ORIGINAL RESEARCH

# Relationship Between Body Mass Index, Antidiabetic Agents, and Midterm Mortality in Patients With Both Type 2 Diabetes Mellitus and Acute Coronary Syndrome

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***Background*—**The aim of this study was to determine the influence of various antidiabetic therapies on the relationship between body mass index and all-cause mortality in patients with diabetes mellitus and acute coronary syndrome.

***Methods and Results*—**This was a prospective, observational study comprising 1193 patients diagnosed with type 2 diabetes mellitus and acute coronary syndrome. The patients were stratified into 4 body mass index categories, and their mortality rates were compared using time-dependent Cox regression analysis using normal weight (body mass index, 18.5–23.9) as the reference. Subsequently, the influence of antidiabetic therapies on the association between BMI and mortality were analyzed. Seventy-four patients (6.2%) died over 2 years of follow-up. The mortality rate was lowest in the class I obese group (3.35%) and highest in the normal-weight group (9.67%). After adjusting for covariates, class I obesity paradoxically remained significantly protective against mortality compared with normal weight (hazard ratio, 0.141; $P$=0.049); interaction term analysis showed that insulin therapy influenced this "obesity paradox" ($P$=0.045). When the patients were stratified by insulin use, the protective effect of obesity disappeared in the insulin-treated patients but persisted in the non–insulin-treated patients.

***Conclusions*—**In patients with type 2 diabetes mellitus and acute coronary syndrome, the relationship between body mass index and mortality rate is U-shaped, with class I obesity representing the nadir and normal weight the peak. The protective effect of obesity disappeared in patients treated with insulin. **(*J Am Heart Assoc*. 2019;8:e011215. DOI: 10.1161/JAHA.118.011215.)**

**Key Words:** acute coronary syndrome • insulin • mortality • obesity paradox • type 2 diabetes mellitus

Both diabetes mellitus and overweight are established risk factors for all-cause and cardiovascular-specific mortality. Overweight is closely associated with the development and outcome of type 2 diabetes mellitus, and weight control is therefore recommended as a treatment guideline for this disease. Furthermore, any weight gain associated with antidiabetic therapy is considered an undesired side effect.[1] Nevertheless, the relationship between BMI and mortality among patients with type 2 diabetes mellitus remains unclear,[2,3] and obesity is not associated with worse outcomes

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## Clinical Perspective

### What Is New?

- Obesity paradox does exist in patients with type 2 diabetes mellitus and acute coronary syndrome, but the survival benefit of obesity was absent in those receiving insulin therapy.
- Our findings imply that this paradox phenomenon persisted not only in the high-risk condition but was also modified by antidiabetic therapies.

### What Are the Clinical Implications?

- This study highlighted the safety issue of insulin therapy in obese patients during acute coronary syndrome.
- Further randomized control studies are warranted to evaluate both safety and efficacy of insulin therapy in acute coronary syndrome.

in all populations. In some patients, such as those with heart failure,[4] stable coronary artery disease,[5] and acute coronary syndrome (ACS),[6] obesity is associated with lower mortality than normal weight, a phenomenon referred to as the "obesity paradox."[5]

ACS is among the most important causes of mortality in patients with diabetes mellitus, and weight maintenance or reduction is encouraged by the secondary prevention guidelines for coronary artery diseases.[7] However, this recommendation is not based on direct evidence, especially in patients with ACS. Currently, only a few studies have examined the association between BMI and mortality after ACS manifestation in subjects with type 2 diabetes mellitus.[8,9] Antidiabetic medications can be a confounding factor when investigating body weight and mortality, as they have varying impacts on body weight as well as on cardiovascular events and mortality rates.[10] However, previous studies of the obesity paradox did not sufficiently adjust for administered antidiabetic therapies. Therefore, it is important to stratify data by the antidiabetic therapies administered to patients when investigating the association between overweight and death in patients with diabetes mellitus and ACS.

To address the limitations of previous studies, we conducted a detailed analysis of the association between BMI and risk of death among patients with diabetes mellitus and ACS via a nationwide prospective observational study. We also aimed to evaluate the influences of different antidiabetic agents.

## Methods

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Taiwan society of Cardiology at tsoc@tsoc.org.tw.

### Study Design

The ACS-DM (Acute Coronary Syndrome–Diabetes Mellitus) Registry of the Taiwan Society of Cardiology (TSOC) is based on a prospective, nationwide, multicenter, observational study initiated by the Scientific Committee of the TSOC. This registry collects data pertaining to the population of patients with diabetes mellitus who have ST-segment elevation myocardial infarction, non–ST-segment–elevation myocardial infarction (NSTEMI), and unstable angina from 27 participating centers nationwide. Site selection for the registry was decided by the Scientific Committee of the TSOC to ensure good quality and representation of the population with diabetes mellitus and ACS. Patients are treated according to international or local guidelines and evidence-based strategies. The protocol and consent forms were consistent with the Declaration of Helsinki and all relevant regulations. The ethics committees of each participating hospital approved the study, and all enrolled patients provided written informed consent.

