found in major and life-threatening bleeding (Figure 5A), cerebrovascular events (Figure 5C), myocardial infarction (Figure 5D), atrial fibrillation (Figure 5G), and acute kidney injury (Figure 5E) between obesity and normal BMI groups.

All primary and secondary outcomes are summarized in Tables 3 and 4.
3.4. Secondary Outcomes

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All primary and secondary outcomes are summarized in Tables 3 and 4.

### Table 3. Summary of meta-analyses for all outcomes in normal BMI versus patients with overweight.

| Outcomes                  | Studies | Patients | HR/OR | 95% CI, $p$-Value | $I^2$ (%) | Egger Test |
|---------------------------|---------|----------|-------|-------------------|-----------|------------|
| **Primary**               |         |          |       |                   |           |            |
| 30-day Mortality          | 4       | 25,050   | 0.77 (HR) | [0.60, 0.98], $p = 0.03$ | 57.09     | 0.0082     |
|                           | 10      | 6030     | 0.82 (OR) | [0.61, 1.09], $p = 0.17$ | 4.36      | 0.6904     |
| Mid-/long-term Mortality  | 11      | 28,917   | 0.79 (HR) | [0.70, 0.89], $p = 0.00$ | 44.47     | 0.8864     |
|                           | 5       | 3978     | 0.89 (OR) | [0.63, 1.27], $p = 0.52$ | 42.73     | 0.5304     |
| **Secondary**             |         |          |       |                   |           |            |
| Major Bleeding            | 14      | 11,724   | 1.08 (OR) | [0.92, 1.27], $p = 0.33$ | 8.92      | 0.5321     |
| Major Vascular Complications | 14     | 11,875   | 1.09 (OR) | [0.92, 1.29], $p = 0.31$ | 0         | 0.8544     |
| Cerebrovascular events    | 13      | 9940     | 1.11 (OR) | [0.86, 1.42], $p = 0.43$ | 0         | 0.3950     |
| Myocardial Infarction     | 8       | 7427     | 0.69 (OR) | [0.36, 1.34], $p = 0.27$ | 23.37     | 0.8140     |
| Atrial Fibrillation       | 5       | 2362     | 0.78 (OR) | [0.58, 1.04], $p = 0.09$ | 0         | 0.7519     |
| Pacemaker Insertion       | 15      | 10,071   | 1.16 (OR) | [1.03, 1.30], $p = 0.01$ | 0         | 0.9191     |
| Acute Kidney Injury       | 12      | 7338     | 1.04 (OR) | [0.82, 1.32], $p = 0.73$ | 23.73     | 0.9639     |

HR: Hazard ratio; OR: odds ratio; CI: confidence interval.

### Table 4. Summary of meta-analyses for all outcomes in normal BMI versus patients with obesity.

| Outcomes                  | Studies | Patients | HR/OR | 95% CI, $p$-Value | $I^2$ (%) | Egger Test |
|---------------------------|---------|----------|-------|-------------------|-----------|------------|
| **Primary**               |         |          |       |                   |           |            |
| 30-day Mortality          | 3       | 18,613   | 0.87 (HR) | [0.74, 1.01], $p = 0.07$ | 0         | 0.2995     |
|                           | 12      | 6461     | 0.8 (OR) | [0.59, 1.08], $p = 0.14$ | 0         | 0.0711     |
| Mid-/long-term Mortality  | 10      | 21,262   | 0.79 (HR) | [0.73, 0.86], $p = 0.00$ | 0         | 0.7745     |
|                           | 5       | 3173     | 0.62 (OR) | [0.40, 0.95], $p = 0.03$ | 40.83     | 0.8486     |
| **Secondary**             |         |          |       |                   |           |            |
| Major Bleeding            | 16      | 10,042   | 1.1 (OR) | [0.86, 1.41], $p = 0.46$ | 54.36     | 0.3594     |
| Major Vascular Complications | 15     | 10,033   | 1.33 (OR) | [1.05, 1.68], $p = 0.02$ | 40.85     | 0.4458     |
| Cerebrovascular events    | 14      | 9383     | 1.01 (OR) | [0.76, 1.35], $p = 0.94$ | 0         | 0.4143     |
| Myocardial Infarction     | 8       | 5804     | 0.72 (OR) | [0.39, 1.34], $p = 0.3$ | 0         | 0.7074     |
| Atrial Fibrillation       | 5       | 1876     | 0.68 (OR) | [0.40, 1.17], $p = 0.16$ | 46.85     | 0.0648     |
| Pacemaker Insertion       | 17      | 9878     | 1.26 (OR) | [1.06, 1.50], $p = 0.01$ | 37.33     | 0.5568     |
| Acute Kidney Injury       | 14      | 7485     | 1.09 (OR) | [0.93, 1.29], $p = 0.28$ | 0         | 0.2912     |

