Impact of body mass index on long-term outcomes in Japanese patients following percutaneous coronary intervention: The Juntendo PCI Registry

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ABSTRACT

Background: The prognostic long-term impact of body mass index (BMI) on East Asian patients with coronary artery disease remains unclear.

Methods: An observational retrospective cohort study was carried out involving 3571 patients who had undergone percutaneous coronary intervention (PCI) from 2000 to 2013. Patients were divided into the following five groups according to baseline BMI: Group 1 (underweight, BMI < 20.0 kg/m²); Group 2 (underweight 2, BMI = 20.1–22.5 kg/m²); Group 3 (normal weight, BMI = 22.6–25.0 kg/m²); Group 4 (overweight 1, BMI = 25.1–27.5 kg/m²); and Group 5 (overweight 2, BMI ≥ 27.6 kg/m²). We then evaluated the association between BMI and both all-cause and cardiac death after PCI.

Results: The ratio of patients in the five groups was as follows: Group 1, 9.2%; Group 2, 21.6%; Group 3, 34.1%; Group 4, 21.1%; and Group 5, 14.5%. A decrease in age was observed from underweight to overweight, as was an increased prevalence of hypertension, diabetes mellitus, dyslipidemia, and smoking. The median follow-up period was 6.3 years (interquartile range, 3.2–9.6 years). In total, 473 deaths (frequency, 13.2%) were identified, including 183 (5.1%) cardiac deaths during follow-up. In an unadjusted Cox proportional hazard analysis, using normal weight as the reference, underweight, but not overweight, was associated with a greater risk of both all-cause and cardiac death. In an adjusted model, Group 1 had the highest risk for all-cause death (hazard ratio, 1.58; 95% confidence interval, 1.19–2.10; p = 0.0019); however, no significant differences were found for the risk of all-cause and cardiac death between normal weight and overweight patients.

Conclusion: The results of the present long-term follow-up study do not support the so-called “obesity paradox,” but rather, suggest that underweight Japanese patients are at greater risk for all-cause mortality following PCI.

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Introduction

Obesity is a metabolic disorder associated with cardiovascular disease and increased morbidity and mortality, and has been shown to be a risk factor for the development of coronary artery disease (CAD) [1–3]. Obesity increases insulin resistance, which can lead to type 2 diabetes mellitus, worsens plasma lipid profiles, and increases arterial blood pressure (BP) [4]. Furthermore, obesity is associated with obstructive sleep apnea and sleep-disordered breathing [5]. Nevertheless, numerous studies over the years have shown the so-called “obesity paradox,” whereby obesity is related to better clinical outcomes [6–8]. This paradox suggests that being overweight as measured by body mass index (BMI) is associated with lower mortality and morbidity from chronic heart failure and
underwent exami ned density into variables.

Methods

Study population and data collection

The present study was a single-center, observational, retrospective cohort study. Among consecutive patients with CAD who underwent first-time PCI at Juntendo University Hospital from 2000 to 2013, we included only those for whom preprocedural BMI values were available. Patients were then divided into the following five groups according to baseline BMI: Group 1 (underweight 1, BMI <20.0 kg/m²); Group 2 (underweight 2, BMI = 20.1–22.5 kg/m²); Group 3 (normal weight, BMI = 22.6–25.0 kg/m²); Group 4 (overweight 1, BMI = 25.1–27.5 kg/m²); and Group 5 (overweight 2, BMI ≥27.6 kg/m²).

Demographic data, coronary risk factors, and medication use at the time of PCI were collected from our institutional database. Blood samples were collected in the early morning after overnight fasting, and BP was measured on admission. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m², as calculated using the Modification of the Diet in Renal Disease study equation modified with a Japanese coefficient using baseline serum creatinine [11]. Patients with BP >140/90 mmHg or who were receiving antihypertensive agents were regarded as hypertensive. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) >140 mg/dL, high-density lipoprotein (HDL-C) <40 mg/dL, triglyceride (TG) ≥150 mg/dL, or receiving treatment with statins and/or lipid-lowering agents. Diabetes mellitus was defined as either hemoglobin A1C ≥6.5% or receiving treatment with insulin or oral hypoglycemic agents. Written informed consent was obtained from all patients prior to PCI. This study proceeded in accordance with the Declaration of Helsinki and with approval from our institutional review board. The ethics application approval number was 17-206.

