Overweight or obesity are increasing in epidemic prevalence throughout the world. Among the general population, it is well established that overweight or obese people with a high body mass index (BMI; weight in kilograms divided by the square of the height in meters) have a higher risk of cardiovascular disease and death from heart disease or stroke. Despite known adverse effects of overweight or obesity as risk factor for coronary artery disease (CAD) and cardiovascular mortality, once CAD has been established, the close relation of obesity with total or cardiovascular mortality and cardiovascular events is unclear. Moreover, several studies have suggested that overweight or obese groups seem to have a better prognosis compared with normal or lower BMI groups in patients with established CAD and heart failure, a phenomenon termed as the obesity paradox.

BMI is associated with atherosclerotic burden of CAD, plaque vulnerability, and adjunct drug responses affecting clinical outcomes, especially among patients with documented CAD undergoing percutaneous coronary intervention (PCI). However, conflicting data exist regarding the relation between BMI and the risks of cardiovascular events and mortality after PCI. Pooled analyses provide the opportunity to address these issues carefully in a large dataset with the use of a standard analytic approach across studies, providing a reliable estimate of the link between BMI and clinical outcomes. We examined, therefore, the relation between BMI and risks of major cardiovascular events and death. However, there were no excess risks of these events associated with a high BMI.

Methods

Study Population and Procedures

For the present analysis, databases from 11 independent, prospective clinical studies (8 randomized clinical trials and 3 registries) were pooled to provide a patient-level data analysis. All studies were conducted in South Korea and performed in Asian population. The study designs and results of individual studies have been published previously. Among all studies included, the baseline BMI was calculated with the use of weight and height measured at enrollment and data on adverse cardiovascular events and mortality were prospectively collected. These studies contain information on

Original Article

Association of Body Mass Index With Major Cardiovascular Events and With Mortality After Percutaneous Coronary Intervention

Duk-Woo Park, MD; Young-Hak Kim, MD; Sung-Cheol Yun, PhD; Jung-Min Ahn, MD; Jong-Young Lee, MD; Won-Jang Kim, MD; Soo-Jin Kang, MD; Seung-Whan Lee, MD; Cheol Whan Lee, MD; Seong-Wook Park, MD; Seung-Jung Park, MD

Background—Conflicting data exist regarding the relation between body mass index (BMI) and cardiovascular events and mortality after percutaneous coronary intervention.

Methods and Results—We performed pooled analyses to evaluate the association between BMI (weight in kilograms divided by the square of the height in meters) and the risks of major cardiovascular events (defined as death from cardiovascular causes, nonfatal myocardial infarction, stent thrombosis, or stroke) and death among 23,181 patients from 11 prospective percutaneous coronary intervention studies. Overall, mean (±SD) BMI was 24.9±3.0. During follow-up (median, 2.1 years), 2381 patients had a major cardiovascular event, and 1004 patients died. After adjusting covariates, there was an inverse relationship between BMI and adverse outcomes. With a BMI of 22.5 to 24.9 as the reference category, the risk of major cardiovascular events was elevated among patients with a lower BMI (by a factor of 1.52 for a BMI <18.5; 1.05 for a BMI of 18.5–19.9; 1.03 for a BMI of 20.0–22.4); by contrast, the risk declined among patients with a higher BMI (by a factor of 0.97 for a BMI of 25.0–27.4; 0.97 for a BMI of 27.5–29.9; and 0.78 for a BMI of ≥30.0). In general, the hazard ratios for deaths were similar.

Conclusions—Among patients undergoing percutaneous coronary intervention, a low BMI was associated with increased risks of major cardiovascular events and death. However, there were no excess risks of these events associated with a high BMI.

Key Words: body mass index outcomes percutaneous coronary intervention

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WHAT IS KNOWN

• A high body mass index is associated with a higher risk of cardiovascular disease and mortality.

• Once coronary artery disease has been established, the obesity paradox has been reported with overweight or obese patients having a better prognosis compared with normal or lower body mass index groups.

• The relationship between body mass index and adverse cardiovascular events after percutaneous coronary intervention is unknown.

WHAT THE STUDY ADDS

• This study supports the inverse relationship of body mass index with major cardiovascular events and all-cause mortality after percutaneous coronary intervention.