HR: Hazard ratio; OR: odds ratio; CI: confidence interval.
Figure 4. Complication rates after TAVR between normal BMI and overweight categories. (A) Major bleeding. (B) Major vascular complications. (C) Cerebrovascular events. (D) Myocardial infarction. (E) Acute kidney injury. (F) Permanent pacemaker insertion. (G) Atrial fibrillation. NI: normal BMI; OW: overweight; OB: obesity; OR: odds ratio \([7,9,12,22–26,29,31,32,34–37,42,43]\).
Figure 4. Complication rates after TAVR between normal BMI and overweight categories. (A) Major bleeding. (B) Major vascular complications. (C) Cerebrovascular events. (D) Myocardial infarction. (E) Acute kidney injury. (F) Permanent pacemaker insertion. (G) Atrial fibrillation. Nl: normal BMI; OW: overweight; OB: obesity; OR: odds ratio [7,9,12,22–26,29,31,32,34–37,42,43].

Figure 5. Complication rates after TAVR between normal BMI and obesity categories. (A) Major bleeding. (B) Major vascular complications. (C) Cerebrovascular events. (D) Myocardial infarction. (E) Acute kidney injury. (F) Permanent pacemaker insertion. (G) Atrial fibrillation. Nl: normal BMI; OW: overweight; OB: obesity; OR: odds ratio [9,10,12,23–26,29–32,34–37,42,43].
3.5. Publication Bias and Meta-Regression

The funnel plots and Egger’s test assessing for publication bias are presented in Supplementary Materials Figures S1 and S2 and Table S3, respectively. Only the comparison between overweight and normal BMI patients for short-term mortality showed significant publication bias (Egger test $p = 0.0082$). No significant associations between baseline characteristics and primary mortality outcomes were identified in our meta-regression analyses (Supplementary Materials Table S2).

4. Discussion

Our study presents a systematic review and meta-analysis on the effect of BMI on clinical outcomes after TAVR. The key findings of our study can be summarized as follows: (i) overweight status was associated with lower risk for short- and mid-/long-term mortality; (ii) obesity was associated with lower risk of mid-/long-term mortality; (iii) overweight and obesity were associated with higher risk of receiving permanent pacemakers after TAVR; and (iv) the obesity group was associated with a higher likelihood of major vascular complications.

While some studies have found one point increments in BMI (kg/m$^2$) to be associated with progressively improved long-term mortality [5,6], other studies such as the one conducted by Gilard et al. [45] including 4571 TAVR patients found a higher risk of mortality with increasing BMI among patients with BMI > 32 kg/m$^2$. Similarly, a study of 31,929 TAVR patients [41] showed that in patients with BMI > 30 kg/m$^2$, a unit increase in BMI was associated with a 3% increased risk of short-term mortality. Both studies limited their analyses among patients with obesity. This probably shows that when studying the obesity-only sub-group, higher BMI is associated with worse outcomes. Contrary to that, when comparing any obesity or overweight status to patients with underweight or normal BMI, extra weight seems to be associated with protective effects. This can be explained by higher frailty or life-threatening diseases (i.e., end-stage cancer, advanced heart failure) associated with underweight and low-normal BMI populations both in procedures such as TAVR and under transcatheter interventions such as Transcatheter Edge-to-Edge Repair [11,46–49]. Although our study excluded the underweight population, there was inconsistency among included studies that compared frailty in different BMI groups: Abawi [24] and Berti [22] reported no difference between BMI groups; Tokarek [7] and Abramowitz [9] reported lower frailty in the obesity group compared to normal BMI and overweight counterparts; Luo [34] and Quine [37] reported rather higher frailty in the higher BMI group compared to other BMI groups. No included studies reported malnutrition data. Our study used multivariate hazard ratios for the outcome of mortality to adjust for all these confounding factors when comparing normal BMI versus overweight and obesity groups. However, different studies adjusted for different characteristics and thus, even if the meta-analysis included adjusted HRs, this does not necessarily mean that it is adjusted for the same factors.