### Data Collection

Patients' demographic data, clinical characteristics, biochemistry data, in-patient therapies, coronary lesion morphology, transthoracic echocardiography results, and in-hospital outcomes (including mortality, recurrent nonfatal myocardial infarction, and nonfatal stroke) were collected by trained study coordinators at the study sites. After hospital discharge, information from the first clinical follow-up visit as well as from 6-month, 1-year, and 2-year visits were acquired by telephone contact or review of the medical records. Medications at admission, during hospital stay, at discharge, and during regular follow-up were also collected retrospectively and prospectively. All data were then submitted electronically to a central laboratory for verification. To establish a complete lipid profile, we used the Friedewald formula to estimate low-density lipoprotein cholesterol levels if they had not been directly measured. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of $<60$ mL/min per 1.73 $m^2$ calculated using the modification of diet in renal disease formula.

### Study Population

This study was based on the 1535 subjects enrolled in the TSOC ACS-DM registry between November 1, 2013, and September 30, 2016, who were diagnosed with ACS and type 2 diabetes mellitus according to current international guidelines. Briefly, patients who were 20 years of age or older and diagnosed with ACS were enrolled. The registry enrolls patients only once; that is, at the first ACS event, while subsequent ACS episodes are recorded as adverse events.

The diagnosis of type 2 diabetes mellitus was based on the World Health Organization and American Diabetes Association criteria: hemoglobin $A_{1c}$ level of 6.5% or higher, or fasting plasma glucose concentration of 7.0 mmol/L (126 mg/dL) or higher, or 2-hour post-glucose load venous plasma glucose of 11.1 mmol/L (200 mg/dL) or higher, confirmed on 2 occasions. The exclusion of type 1 diabetes mellitus was based on the clinical distinction of respective attending physicians, such as risk type 2 diabetes mellitus, young age of onset, and history of insulin-dependent glycemic control. The patients were followed until January 18, 2017. We excluded 145 subjects who had missing BMI data, as well as 154 subjects with malignancy, advanced CKD (estimated glomerular filtration rate <30 mL/min per 1.73 $m^2$), or end-stage renal disease who received regular hemodialysis or peritoneal dialysis. Furthermore, 15 subjects who were underweight (BMI <18.5 $kg/m^2$) were excluded because they comprised only 1.2% of the cohort; excluding these patients helped avoid the potential skewing of the BMI/mortality data by patients with cachexia and occult malignancy. Finally, 28 subjects with unavailable data on mortality were also excluded. Ultimately, the final data set included 1193 subjects.

## Exposure and Outcome Variables

BMI was calculated as weight (kg)/height ($m^2$), which were either measured or self-reported at admission. The patients were divided into 5 different BMI categories according to the definitions proposed by the Department of Health in Taiwan: <18.5 $kg/m^2$ (underweight), 18.5 to 23.9 $kg/m^2$ (normal weight), 24 to 26.9 $kg/m^2$ (overweight), 27 to 29.9 $kg/m^2$ (class I obese), and >30 $kg/m^2$ (class II/III obese).[11] The primary outcome was the cumulative incidence of all-cause mortality as related to the BMI categories within the study period. The beginning of the follow-up period was the date of index admission, while the end was the date of death or the end of the study, whichever occurred first. The predetermined confounding factors including BMI, age, sex, CKD, left ventricular ejection fraction <40%, left main disease, ACS subtype, percutaneous coronary intervention treatment, coronary artery bypass grafting treatment, hemoglobin $A_{1c}$, discharge medications (including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, dual-antiplatelet medications, or statins), and current cigarette smoking status. These variables were selected based on traditional risk factors, established clinical factors for mortality after ACS, evidence-based medication, management that influences mortality after ACS, and the control status of hyperglycemia during ACS. Moreover, we evaluated the effects of various antidiabetic agents on the association between BMI and all-cause mortality. These antidiabetic agents were classified as (1) insulin sensitizers (including metformin and pioglitazone), (2) insulin secretagogues (including sulfonylurea and meglitinides), (3) inhibitors of dipeptidyl peptidase-4 enzyme, and (4) insulin. Medication information was obtained from the prescriptions upon discharge following the index admission.

## Statistical Analysis

Categorical variables were expressed as percentages and continuous variables as mean values with SDs. The differences in the categorical variables among the 4 BMI groups were examined using the chi-square or Fisher's exact test, while differences in continuous variables were tested by 1-way ANOVA. The survival curves of the 4 analyzed BMI groups (underweight patients were excluded) were generated using the Kaplan–Meier method and were compared using the log-rank test. Cox proportional-hazard regression analyses were performed to identify the association between BMI categories and all-cause mortality. Variables entered into the univariate analysis were elected focusing on clinical factors, severity factors, procedural factors, and medication factors. Because the proportional hazard assumption was not valid for BMI categories by graphical method, a time-dependent Cox model was used instead. Variables with $P<0.2$ in the univariate analysis and relevant factors related to mortality after ACS, including CKD, hemoglobin $A_{1c}$, and beta-blocker, were entered into the multivariable Cox model. The residual patterns of final model were examined across the covariates. We further conducted propensity score–adjusted analysis to examine the robustness of our results. The interactions of antidiabetic agents, age, smoking, and CKD on the relationship between BMI and mortality were assessed by introducing cross-product interaction terms as independent variables (ie, antidiabetic agents×BMI categories) in the Cox regression model separately. As we found the association between obesity and mortality was modified by insulin therapy, we divided the study cohort into the insulin and noninsulin groups. Time-dependent Cox proportional hazard regression analysis was performed for each of these 2 groups with the same prespecified covariates described above. All analyses were performed using SAS statistical software (SAS System for Windows, version 9.4; SAS Institute, Cary, NC). All *P* values reported are 2-sided, and the significance level was set at <0.05.