Study endpoints

The study endpoints were all-cause and cardiac death, including CAD, cardiogenic shock, and sudden death. We classified the cause of death into five groups, cardiac death, stroke, cancer, infectious disease, and others. Clinical follow-up included a review of medical charts, telephone contact, and questionnaires sent to patients or their families. Mortality data were collected from the medical records of patients who died or who had been treated at our institution, and the details and cause of death were requested from other hospitals to which patients had been admitted.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range; IQR). Categorical variables are expressed as a percentage. Patients were divided into five groups based on preprocedural BMI values and then analyzed. Continuous variables were compared using one-way analysis of variance or the Kruskal–Wallis test. Categorical variables (presented as frequencies) were compared using the chi-square test. Unadjusted cumulative event rates were estimated using Kaplan–Meier curves and compared across groups. The association between BMI and all-cause or cardiac death after PCI was determined using multivariate Cox proportional hazard regression analysis. All variables showing values of p < 0.05 in univariate analyses were included in multivariate analyses. The variables showing values of p < 0.05 in univariate analysis were acute coronary syndrome (ACS), age, CKD, diabetes mellitus, multivessel disease, use of drug-eluting stents, and use of statins. BMI values were included in the multivariate model, and hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Values of p < 0.05 were considered to indicate statistical significance. All data were analyzed using JMP version 12.0 for Windows (SAS Institute, Cary, NC, USA).

Results

Baseline and procedural characteristics

Of the 3579 patients who underwent first-time PCI, preprocedural BMI values were available for 3571 (99.8%). For these patients, the median and mean BMI values were 23.9 (IQR: 22.0, 26.2) and 24.2 ± 3.4, respectively. The ratio of patients in the five groups was as follows: Group 1, 9.2%; Group 2, 21.6%; Group 3, 34.1%; Group 4, 21.1%; and Group 5, 14.5%. The clinical and procedural characteristics of the patients, stratified by preprocedural BMI, are shown in Tables 1 and 2. A decrease in age was observed from underweight to overweight, as was an increased prevalence of hypertension, diabetes mellitus, dyslipidemia, and smoking. No significant differences were found in the proportions of patients having a family history of CAD. Meanwhile, patients with lower BMI exhibited a significantly higher incidence of ACS, CKD, and hemodialysis. The number of patients taking renin–angiotensin–aldosterone system (RAAS) inhibitors, β-blockers, and statins increased with increasing BMI, as did baseline levels of LDL-C, TG, hemoglobin A1C, and BP.

Clinical outcomes

The median follow-up period was 6.3 years (IQR, 3.2–9.6 years). In total, 473 deaths (frequency, 13.2%) were identified during follow-up. The cause of death was as follows: cardiac death, 38.7% (183 deaths); stroke, 7.2% (34 deaths); cancer, 32.4% (153 deaths); infectious disease, 8.7% (41 deaths); and others, 13.1% (62 deaths). On cause-specific death, underweight patients (Group 1 and Group 2) had a higher rate of infectious disease than normal-weight and overweight patients (Groups 3, 4, and 5); 6.2% (29 deaths) vs. 2.5% (12 deaths), p < 0.001.

All-cause and cardiac death in patients, stratified by preprocedural BMI, are presented in Figs. 1 and 2. Kaplan–Meier curves revealed that underweight patients had a significantly higher incidence of both all-cause and cardiac death (log-rank test, both p < 0.0001).

Tables 3 and 4 show the results of Cox proportional hazard analysis for all-cause and cardiac death (normal weight, BMI = 22.6–25.0 kg/m², as a reference). In unadjusted Cox modeling, the risk of all-cause and cardiac death progressively elevated with decreasing BMI (both p < 0.001, for trend). However, this relation diminished substantially after adjustment for the other important variables. Interestingly, a J-shaped association was observed between preprocedural BMI and the risk of all-cause death (Fig. 3). In the adjusted model, Group 1 (underweight 1) had the highest risk for all-cause death (HR, 1.58; 95%CI, 1.19–2.10; p = 0.0019). Furthermore, no statistically significant differences were seen in the rate of all-cause or cardiac death between normal and overweight patients (Groups 4 and 5).

Table 4 summarizes the findings of multivariate Cox hazard regression analysis with BMI as the continuous variable. Increasing BMI values were significantly associated with all-cause death (per
kg/m²; HR, 0.94; 95%CI, 0.91–0.97; p < 0.001), but not with cardiac death (per kg/m²; HR, 0.97; 95%CI, 0.92–1.02; p = 0.23).

Discussion

The major findings of the present study are as follows: (1) underweight patients showed a significantly higher incidence of all-cause death than did normal and overweight patients; (2) multivariate analysis showed that preprocedural BMI values were an independent predictor of all-cause death in patients who had undergone PCI; and (3) a J-shaped association was observed between preprocedural BMI and the risk of all-cause death. In other words, our results do not support the “obesity paradox” in Japanese patients undergoing PCI.