We found that obesity was associated with significantly higher likelihood of major vascular complications. It is interesting that our analysis shows that this is an issue only for the obesity group and not for individuals with overweight. This is expected, given how challenging femoral large-bore arterial access can be in individuals with significant fat tissue around groin. However, this was not shown by prior studies, with some of them finding no difference [5]. The Valve Academic Research Consortium (VARC)-3 strongly recommends recording detailed information regarding the access site and pre-planned vascular closure technique to better assess vascular complications in TAVR patients [50]. It also even provides different cut-off values for patients with obesity (BMI > 30) when assessing device success and prosthesis–patient mismatch, which is directly associated with all-cause and cardiac mortality [51]. This indicates that distinction should be made when studying outcomes of TAVR patients with different BMIs. Studies included in our meta-analyses, however, combined different access sites and vascular techniques, making it unclear whether specific access sites and/or vascular closure techniques are superior to others in limiting major vascular complication across different BMI categories.
An estimated 6–28% of patients undergoing TAVR receive permanent pacemakers [52]. The association between overweight or obesity and an increased risk of requiring permanent pacemakers after TAVR is not well-established in current literature. However, our study found both overweight and obesity to be associated with an increased risk of permanent pacemaker implantation after TAVR. Although multiple etiologies have been postulated to explain the occurrence of bradycardia requiring a pacemaker after TAVR (pre-existence of right bundle branch block, direct injury to atrioventricular and infranodal tissues, the use of self-expandable valve, male gender, baseline conduction abnormalities, larger prosthesis size, porcelain aorta, and increased implantation depth) [25,52–55], we suspect that larger prosthesis size requirements in patients with high BMI is probably contributing to our study findings [9,10,23,25].

Our study was unable to provide insights on the pathophysiology of obesity influencing favorable TAVR outcomes. Many possible mechanisms were introduced in other studies to explain the paradoxical phenomenon, including less frailty, younger population, early-on intensive medical interventions, protective peripheral body fat, and reduced inflammatory response with increased TNF-α receptors, but still the exact etiology remains unclear [5,6,9,56,57]. It is possible that the non-overweight/non-obesity groups had much higher likelihood of frailty, which is known to be associated with adverse outcomes post-TAVR [11,46], although no association between age and mortality was identified in our meta-regression analysis. It also remains unclear whether BMI can be adopted as the appropriate surrogate to investigate the true effect of overweight and obesity status of TAVR patients. Even if BMI is commonly used to define obesity, it is a relatively crude marker without accounting for the distribution of adipose tissue, especially visceral fat, which has been reported to have strong association with outcomes in cardiovascular disease, including for TAVR patients [58–61]. Future studies using other indicators such as body surface area (BSA) [62], pre-TAVR assessment of visceral abdominal fat using CT scan [10,63], waist-to-hip ratio of central obesity, or a combination of these may provide better understanding of obesity’s effect on TAVR outcomes.