## Results

The baseline characteristics of our cohort are shown in Table 1. Overall, the mean age was 64.1±11.9 years, and 74% of the patients were male. The mean hemoglobin $A_{1c}$ level was 8.2±1.9% (66 mmol/mol), and the mean follow-up duration was 556 days. The proportions of patients in the 4 BMI categories were as follows: normal weight, 30.3%; overweight, 30.5%; class I obese, 22.6%; and class II/III

**Table 1.** Baseline Characteristics, Revascularization Strategy, and Medications at Discharge of All Subjects Stratified by BMI Groups

| Variables | BMI Group | | | | | *P* Value |
|---|---|---|---|---|---|---|
| | All (n=1193) | 18.5–23.9 (n=374) | 24–26.9 (n=372) | 27–29.9 (n=272) | ≥30 (n=203) | |
| Age, y | 64.1±12 | 68±11 | 65±11 | 62±12 | 59±12 | <0.001 |
| <65, n (%) | 632 (53) | 150 (41) | 188 (52) | 158 (59) | 136 (69) | <0.001 |
| 65–75, n (%) | 324 (27) | 109 (30) | 107 (29) | 67 (25) | 41 (21) | |
| >75, n (%) | 237 (20) | 103 (29) | 69 (19) | 44 (16) | 21 (11) | |
| Male, n (%) | 881 (73.9) | 250 (69.1) | 280 (76.9) | 204 (75.8) | 147 (74.2) | 0.084 |
| Risk factors and previous medical history, n (%) | | | | | | |
| Hypertension | 913 (76.5) | 261 (72.1) | 274 (75.2) | 217 (80.7) | 161 (81.3) | 0.025 |
| Dyslipidemia | 603 (50.5) | 146 (40.3) | 193 (53.0) | 141 (52.4) | 123 (62.1) | <0.001 |
| Smoking status | | | | | | |
| Current | 402 (33.7) | 106 (29.3) | 122 (33.5) | 101 (37.6) | 73 (36.9) | 0.120 |
| Unknown/former | 791 (66.3) | 256 (70.7) | 242 (66.5) | 168 (62.5) | 125 (63.1) | |
| Myocardial infarction | 182 (15.3) | 45 (12.4) | 48 (13.2) | 58 (21.6) | 31 (15.7) | 0.008 |
| Stroke | 124 (10.4) | 32 (8.8) | 46 (12.6) | 25 (9.3) | 21 (10.6) | 0.353 |
| CKD | 412 (34.5) | 105 (29.0) | 134 (36.8) | 103 (38.3) | 70 (35.4) | 0.058 |
| Biochemical data | | | | | | |
| eGFR, mL/min per 1.73 $m^2$ | 63.2±36.4 | 63.4±39.6 | 64.2±36.1 | 62.5±33.0 | 62.0±35.7 | 0.891 |
| Peak CK-MB, ng/mL | 81.3±115.1 | 76.5±98.0 | 77.7±113.0 | 91.6±138.6 | 82.7±112.4 | 0.446 |
| LDL, mg/dL | 103±40 | 102±40 | 103±41 | 105±39 | 104±37 | 0.803 |
| Hemoglobin $A_{1c}$, % | 8.2±1.9 | 8.1±1.9 | 8.1±1.8 | 8.4±1.9 | 8.5±2.0 | 0.079 |
| Hemoglobin $A_{1c}$, mmol/mol | 66 | 65 | 65 | 68 | 69 | |
| ACS subtype at presentation, n (%) | | | | | | |
| Unstable angina | 283 (23.8) | 66 (18.3) | 96 (26.5) | 73 (27.1) | 48 (24.2) | 0.127 |
| Non-ST elevation MI | 365 (30.7) | 119 (33.0) | 111 (30.7) | 74 (27.5) | 61 (30.8) | |
| ST elevation MI | 542 (45.6) | 176 (48.8) | 155 (42.8) | 122 (45.4) | 89 (45.0) | |
| Severity of disease, n (%) | | | | | | |
| LVEF <40% | 145 (12.2) | 56 (15.5) | 42 (11.5) | 28 (10.4) | 19 (9.6) | 0.120 |
| IABP/inotropes therapies | 267 (22.4) | 85 (23.5) | 84 (23.1) | 57 (21.2) | 41 (20.7) | 0.827 |
| Left main disease | 92 (7.7) | 37 (10.2) | 30 (8.2) | 17 (6.3) | 8 (4.0) | 0.050 |
| Multiple-vessel disease | 698 (58.5) | 215 (59.4) | 203 (55.8) | 163 (60.6) | 117 (59.1) | 0.626 |
| Revascularization therapy, n (%) | | | | | | |
| PCI | 964 (80.8) | 289 (79.8) | 300 (82.4) | 215 (79.9) | 160 (80.8) | 0.810 |
| CABG | 50 (4.2) | 21 (5.8) | 14 (3.9) | 9 (3.4) | 6 (3.0) | 0.310 |
| Conservative | 191 (16.0) | 58 (16.0) | 52 (14.3) | 48 (17.8) | 33 (16.7) | 0.673 |
| Successful PCI* | 879 (91) | 263 (91) | 274 (91) | 196 (92) | 146 (91) | 0.999 |
| Secondary prevention medication at discharge, n (%) | | | | | | |
| ACEI/ARB | 775 (65.0) | 205 (56.6) | 242 (66.5) | 187 (69.5) | 141 (71.2) | 0.001 |
| Beta-blocker | 781 (65.5) | 226 (62.4) | 246 (67.6) | 175 (65.1) | 134 (67.7) | 0.450 |
| Dual-antiplatelet therapy | 1011 (84.7) | 308 (85.1) | 309 (84.9) | 233 (86.6) | 161 (81.3) | 0.463 |
| Statin | 955 (80.1) | 276 (76.2) | 298 (81.9) | 217 (80.7) | 164 (82.8) | 0.167 |