Based on the statistics of the Organization for Economic Co-operation and Development (OECD), as of 2014, an average of 28.5% of females and 25.5% of males in Asian countries were overweight (BMI of ≥25.0 kg/m²), compared with 52.6% and 63.6% in Western countries, respectively. However, the prevalence of overweight in Asian countries has increased more rapidly than that in OECD countries [12].

Furthermore, according to the report of The Global BMI Mortality Collaboration, the regional differences in BMI in the general population are large. While the proportion of participants in BMI 30.0 kg/m² or more are 15% in Europe and North America, it is only 2.6% in East Asia. In the population of BMI 35.0 kg/m² or more, it is extremely low as 0.2% in East Asia, compared to 4% in Europe and North America [13].
Fig. 1. Kaplan–Meier curves for all-cause death. Kaplan–Meier curves show significant differences in all-cause death among the BMI categories (log-rank test, $p < 0.0001$). BMI, body mass index.

Fig. 2. Kaplan–Meier curves for cardiac death. Kaplan–Meier curves revealed that underweight patients had a significantly higher incidence of cardiac death (log-rank test, both $p < 0.0001$). BMI, body mass index.

Table 3

<table>
<thead>
<tr>
<th></th>
<th>All-cause death</th>
<th></th>
<th>Cardiac death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
<td>$p$</td>
<td>$p$ for trend</td>
</tr>
<tr>
<td>Unadjusted model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>2.52</td>
<td>1.92–3.29</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.54</td>
<td>1.21–1.95</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group 3</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>0.79</td>
<td>0.59–1.06</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Group 5</td>
<td>0.77</td>
<td>0.55–1.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>1.58</td>
<td>1.19–2.10</td>
<td>0.0019</td>
<td>0.0010</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.29</td>
<td>1.01–1.65</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>0.84</td>
<td>0.63–1.12</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Group 5</td>
<td>1.01</td>
<td>0.71–1.41</td>
<td>0.94</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for variables were acute coronary syndrome, age, chronic kidney disease, diabetes mellitus, multivessel disease, use of drug-eluting stents, and use of statins. HR, hazard ratio; 95% CI, 95% confidence interval.

Group 1: Body mass index $<$20.0; Group 2: 20.1–22.5; Group 3: 22.6–25.0; Group 4: 25.1–27.5; Group 5: $\geq$27.6.
In patients with CAD, the mean value of BMI is higher than in the general population. However, the proportion of participants with CAD in BMI 30.0 kg/m² or more is clearly low as 5–6% in Japanese cohorts [14–16] compared to 17–34% in Western countries [17–22] (Table 5). Mean BMI values are still remarkably lower in East Asian patients with CAD. In a recent Japanese cohort study involving 10,142 patients with CAD, Numasawa et al. reported that the mean BMI value was 24.2 kg/m² [14], while in the CLARIFY registry comprising 22,672 patients from 45 countries, Vidal-Petiot et al. reported that the median BMI value was 27.7 kg/m² [23]. Therefore, it is reasonable to use a lower BMI cut-off point for overweight/obesity in Asian patients.

Zheng et al. reported that the relationship between mortality hazard and BMI showed a U-curve pattern in an East-Asian population including Japanese and Chinese participants [24]. In their study, the BMI ranges of 22.6–25.0 and 25.1–27.5 had the lowest risk for death from any cause. Therefore, we investigated an ideal BMI cut-off value for clinical outcomes in patients with CAD using the range of 22.5–25.0 as normal-weight. The relationship between BMI and mortality hazard showed a J-curve pattern, but not a U-curve pattern or a linear association. This finding was similar to that in a previous report involving Japanese patients who had undergone PCI [16], and could be the result of the differences in the distribution of BMI in patients with CAD, especially overweight patients (BMI of ≥30 kg/m²). In other words, we think that the low rate of extremely obese patients in Asia is one of the main reasons that the typical “obesity paradox” was not observed.

### Table 4
Multivariable Cox proportional hazard model for all-cause and cardiac death.

<table>
<thead>
<tr>
<th></th>
<th>All-cause death</th>
<th>Cardiac death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
</tr>
<tr>
<td>BMI, 1 kg/m² increase</td>
<td>0.94</td>
<td>0.91–0.97</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1.22</td>
<td>0.99–1.49</td>
</tr>
<tr>
<td>Age, 1 year increase</td>
<td>1.06</td>
<td>1.05–1.07</td>
</tr>
<tr>
<td>CKD</td>
<td>1.84</td>
<td>1.52–2.23</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.10</td>
<td>1.08–1.56</td>
</tr>
<tr>
<td>Drug-eluting stents</td>
<td>0.38</td>
<td>0.30–0.48</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.34</td>
<td>1.11–1.63</td>
</tr>
<tr>
<td>Statins</td>
<td>0.74</td>
<td>0.62–0.90</td>
</tr>
</tbody>
</table>

BMI, body mass index; CKD, chronic kidney disease; 95%CI, 95% confidence interval; HR, hazard ratio.