5. Limitations

Our study has several important limitations. First, all studies included in our meta-analysis were retrospective in nature and were inherently susceptible to confounding factors. Second, the limited number of studies for certain important outcomes could have influenced the generalizability of our findings and precluded us from analyzing outcomes such as risk of readmission. Third, post-TAVR complications were derived from unadjusted, univariate data, which could not be adjusted by other confounding factors such as age or frailty. Frailty is known to be associated with negative outcomes after TAVR [64,65]. A multi-variate analysis would be helpful to draw additional conclusions. Fourth, various definitions of BMI categorization among all the included studies may have led to the heterogeneity observed in our analysis, necessitating the usage of standardized BMI classification (i.e., WHO definition) in future studies. Nonetheless, this study serves as the most updated meta-analysis on this topic to the best of our knowledge and highlights significant knowledge gaps and areas of future research.

6. Conclusions

Overweight and obesity—despite increasing the risk for vascular complications and permanent pacemaker insertion—were associated with improved survival likelihood after TAVR. Despite this strong association observed in the included observational analyses and in our systematic review and meta-analysis, we think that this might be driven by residual confounding by age, frailty, and other similar factors, which are more common in the normal or low BMI groups. We hope that future, well-designed, prospective cohort studies will shed light into this association and confirm whether there is a true obesity paradox or just unmeasured confounding.
Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcdd9110386/s1, Table S1: Newcastle–Ottawa scale; Table S2. Meta-regression analyses for primary outcomes in normal BMI versus patients with overweight and obesity; Figure S1. Funnel plots for mortality outcomes in normal BMI (Nl) versus patients with overweight (OW); Figure S2. Funnel plots for mortality outcomes in normal BMI (Nl) versus patients with obesity (OB).

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References
1. World Health Organization. Obesity and Overweight. Available online: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed on 23 July 2022).
2. Poirier, P.; Giles, T.D.; Bray, G.A.; Hong, Y.; Stern, J.S.; Pi-Sunyer, F.X.; Eckel, R.H. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss: An update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006, 113, 898–918. [CrossRef]
3. Alperi, A.; McInerney, A.; Modine, T.; Chamandi, C.; Tafur-Soto, J.D.; Barbanti, M.; Lopez, D.; Campelo-Parada, F.; Cheema, A.N.; Toggweiler, S.; et al. Transcatheter aortic valve replacement in obese patients: Procedural vascular complications with the trans-femoral and trans-carotid access routes. Interact. CardioVascular Thorac. Surg. 2021, 34, 982–989. [CrossRef]
4. Carroll, J.D.; Mack, M.J.; Vemulapalli, S.; Herrmann, H.C.; Gleason, T.G.; Hanzel, G.; Deeb, G.M.; Thourani, V.H.; Cohen, D.J.; Desai, N.; et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. J. Am. Coll. Cardiol. 2020, 76, 2492–2516. [CrossRef]
5. Lv, W.; Li, S.; Liao, Y.; Zhao, Z.; Che, G.; Chen, M.; Feng, Y. The ‘obesity paradox’ does exist in patients undergoing transcatheter aortic valve implantation for aortic stenosis: A systematic review and meta-analysis. Interact. Cardiovasc. Thorac. Surg. 2017, 25, 633–642. [CrossRef]
6. Sannino, A.; Schiattarella, G.G.; Toscano, E.; Gargiulo, G.; Giugliano, G.; Galderisi, M.; Losi, M.A.; Stabile, E.; Cirillo, P.; Imbriaco, M.; et al. Meta-Analysis of Effect of Body Mass Index on Outcomes After Transcatheter Aortic Valve Implantation. Am. J. Cardiol. 2017, 119, 308–316. [CrossRef]
7. Tokarek, T.A.; Dziewierz, A.; Sorysz, D.; Bagienski, M.; Rzeszutko, L.; Krawczyk-Ożóg, A.; Dudek, D.; Kleczyński, P. The obesity paradox in patients undergoing transcatheter aortic valve implantation: Is there any effect of body mass index on survival? Kardiol. Pol. 2019, 77, 190–197. [CrossRef]
8. van Nieuwkerk, A.; Santos, R.B.; Sartori, S.; Regueiro, A.; Tchetché, D.; Mehran, R.; Delevi, R.; the CENTER collaboration. Impact of body mass index on outcomes in patients undergoing transfemoral transcatheter aortic valve implantation. JTCVS Open 2021, 6, 26–36. [CrossRef]
9. Abramowitz, Y.; Chakravarty, T.; Jilaihawi, H.; Cox, J.; Sharma, R.P.; Mangat, G.; Nakamura, M.; Cheng, W.; Makkar, R.R. Impact of body mass index on outcomes following transcatheter aortic valve implantation. Catheter. Cardiovasc. Interv. 2016, 88, 127–134. [CrossRef]
10. McInerney, A.; Tirado-Conte, G.; Rodes-Cabau, J.; Campelo-Parada, F.; Tafur Soto, J.D.; Barbanti, M.; Munoz-Garcia, E.; Arif, M.; Lopez, D.; Toggweiler, S.; et al. Impact of Morbid Obesity and Obesity Phenotype on Outcomes After Transcatheter Aortic Valve Replacement. J. Am. Heart Assoc. 2021, 10, e019051. [CrossRef]
11. Tzoumas, A.; Kokkinidis, D.G.; Giannopoulos, S.; Giannakoulas, G.; Palaiodimos, L.; Avgierinos, D.V.; Kampaktsis, P.N.; Faillace, R.T. Frailty in patients undergoing transcatheter aortic valve replacement: From risk scores to frailty-based management. J. Geriatr. Cardiol. 2021, 18, 479–486. [CrossRef]
12. Boukhris, M.; Forcillo, J.; Potvin, J.; Noisieux, N.; Stevens, L.M.; Badreddine, M.; Gobeil, J.F.; Masson, J.B. Does “obesity paradox” apply for patients undergoing transcatheter aortic valve replacement? Arch. Cardiovasc. Dis. Suppl. 2022, 14, 69. [CrossRef]
13. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021, 372, n71. [CrossRef]