Continued

**Table 1.** Continued

| Variables | BMI Group | | | | | *P* Value |
|---|---|---|---|---|---|---|
| | All (n=1193) | 18.5–23.9 (n=374) | 24–26.9 (n=372) | 27–29.9 (n=272) | ≥30 (n=203) | |
| Antidiabetic therapy at discharge, n (%) | | | | | | |
| Diet control alone | 141 (11.8) | 43 (11.9) | 42 (11.5) | 35 (13.0) | 21 (10.6) | 0.879 |
| Metformin/pioglitazone | 646 (54.2) | 190 (52.5) | 203 (55.8) | 144 (53.5) | 109 (55.1) | 0.827 |
| Sulfonylurea/mitiglinide | 503 (42.2) | 153 (42.3) | 162 (44.5) | 106 (39.4) | 82 (41.4) | 0.636 |
| DPP4 inhibitor | 441 (37.0) | 122 (33.7) | 142 (39.0) | 106 (39.4) | 71 (35.9) | 0.377 |
| Insulin | 316 (26.5) | 101 (27.9) | 83 (22.8) | 75 (27.9) | 57 (28.8) | 0.294 |
| Outcome | | | | | | |
| Death, n (%) | 74 (6.20) | 35 (9.67) | 20 (5.49) | 9 (3.35) | 10 (5.05) | |
| Death, per 1000 person-years | 41 (33, 51) | 65 (47, 91) | 37 (24, 58) | 21 (11, 40) | 33 (18, 61) | |

*Successful PCI: TIMI (Thrombosis in Myocardial Infarction) 2 or 3 flow after PCI. Values are the mean±standard deviation or number (percentage). Differences between groups were evaluated by the chi-square test, Fisher's exact test, and 1-way ANOVA. ACEI indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

obese, 16.6%. The obese patients were younger with more comorbidities such as hypertension, hyperlipidemia, and a higher prevalence of myocardial infarction history. No significant differences in the indicators of ACS severity were found among the BMI groups, including left ventricular dysfunction, intra-aortic balloon counterpulsation/inotropic agent support, or multiple-vessel diseases (except left main coronary artery disease, which was marginally lower in the obesity group). Most patients received revascularization therapy during the index hospitalization, including percutaneous coronary intervention (80%) and coronary artery bypass grafting (4%). The types and proportions of revascularization therapy did not differ between the BMI groups, and the administered evidence-based medications for ACS were not different at discharge except for greater angiotensin-converting enzyme inhibitor /angiotensin II receptor blocker use in the overweight and all classes of obesity groups. Moreover, the proportions of each administered antidiabetic agent were similar between the BMI groups (Table 1).

The cumulative mortality rate in this study was 41 deaths per 1000 person-years (n=74) during the follow-up period. This mortality rate was highest in the normal weight group (65 deaths per 1000 person-years; n=35) and lowest in the class I obese group (21 deaths per 1000 person-year; n=9). Kaplan–Meier survival analysis demonstrated significant differences in mortality between the BMI groups (*P*=0.006, log-rank test for trend) (Figure 1). The crude analyses of BMI levels showed a significant protective effect for class I obesity in comparison to normal weight with respect to all-cause mortality in time-dependent Cox regression model (Table 2). In the final multivariable-adjusted model, decreased left ventricular ejection fraction, use of dual-antiplatelet

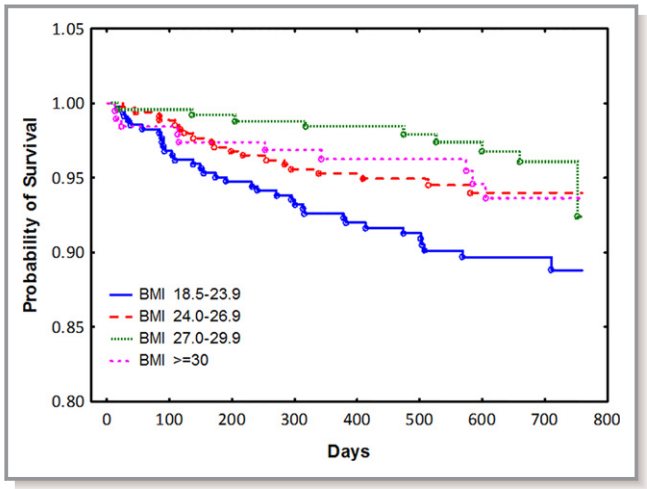


**Figure 1.** Kaplan–Meier survival curves of study participants according to all cohort stratified by the 4 BMI categories (log-rank *P*=0.006). BMI indicates body mass index.