• The mechanism for the obesity paradox is not clear and further studies are needed.
Table 1. Major Baseline Characteristics of Each Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>ZEST&lt;sup&gt;17&lt;/sup&gt;</th>
<th>ZEST-AMI&lt;sup&gt;18&lt;/sup&gt;</th>
<th>LONG-DES&lt;sup&gt;II&lt;/sup&gt;</th>
<th>LONG-DES&lt;sup&gt;III&lt;/sup&gt;</th>
<th>ESSENCE-Diabetes&lt;sup&gt;22&lt;/sup&gt;</th>
<th>DECLARE-LONG&lt;sup&gt;II&lt;/sup&gt;</th>
<th>REAL-LATE&lt;sup&gt;30&lt;/sup&gt;</th>
<th>ASAN-PCI&lt;sup&gt;25&lt;/sup&gt;</th>
<th>ASAN-VERIFY&lt;sup&gt;36&lt;/sup&gt;</th>
<th>IRIS-DES&lt;sup&gt;17&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>23604</td>
<td>2645</td>
<td>328</td>
<td>500</td>
<td>450</td>
<td>500</td>
<td>300</td>
<td>499</td>
<td>1625</td>
<td>7221</td>
<td>3370</td>
</tr>
<tr>
<td>Age, y</td>
<td>62 (10)</td>
<td>62 (10)</td>
<td>60 (11)</td>
<td>61 (9)</td>
<td>63 (10)</td>
<td>63 (10)</td>
<td>63 (8)</td>
<td>62 (9)</td>
<td>63 (10)</td>
<td>60 (10)</td>
<td>62 (10)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 (3)</td>
<td>25 (3)</td>
<td>24 (3)</td>
<td>25 (3)</td>
<td>25 (3)</td>
<td>25 (3)</td>
<td>25 (3)</td>
<td>25 (3)</td>
<td>25 (3)</td>
<td>25 (3)</td>
<td>25 (3)</td>
</tr>
<tr>
<td>Men</td>
<td>16424 (70)</td>
<td>1759 (67)</td>
<td>270 (82)</td>
<td>321 (64)</td>
<td>314 (70)</td>
<td>365 (73)</td>
<td>177 (59)</td>
<td>353 (71)</td>
<td>1156 (71)</td>
<td>5132 (71)</td>
<td>2446 (73)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6995 (30)</td>
<td>760 (29)</td>
<td>85 (26)</td>
<td>166 (33)</td>
<td>133 (30)</td>
<td>144 (23)</td>
<td>300 (100)</td>
<td>176 (35)</td>
<td>426 (26)</td>
<td>1700 (24)</td>
<td>956 (28)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13101 (56)</td>
<td>1609 (61)</td>
<td>153 (47)</td>
<td>275 (55)</td>
<td>265 (59)</td>
<td>285 (57)</td>
<td>212 (71)</td>
<td>307 (62)</td>
<td>917 (56)</td>
<td>3273 (45)</td>
<td>1958 (58)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9752 (41)</td>
<td>1363 (52)</td>
<td>148 (45)</td>
<td>146 (29)</td>
<td>255 (57)</td>
<td>277 (55)</td>
<td>115 (38)</td>
<td>218 (44)</td>
<td>609 (38)</td>
<td>2228 (31)</td>
<td>1996 (59)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>2249 (10)</td>
<td>110 (4)</td>
<td>5 (2)</td>
<td>12 (2)</td>
<td>17 (4)</td>
<td>8 (2)</td>
<td>5 (2)</td>
<td>18 (4)</td>
<td>63 (4)</td>
<td>1426 (20)</td>
<td>201 (6)</td>
</tr>
<tr>
<td>ACS</td>
<td>13656 (58)</td>
<td>1463 (55)</td>
<td>328 (100)</td>
<td>273 (55)</td>
<td>190 (42)</td>
<td>180 (36)</td>
<td>125 (42)</td>
<td>263 (53)</td>
<td>1102 (68)</td>
<td>4579 (64)</td>
<td>1616 (48)</td>
</tr>
<tr>
<td>Follow-up (median, month)</td>
<td>25</td>
<td>25</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>39</td>
<td>59</td>
<td>25</td>
</tr>
</tbody>
</table>