14. Kapkepete, A.P.; Head, S.J.; Genervux, P.; Piazza, N.; van Mieghem, N.M.; Blackstone, E.H.; Brott, T.G.; Cohen, D.J.; Cutillo, D.E.; van Es, G.A.; et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document (VARC-2). Eur. J. Cardiothorac. Surg. 2012, 42, S45–S60. [CrossRef]

15. Zeng, X.; Zhang, Y.; Kwong, J.S.; Zhang, C.; Li, S.; Sun, F.; Niu, Y.; Du, L. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. J. Evid. Based Med. 2015, 8, 2–10. [CrossRef]

16. Wells, G.A.; Shea, B.; O’Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Ottawa Hospital Research Institute: Ottawa, ON, Canada, 2000.

17. Wan, X.; Wang, W.; Liu, J.; Tong, T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med. Res. Methodol. 2014, 14, 135. [CrossRef]

18. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. Control Clin. Trials 1986, 7, 177–188. [CrossRef]

19. Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. BMJ 2003, 327, 557–560. [CrossRef]

20. Sterne, J.A.; Sutton, A.J.; Ioannidis, J.P.; Terrin, N.; Jones, D.R.; Lau, J.; Carpenter, J.; Rucker, G.; Harbord, R.M.; Schmid, C.H.; et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011, 343, d4002. [CrossRef]

21. Hunter, J.P.; Satarzadeh, A.; Sutton, A.J.; Boucher, R.H.; Sayers, R.D.; Bown, M.J. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J. Clin. Epidemiol. 2014, 67, 897–903. [CrossRef]

22. Berti, S.; Bartorelli, A.L.; Konis, E.; Giordano, A.; Petronio, A.S.; Iadanza, A.; Bedogni, F.; Reimers, B.; Spaccarotella, C.; Trani, C.; et al. Impact of High Body Mass Index on Vascular and Bleeding Complications After Transcatheter Aortic Valve Implantation. Am. J. Cardiol. 2021, 155, 86–95. [CrossRef]