medications, use of statins, and class I obesity remained independent predictors of mortality (adjusted hazard ratio for class I obesity: 0.14; 95% CI, 0.02–0.99; *P*=0.049), even after stratification by follow-up intervals (Table 2). In the analysis by propensity score-adjusted model, all the overweight and obesity groups showed protective effect compared with the reference normal-weight group, with the risk nadir at type 1 obesity group (Table 3, all cohort). The relationship between BMI and mortality was reexamined after exclusion of in-hospital mortality data. The sensitivity analysis after excluding in-hospital mortality showed a consistent relationship, hazard ratio of mortality, 0.78 (CI, 0.29–2.09; *P*=0.616) for overweight group, 0.11 (CI, 0.02–0.56; *P*=0.009) for class I

**Table 2.** Adjusted and Unadjusted Hazard Ratios (95% CI) of Different Covariates on All-Cause Mortality by Time-Dependent Cox Regression Model

| | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| BMI categories | | | | |
| BMI (18.5–23.9) | 1.0 | | 1.0 | |
| BMI (24.0–26.9) | 0.58 (0.24–1.39) | 0.222 | 0.62 (0.19–2.02) | 0.431 |
| BMI (27.0–29.9) | 0.13 (0.03–0.54) | 0.005 | 0.14 (0.02–0.99) | 0.049 |
| BMI (≥30) | 0.51 (0.17–1.55) | 0.236 | 1.52 (0.43–5.36) | 0.512 |
| Demographics | | | | |
| Age | 1.06 (1.03–1.08) | <0.001 | 1.03 (0.99–1.06) | 0.136 |
| Male | 0.72 (0.44–1.16) | 0.178 | 0.53 (0.24–1.16) | 0.114 |
| Risk factors and co-morbid diseases | | | | |
| CKD | 1.32 (0.83–2.09) | 0.246 | 1.75 (0.88–3.45) | 0.108 |
| Smoking | 0.54 (0.31–0.93) | 0.027 | 1.19 (0.56–2.55) | 0.656 |
| Severity | | | | |
| LVEF<40% | 3.54 (2.17–5.77) | <0.001 | 2.86 (1.43–5.72) | 0.003 |
| Left main disease | 2.02 (1.04–3.93) | 0.039 | 2.29 (0.83–6.36) | 0.111 |
| $HbA_{1c}$ | 1.02 (0.87–1.19) | 0.805 | 1.08 (0.91–1.28) | 0.407 |
| Medication | | | | |
| ACEI/ARB | 0.68 (0.43–1.08) | 0.104 | 0.63 (0.32–1.24) | 0.180 |
| Beta-blocker | 0.79 (0.49–1.26) | 0.317 | 0.72 (0.38–1.36) | 0.306 |
| Dual antiplatelet | 0.35 (0.21–0.57) | <0.001 | 0.42 (0.20–0.91) | 0.028 |
| Statin | 0.45 (0.27–0.72) | 0.001 | 0.42 (0.22–0.80) | 0.009 |
| ACS subtype | | | | |
| NSTEMI | 1.0 | | 1.0 | |
| Unstable angina | 0.37 (0.19–0.72) | 0.004 | 0.44 (0.16–1.19) | 0.106 |
| STEMI | 0.34 (0.18–0.64) | 0.001 | 0.69 (0.31–1.54) | 0.363 |
| Revascularization | | | | |
| PCI treatment | 0.44 (0.27–0.70) | 0.001 | 1.04 (0.45–2.37) | 0.935 |
| CABG treatment | 3.57 (1.77–7.17) | <0.001 | 0.80 (0.26–2.45) | 0.698 |

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; $HbA_{1c}$, hemoglobin $A_{1c}$; HR, hazard ratio; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

obesity, and 0.57 (CI, 0.16–2.03; *P*=0.382) for class II obesity.

Because the interaction term analysis was limited by the absence of mortality events in patients of the class I obese group receiving insulin sensitizer therapy, class I and class II/III obese patients were considered a single "obese group" when exploring the roles of different antidiabetic agents. The interaction analysis showed that the use of insulin therapy modified the obesity paradox (*P* for interaction=0.045); however, factors that modified the obesity paradox in previous studies, including age, smoking, and CKD, did not modify the BMI-mortality relationship in our study.[12,13] When the patients were stratified by insulin use, the protective effect of obesity was absent in insulin-treated patients (adjusted hazard ratio, 0.95; 95% CI, 0.26–3.56; *P*=0.944) but present in non–insulin-treated patients (adjusted hazard ratio, 0.26; 95% CI, 0.08–0.89; *P*=0.032). (Figure 2). Kaplan–Meier analysis demonstrated that survival in the non–insulin-treated group was similar to the main cohort overall (Figure 3). The discrepancy between insulin- and non–insulin-treated groups remained in the propensity score-adjusted analysis (Table 3).