### Table 5
Previous clinical trials of coronary artery disease and BMI.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Year</th>
<th>Country/region</th>
<th>Patient profile</th>
<th>Number of patients</th>
<th>Rate of obese patients, (BMI ≥ 30 kg/m²) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numasawa et al. [14]</td>
<td>2015</td>
<td>Japan</td>
<td>CAD post PCI</td>
<td>10,142</td>
<td>6.2</td>
</tr>
<tr>
<td>Hioki et al. [15]</td>
<td>2015</td>
<td>Japan</td>
<td>CAD post PCI</td>
<td>1857</td>
<td>4.9</td>
</tr>
<tr>
<td>Kaneko et al. [16]</td>
<td>2013</td>
<td>Japan</td>
<td>CAD post PCI</td>
<td>1205</td>
<td>4.6</td>
</tr>
<tr>
<td>Herrmann et al. [17]</td>
<td>2014</td>
<td>USA</td>
<td>AMI</td>
<td>3579</td>
<td>24.9</td>
</tr>
<tr>
<td>McAuley et al. [18]</td>
<td>2012</td>
<td>USA</td>
<td>CAD</td>
<td>9563</td>
<td>17.0</td>
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<tr>
<td>Akin et al. [19]</td>
<td>2012</td>
<td>Germany</td>
<td>CAD post PCI</td>
<td>5806</td>
<td>26.4</td>
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<tr>
<td>Sarno et al. [20]</td>
<td>2011</td>
<td>Switzerland and the Netherlands</td>
<td>CAD post PCI</td>
<td>7427</td>
<td>22.4</td>
</tr>
<tr>
<td>Sarno et al. [21]</td>
<td>2010</td>
<td>European multicenter</td>
<td>CAD post PCI</td>
<td>1701</td>
<td>20.2</td>
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<tr>
<td>Steinberg et al. [22]</td>
<td>2007</td>
<td>USA</td>
<td>CAD</td>
<td>130,139</td>
<td>34.0</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; BMI, body mass index; CAD, coronary artery disease; PCI, percutaneous coronary intervention.
Elevated risk among underweight patients has been reported by many other cohort studies [15,25]. Phung et al. reported that a J-shaped relationship between BMI and risk of community-acquired pneumonia was observed [26]. In our study, underweight patients had a higher risk of mortality, especially from infectious disease, than normal and overweight patients. There could be several explanations for this association, namely, that lean mass acts as a nutritional disorder, and is less resistant to infection, respiratory failure, and preexisting disease linked to risk of death and sarcopenia because of physical inactivity [27,28]. Moreover, Affilalo et al. reported that the prevalence of frailty was strongly associated with mortality and morbidity in patients with cardiovascular disease [29]. The enrolled patients in our study as well as in general theory may have been carefully treated and followed up at the cardiovascular department of the hospital after PCI. The risk of cardiac death in patients with all BMI categories might be reduced by the long-term careful management by cardiologists, thereby diminishing the influence of low BMI on cardiac death.

In addition, our data showed that decreased BMI was associated with less use of guideline-recommended medical therapies on admission. Aspirin, RAAS inhibitors, β-blockers, and statins were prescribed less frequently for underweight patients. Although statins are the most promising agents for the treatment of CAD [30–32], lipid-lowering therapy remains controversial for lean, elderly, and low LDL-C patients. The Cholesterol Treatment Trialists’ Collaboration reported finding no evidence that lowering LDL-C using statins increased the risk of developing cancer [33]. Furthermore, in another recent study, aggressive lipid-lowering therapy using monoclonal antibodies inhibiting proprotein convertase subtilisin-kexin type 9 did not increase the risk of adverse events [34]. Only 45.2% of the underweight patients in the present study received statins after PCI. Regardless of whether physicians add statin therapy after PCI, LDL-C levels <70 mg/dL need to be achieved, particularly in regard to secondary prevention.

Study limitations

This study did have several limitations. First, only cross-sectional data were used for analysis. Changes in BMI values, especially decreasing body weight, might have influenced poor prognoses. Second, because of the small number of obese/extreme obese patients in the present study, the statistical power might not be strong enough for assessing the risk of clinical events. Further longitudinal studies with larger populations are therefore needed.

Conclusion

Our long-term follow-up study showed that being underweight is a significant risk factor for all-cause mortality in Japanese CAD patients following PCI. In addition, a J-shaped association was observed between preprocedural BMI values and the risk of all-cause death. Stratified by age, sex, race, and important clinical comorbidities, an individual BMI cut-off value for the prediction of adverse events might be necessary.

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Disclosures

The authors declare that there is no conflict of interest.

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