23. Corcione, N.; Testa, A.; Ferraro, P.; Morello, A.; Cimmino, M.; Albanese, M.; Giordano, S.; Bedogni, F.; Iadanza, A.; Berti, S.; et al. Baseline, procedural and outcome features of patients undergoing transcatheter aortic valve implantation according to different body mass index categories. Minerva Med. 2021, 112, 474–482. [CrossRef]

24. Abawi, M.; Rozemeijer, R.; Agostoni, P.; van Jaarsveld, R.C.; van Dongen, C.S.; Voskuil, M.; Kraaijeveld, A.O.; Doevendans, P.; Amei, P.; et al. BMI and acute kidney injury post transcatheter aortic valve replacement: Unveiling the obesity paradox. J. Cardiovasc. Med. 2021, 22, 579–585. [CrossRef]

25. De Palma, R.; Ivarsson, J.; Feldt, K.; Saleh, N.; Ruck, A.; Linder, R.; Settergren, M. The obesity paradox in patients undergoing transcatheter aortic valve implantation. Obes. Res. Clin. Pract. 2018, 12, 51–60. [CrossRef]

26. Gonska, B.; Reuter, C.; Morike, J.; Rottbauer, W.; Buckert, D. Vascular Access Site Complications Do Not Correlate With Large Sheath Diameter in TAVI Procedures With New Generation Devices. Front. Cardiovasc. Med. 2021, 8, 738854. [CrossRef]

27. Gonzalez-Ferreiro, R.; Munoz-Garcia, A.J.; Lopez-Otero, D.; Avanzas, P.; Pascual, I.; Alonso-Briales, J.H.; Trillo-Nouche, R.; Pun, F.; et al. The obesity paradox in patients undergoing transcatheter aortic valve implantation: A “J”-shaped curve. Int. J. Cardiol. 2017, 232, 342–347. [CrossRef]

28. Kische, S.; D’Ancona, G.; Agma, H.U.; El-Achkar, G.; Dissmann, M.; Ortak, J.; Oner, A.; Ketterer, U.; Barisch, A.; Levenson, B.; et al. Transcatheter aortic valve implantation in obese patients: Overcoming technical challenges and maintaining adequate hemodynamic performance using new generation prostheses. Int. J. Cardiol. 2016, 220, 909–913. [CrossRef]

29. Koifman, E.; Kiramijyan, S.; Negi, S.I.; Didier, R.; Escarcega, R.O.; Minha, S.; Gai, J.; Torguson, R.; Okubagzi, P.; Ben-Dor, I.; et al. Impact of preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. J. Cardiovasc. Dev. Dis. 2022, 9, 8. [CrossRef]

30. Konigstein, M.; Havakuk, O.; Arbel, Y.; Finkelstein, A.; Ben-Assa, E.; Leshem Rubinow, E.; Abramowitz, Y.; Keren, G.; Banai, S.; et al. The obesity paradox in patients undergoing transcatheter aortic valve implantation. Clin. Cardiol. 2015, 38, 76–81. [CrossRef]

31. Liew, M.; Lauenen, C.; Himbert, D.; Eltchaninoff, H.; Chevreul, K.; Donzeau-Gouge, P.; Fajadet, J.; Leprince, P.; Leguerrier, A.; Lievre, M.; et al. Predictive factors of early mortality after transcatheter aortic valve implantation: Individual risk assessment using a simple score. Heart 2014, 100, 1016–1023. [CrossRef]

32. Luo, Z.R.; Chen, L.W.; Qiu, H.F. Does the “obesity paradox” exist after transcatheter aortic valve implantation? J. Cardiothorac. Surg. 2022, 17, 156. [CrossRef]
54. Bax, J.; Delgado, V.; Bapat, V.; Baumgartner, H.; Collet, J.P.; Erbel, R.; Hamm, C.; Kappetein, A.P.; Leipsic, J.; Leon, M.B.; et al. Open issues in transcatheter aortic valve implantation. Part 2: Procedural issues and outcomes after transcatheter aortic valve implantation. Eur. Heart J. 2014, 35, 2639–2654. [CrossRef] [PubMed]