**Table 3.** Adjusted Hazard Ratio (95% CI) of Different BMI Group on All-Cause Mortality With Propensity Score–Adjusted Model, Stratified by All Cohort, Insulin-Treated Group, and Non–Insulin-Treated Group

| | Overall | | <365 Days | | ≥365 Days | |
|---|---|---|---|---|---|---|
| | aHR (95% CI) | *P* Value | aHR (95% CI) | *P* Value | aHR (95% CI) | *P* Value |
| All cohort | | | | | | |
| BMI (18.5–23.9) | 1.0 | . . . | 1.0 | . . . | 1.0 | . . . |
| BMI (24.0–26.9) | 0.60 (0.43–0.82) | 0.002 | 0.56 (0.39–0.81) | 0.002 | 0.44 (0.23–0.87) | 0.017 |
| BMI (27.0–29.9) | 0.34 (0.22–0.52) | <0.001 | 0.21 (0.12–0.39) | <0.001 | 0.66 (0.35–1.22) | 0.185 |
| BMI (≥30) | 0.54 (0.36–0.81) | 0.003 | 0.63 (0.38–1.04) | 0.068 | 0.54 (0.25–1.15) | 0.109 |
| Insulin-treated group | | | | | | |
| BMI (18.5–23.9) | 1.0 | . . . | 1.0 | . . . | 1.0 | . . . |
| BMI (24.0–26.9) | 1.30 (0.65–2.59) | 0.458 | 0.88 (0.41–1.86) | 0.729 | 0.82 (0.14–4.79) | 0.828 |
| BMI (≥27) | 0.94 (0.48–1.83) | 0.853 | 0.52 (0.22–1.24) | 0.139 | 2.00 (0.55–7.29) | 0.296 |
| Non–insulin-treated group | | | | | | |
| BMI (18.5–23.9) | 1.0 | . . . | 1.0 | . . . | 1.0 | . . . |
| BMI (24.0–26.9) | 0.46 (0.28–0.75) | 0.002 | 0.46 (0.26–0.82) | 0.009 | 0.39 (0.15–0.99) | 0.047 |
| BMI (≥27) | 0.30 (0.18–0.52) | <0.001 | 0.29 (0.14–0.61) | 0.001 | 0.44 (0.18–1.04) | 0.061 |

aHR indicates adjusted hazard ratio; BMI, body mass index.

# Discussion

## Main Finding

We showed that elevated BMI had a significant inverse association with midterm survival of patients with ACS and diabetes mellitus. Interestingly, this reverse association was observed only in patients receiving oral antidiabetic agents.

## BMI and Mortality

The concept of the obesity paradox in coronary heart disease was first introduced in 2002 by Gruberg et al,[5] who noted that overweight and mild obesity patients had lower mortality after percutaneous coronary intervention than normal-weight patients. In patients with ACS, data extracted from the Swedish Coronary Angiography and Angioplasty Registry as well as the National Cardiovascular Data Registry show a U-shaped relationship between BMI and mortality, with the lowest mortality rate in overweight individuals.[6,14] When patients with type 2 diabetes mellitus developed ACS, their mortality rates were nearly twice that of patients without diabetes mellitus. In patients with both diabetes mellitus with ACS, unfavorable clinical outcomes were observed, including more extensive small-vessel coronary artery disease with diffuse atherosclerosis detected via angiography, a higher rate of heart failure, and CKD.[15] However, the presence of the obesity paradox in this very high-risk population remains unclear. In a German population-based acute myocardial infarction registry, elevated BMI was associated with significantly improved survival only in the non–diabetes mellitus group, while the opposite was true in the diabetes mellitus group.[8] However, higher mortality was found in nonobese patients listed in the DIAMOND (Diabetic Acute Myocardial Infarction Disease) Korean multicenter registry.[9] The inconsistent data from these registries might be explained by the different study designs and ethnicities of the subjects. In our cohort, there were higher-risk clinical presentations including left main disease (7.7%), CKD (34.5%), and previous myocardial infarction (15.3%), but fewer evidence-based medications than in the German and Korean registry. Nevertheless, patients with class I obesity had the lowest mortality rates, and those with normal weight the highest.

There are many explanations for the obesity paradox. One is that most obese patients are younger, which usually implies less severe coronary artery disease and the ability to administer more aggressive medical treatments for secondary prevention.[14,16] Our study showed that BMI was inversely correlated with age and directly proportional to the administration of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. Otherwise, beta-blockers, statins, dual-antiplatelet therapy, and coronary revascularization strategies were similar among the BMI groups. Although there was a higher prevalence of left main and multiple-vessel diseases in our cohort (59.8%) than in other published studies, no significant differences between the BMI groups were found. The obesity paradox persisted even after multivariate confounding risk adjustment. In consideration of the