Data are shown as mean (SD) for continuous variables and absolute number (percentage) for dichotomous variables, unless otherwise stated. ACS indicates acute coronary syndrome; ASAN-PCI, Asan Medical Center-Percutaneous Coronary Intervention Registry; ASAN-VERIFY, Asan Medical Center-VerifyNow Registry; BMI, body mass index; DECLARE-LONG, Drug-Eluting Stenting Followed by Clopidogrel Treatment Reduces Late Restenosis in Patients with Long Coronary Lesions; ESSENCE-DM, Randomized Comparison of Everolimus-Eluting Stent Versus Sirolimus-Eluting Stent Implantation for De Novo Coronary Artery Disease in Patients With Diabetes Mellitus; IRIS-DES, Interventional Cardiology Research In-cooperation Society-Drug-Eluting Stents Registry; LONG-DES, Percutaneous Treatment of Long Native Coronary Lesions With Drug-Eluting Stent; MI, myocardial infarction; REAL-LATE, Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated With Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events; ZEST, Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent with Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Lesions; and ZEST-AMI, Comparison of the efficacy and safety of zotarolimus-, sirolimus-, and paclitaxel-eluting stents in patients with ST-elevation myocardial infarction.
Association Between BMI and the Risks of Major Cardiovascular Events and Mortality

The median follow-up was 2.1 years (25th and 75th percentiles; 1.2 and 3.9 years). During follow-up, a total of 2381 major cardiovascular events (392 cardiovascular deaths, 1954 MI, 181 stent thrombosis, and 167 strokes) were reported and 1004 total deaths occurred. Cumulative incidence curves of major cardiovascular events and all-cause mortality are presented in Figure 1. Overall, the rates of major cardiovascular events and mortality have significantly increased with decreasing BMI categories. The cumulative incidence of major cardiovascular events over time showed an initial steep rise, followed by a continuous separation of the curves, with a significantly higher rate of events in a low-BMI group. The incidence of mortality did continuously diverge over time, with a higher rate in a low-BMI group and a lower rate in a high-BMI group.

In unadjusted Cox regression analysis, as compared with the reference range of 22.5 to 24.9, the hazard ratios for the risk of major cardiovascular event increased with progressively lower levels of BMI, whereas the hazard ratios decreased with progressively higher levels of BMI (Table 3). A similar association was also seen between BMI and the risk of all-cause mortality.

To determine the independent association between BMI and clinical outcomes, we performed a multivariable Cox regression analysis after adjusting for a wide range of confounding factors.
Factors. Even after multivariable adjustment, the inverse relationship of BMI with major cardiovascular events and with all-cause mortality were maintained (Table 4 and Figure 2). As compared with the reference of 22.5 to 24.9, the risks of major cardiovascular events were higher among patients with a lower BMI (by a factor of 1.52 for a BMI <18.5; 1.05 for a BMI of 18.5–19.9; 1.03 for a BMI of 20.0–22.4), but the risks of these events were lower among patients with a higher BMI (by a factor of 0.97 for a BMI of 25.0–27.4; 0.97 for a BMI of 27.5–29.9; and 0.78 for a BMI of ≥30.0). The adjusted hazard ratios for all-cause mortality were also similar.

In sensitivity analyses excluding events at <7 days, overall findings suggesting the inverse relationship of BMI with major cardiovascular events and all-cause mortality were consistent (Table 5).

Discussion

This is the largest study to evaluate systematically the relationship of BMI with major cardiovascular events and total mortality after PCI using individual patient-level data from several prospective PCI clinical studies. As a result, the study shows that after adjusting for potential confounding factors, a low BMI is significantly associated with increased risks of major cardiovascular events and all-cause mortality. The excess risks for these outcomes associated with a high BMI, however, were not observed.

Obesity involves hyperinsulinemia and insulin resistance, enhances free fatty acid turnover, increases sympathetic tone activity, induces platelet and clotting system activation, and causes chronic low-grade inflammation, all of which increase the risks for developing CAD and adverse cardiovascular events. And also, a greater BMI was significantly associated with poorer response of clopidogrel and aspirin, which are mandatory adjunct drugs for PCI. Contrary to these pathophysiology mechanisms induced by obesity, several studies suggested that overweight or obese patients have better PCI outcomes than do normal or leaner patients, supporting protective effect of obesity, known as the obesity paradox.11–14 These studies were, however, hampered by limited

Table 3. Crude Association Between Body Mass Index and Risk of Major Cardiovascular Events and All-Cause Mortality*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Body Mass Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>No. of patients</td>
<td>339</td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td></td>
</tr>
<tr>
<td>Total number of events</td>
<td>60</td>
</tr>
<tr>
<td>Cumulative rate at 2 y†</td>
<td>17.1</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.82 (1.38–2.39)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
</tr>
<tr>
<td>Total number of events</td>
<td>43</td>
</tr>
<tr>
<td>Cumulative rate at 2 y†</td>
<td>11.1</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>3.70 (3.30–4.14)</td>
</tr>
</tbody>
</table>

Major cardiovascular events were defined as a composite of cardiovascular death, nonfatal myocardial infarction, stent thrombosis, or stroke. CI indicates confidence interval.