55. Ledwoch, J.; Franke, J.; Gerckens, U.; Kuck, K.H.; Linke, A.; Nickenig, G.; Krulls-Munch, J.; Vohringer, M.; Hambrecht, R.; Erbel, R.; et al. Incidence and predictors of permanent pacemaker implantation following transcatheter aortic valve implantation: Analysis from the German transcatheter aortic valve interventions registry. Catheter. Cardiovasc. Interv. 2013, 82, E569–E577. [CrossRef] [PubMed]

56. Mohamed-Ali, V.; Goodrick, S.; Bulmer, K.; Holly, J.M.; Yudkin, J.S.; Coppack, S.W. Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. Am. J. Physiol. 1999, 277, E971–E975. [CrossRef] [PubMed]

57. Chrysant, S.G.; Chrysant, G.S. New insights into the true nature of the obesity paradox and the lower cardiovascular risk. J. Am. Soc. Hypertens. 2013, 7, 85–94. [CrossRef]

58. Srikanthan, P.; Horwich, T.B.; Tseng, C.H. Relation of Muscle Mass and Fat Mass to Cardiovascular Disease Mortality. Am. J. Cardiol. 2016, 117, 1355–1360. [CrossRef]

59. Mok, M.; Allende, R.; Leipsic, J.; Altisent, O.A.; Del Trigo, M.; Campelo-Parada, F.; DeLarochelliere, R.; Dumont, E.; Doyle, D.; Cote, M.; et al. Prognostic Value of Fat Mass and Skeletal Muscle Mass Determined by Computed Tomography in Patients Who Underwent Transcatheter Aortic Valve Implantation. Am. J. Cardiol. 2016, 117, 828–833. [CrossRef]

60. Carbone, S.; Billingsley, H.E.; Rodriguez-Miguelez, P.; Kirkman, D.L.; Garten, R.; Franco, R.L.; Lee, D.C.; Lavie, C.J. Lean Mass Abnormalities in Heart Failure: The Role of Sarcopenia, Sarcopenic Obesity, and Cachexia. Curr. Probl. Cardiol. 2020, 45, 100417. [CrossRef]

61. Ortega, F.B.; Sui, X.; Lavie, C.J.; Blair, S.N. Body Mass Index, the Most Widely Used But Also Widely Criticized Index: Would a Criterion Standard Measure of Total Body Fat Be a Better Predictor of Cardiovascular Disease Mortality? Mayo Clin. Proc. 2016, 91, 443–455. [CrossRef]

62. Arsalan, M.; Filardo, G.; Kim, W.K.; Squiers, J.J.; Pollock, B.; Liebetrau, C.; Blumenstein, J.; Kempfert, J.; Van Linden, A.; Arsalan-Werner, A.; et al. Prognostic value of body mass index and body surface area on clinical outcomes after transcatheter aortic valve implantation. Clin. Res. Cardiol. 2016, 105, 1042–1048. [CrossRef]

63. Kandathil, A.; Mills, R.A.; Hanna, M.; Merchant, A.M.; Wehrmann, L.E.; Minhaajuddin, A.; Abbara, S.; Fox, A.A. Abdominal adiposity assessed using CT angiography associates with acute kidney injury after transcatheter aortic valve replacement. Clin. Radiol. 2020, 75, 921–926. [CrossRef] [PubMed]

64. Kokkinidis, D.G.; Armstrong, E.J.; Giri, J. Balancing Weight Loss and Sarcopenia in Elderly Patients With Peripheral Artery Disease. J. Am. Heart Assoc. 2019, 8, e013200. [CrossRef] [PubMed]

65. Green, P.; Arnold, S.V.; Cohen, D.J.; Kirtane, A.J.; Kodali, S.K.; Brown, D.L.; Rihal, C.S.; Xu, K.; Lei, Y.; Hawkey, M.C.; et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER trial). Am. J. Cardiol. 2015, 116, 264–269. [CrossRef] [PubMed]