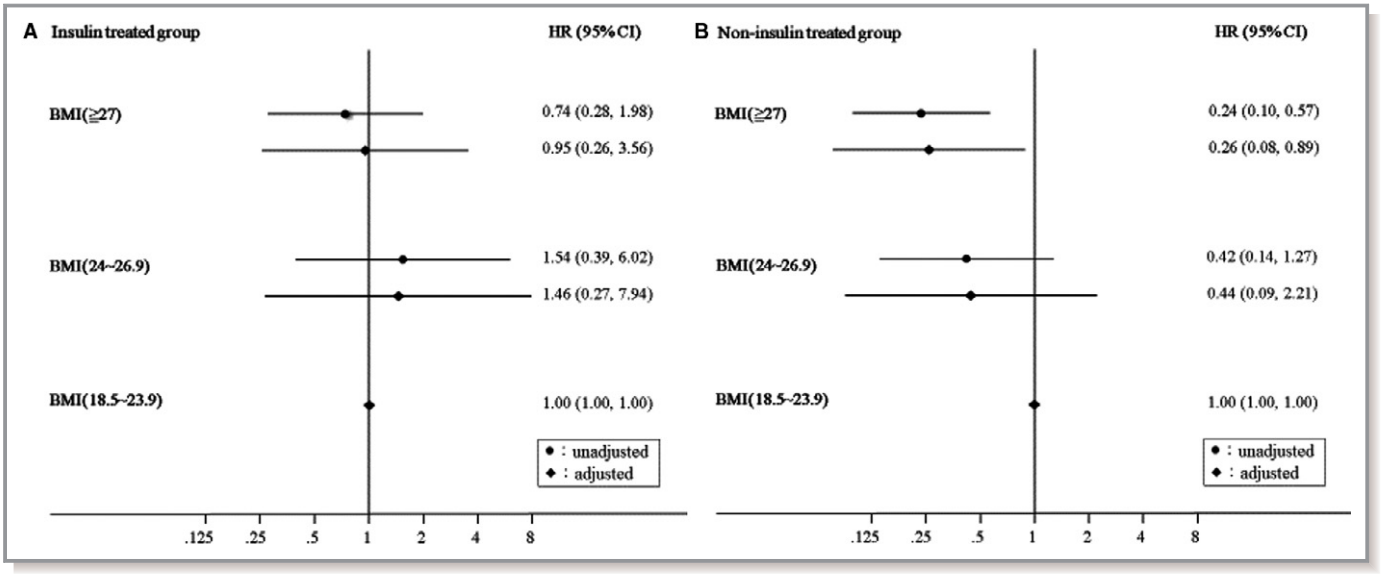


**Figure 2.** Adjusted and unadjusted hazard ratios of all-cause mortality by time-dependent covariates Cox regression, according to the BMI categories, stratified by insulin therapy administration. (**A**) insulin-treated group; (**B**) non–insulin-treated group. Normal weight (BMI: 18.5–23.9) as the reference. BMI indicates body mass index; HR, hazard ratio.

possibility that age may drive the BMI relationships to mortality, interaction term analysis and residual analysis were conducted, and both analyses showed no interference by age. In addition to the standard regression approach, adjustment of confounders by propensity score approach revealed agreements in the results.

Another possible explanation for the obesity paradox is reverse causality secondary to an underlying malignancy, chronic medical illness, or frailty. These conditions may be associated with higher mortality in and of themselves, or with a decreased metabolic reserve to cope with the increased metabolic demands of acute stress or revascularization.[6] To

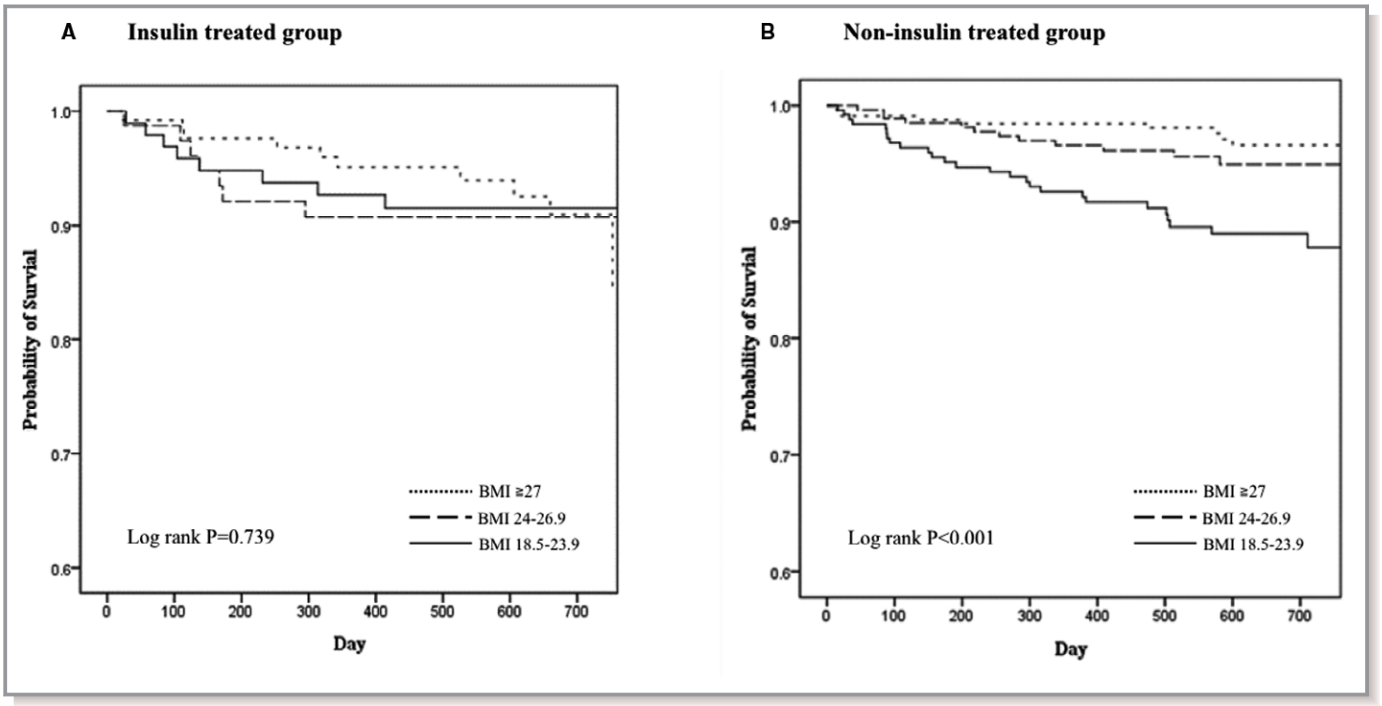


**Figure 3.** Kaplan–Meier survival curve of different subgroup, stratified by insulin therapy administration. (**A**) insulin-treated group; (**B**) non–insulin-treated group. BMI indicates body mass index.