The hazard ratios represent the effect per category of body mass index relative to the reference category (22.5–24.9).

Cumulative event rates are derived from Kaplan–Meier estimates.

Figure 1. Kaplan–Meier curves of the cumulative probability of major cardiovascular events and death according to body mass index categories. Major cardiovascular event was defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, stent thrombosis, or stroke. P values were calculated with the use of the log-rank test.
number of patients, a relatively short follow-up period, or a retrospective observational study design. A recent large-sized meta-analysis, including >250,000 patients with documented CAD, showed that a low-BMI group had the highest all-cause and cardiovascular mortality, whereas better survival was observed in higher BMI groups. Especially, these trends were mostly prominent in patients who received PCI than in those who underwent coronary artery bypass grafting or had a history of MI. Consistent with these findings, our patient-level pooled analysis of PCI patients also showed that there was an inverse relationship between BMI and mortality after PCI. Apart from the association between BMI and total mortality, an inverse relationship of BMI with major cardiovascular events, which are more specific measure of PCI outcomes, was also demonstrated.

Our study does not fully clarify the exact mechanism of an absence of association or an inverse association of BMI and clinical outcomes after PCI. However, there could be some possible explanations for this phenomenon. First, the discriminatory ability of BMI is relatively limited to make a clear distinction between body fat, which have negative impact on prognosis, and lean body mass, which is associated with better prognosis in patients with cardiovascular disease. Therefore, a high BMI does not solely imply excess body adiposity, and may reflect a preserved or increased lean body mass. It would be a plausible explanation of the better outcomes in overweight or obese patients. Second, higher BMI groups were associated with a higher prevalence of coexisting cardiovascular conditions, such as diabetes mellitus, hypertension, hyperlipidemia, and history of MI and PCI. Therefore, there is the possibility that patients with a high BMI were on more aggressive secondary preventive drug therapies rather than those with a normal or low BMI. Previous study demonstrated that overweight or obese patients were more likely to be adherent to guideline-recommended medical treatment. Third, although our analysis excluded patients with terminal illness or cancer to minimize the influence of possible reverse causation, other unmeasured factors that influence a low BMI, presumably, remain to be identified. Lastly, further studies are warranted to address the novel suggested mechanisms; a higher BMI is related to larger vessels treated with larger stent diameter or to the cardio-protective effect of adipokines.

The current analysis includes a large number of patients specifically treated with PCI in which contemporary devices and techniques were used. From the clinical standpoint, an important issue that deserves comment is that most devices used in PCI have been manufactured targeting patients with the average BMI. Although exact mechanism linking low BMI
with poorer PCI outcomes is still unclear, future studies are needed to determine whether patients with extreme small BMI may specifically need tailored PCI devices or not.

Potential limitations of the current study warrant discussion. First, the database merged several clinical studies and interstudy variability may exist that could have influenced results in the pooled patient population. Second, although we adjusted possible confounding factors, unmeasured confounders associated with BMI still exist. Third, we did not capture the measurements of body composition or body fat distribution (ie, waist circumference or waist-to-hip ratio regarding central obesity), which are suggested to be more closely related with adiposity-related outcomes. Fourth, as this analysis was performed in Asian population, it is uncertain whether this finding can be directly applied to other ethnic groups. Compared with Western population, the proportion of severe or extreme obese patients was too small in our population; 0.3% (59) patients with class II obese (BMI ≥35 kg/m² ≤ BMI <40 kg/m²) and 0.02% (4) patients with class III obese (BMI ≥40 kg/m²). In addition, it has been suggested that the relationship between BMI and mortality may differ across racial and ethnic groups. Fifth, we did not perform serial measurements of BMI during follow-up. There has been report suggesting a relation between weight change and cardiovascular events. Finally, longer term follow-up are needed to evaluate very long-term effect of BMI on outcomes after PCI.

Conclusions

In this large, pooled population of CAD patients receiving PCI in contemporary practice, patients with a low BMI had a higher risk of major cardiovascular events and death than patients with a normal BMI. However, no elevated risk of major cardiovascular events and mortality were seen in high-BMI groups. Before presumably drawing a conclusion that obesity is protective or harmless for cardiovascular risk among patients receiving PCI, more reliable surrogate markers differentiating excess body fat and muscle mass are needed for future risk stratification in such population, and additional clinical studies are needed to test different methods reflecting adiposity.

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Disclosures

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18. patients with ST-Segment elevation myocardial infarction.


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