eliminate these confounding effects, we excluded patients with potential cachexia (BMI <18.5 kg/m$^2$), malignancy, and advanced CKD and end-stage renal disease, as these patients presumably respond poorly to current evidence-based medicine and have high mortality rates despite optimal management. In the excluded cohort of 314 patients, 50 died (a mortality rate of 15.9%; data not shown). Furthermore, there is considerable evidence that the adiponectin produced in adipose tissue has direct cardioprotective effects on the infarcted myocardium,[17] which may potentially explain the role of obesity in reducing mortality rates in ACS patients.

## Role of Antidiabetic Therapy

Patients with type 2 diabetes mellitus have an elevated risk of cardiovascular morbidity and mortality, and data describing the effects of different antidiabetic medications have shown variability in cardiovascular outcomes and mortality. Furthermore, such antidiabetic agents have different impacts on body weight change, which is decreased by SGLT2 (sodium-glucose cotransporter 2) inhibitors and glucagon-like peptide-1 agonists, unchanged by metformin and dipeptidyl peptidase-4 inhibitors, and increased by sulfonylurea, meglitinides, thiazolidinediones, and insulin.[18] The change in body weight due to antidiabetic therapies has been proposed as a possible mechanism of their exerting of survival benefits, which is why such therapies constitute an important confounder that requires further investigation. In our subgroup analyses of antidiabetic therapies, the inverse relationship between BMI and mortality persisted only in patients who were using oral antidiabetic agents but not in those on insulin therapy. Our data might partly explain the inconsistent results between the previous DIAMOND registry study, in which the obesity paradox was present and only 12% of patients received insulin therapy, versus the German population-based registry study, in which 47% of patients received insulin therapy and no survival benefit was observed in the high-BMI group.[8,9]

Insulin therapy may modify the BMI-mortality relationship for several reasons. Generally, patients who receive insulin therapy have long durations of diabetes mellitus, decreased pancreatic reserve, increased insulin resistance, and more diabetes mellitus-related comorbidities. Hence, an advanced disease state may dampen any benefits of obesity. Moreover, insulin therapy has been shown to reduce the levels of potentially cardioprotective adiponectin in obese patients.[19] Nolan et al[20] proposed that exogenous insulin could override the physiologic protective effect of insulin resistance in the myocardium in overweight and obese patients, especially those who cannot restrict caloric intake or experience body weight gain after insulin therapy. Such metabolic stress can deteriorate myocardial contractility and induce arrhythmia. Another possible mechanism is insulin-related weight gain, especially in obese patients, may worsen glucose control as well as the hemodynamic and metabolic profile, which might lead to increased insulin doses and the administration of other preventive medication.[21] Consequently, the rate of severe hypoglycemic events could increase because of high-dose insulin. All the aforementioned factors can potentially affect short-term and midterm mortality in patients in the post-ACS phase. However, our study did not test all these potential mechanisms; hence, the differential effect and safety of insulin therapy in obese patients requires further investigations.

## Limitations

First, this was an observational study that provided only associative, not causative, evidence; hence, our findings should be interpreted with caution. Second, selection bias, residual confounding factors, and survival bias might exist attributable to the fact that only survived, discharged patients were included in the registry. Third, 2.3% of the data on mortality outcomes from 1221 subjects were excluded because of their unavailability (data not shown), mostly because these individuals transferred to other hospitals for long-term follow-up (except for 1 patient who died at an unknown time).

Fourth, we excluded subjects with advanced CKD, end-stage renal disease, and malignancy to minimize the effect of unintentional weight loss or weight gain. Fifth, empagliflozin and liraglutide have been shown to provide survival benefits in recent clinical trials, whereas only a few patients (n=15) were prescribed SGLT2 inhibitors in our study, and none were prescribed glucagon-like peptide-1 agonist. Thus, we suppose that these would not affect the outcome. Finally, the cutoff points of obesity varied slightly between Asia and Western countries, reducing the applicability to other populations. However, the relations between BMI, mortality and antidiabetic agents were still applicable.

To our knowledge, ours is the first prospective cohort study to determine the role of antidiabetic agents in the relationship between BMI and mortality. We confirmed that the obesity paradox is maintained in patients with both type 2 diabetes mellitus and ACS not receiving insulin therapy. The relationship between BMI and all-cause mortality in patients with type 2 diabetes mellitus and ACS was U-shaped, with the lowest and highest mortality rates observed among class I obese patients and the normal weight population, respectively. The survival benefit of obesity was abolished in those receiving insulin therapy. This study highlighted the safety concern of insulin therapy in obese patients during ACS. Further randomized control studies are warranted to evaluate the safety and efficacy of insulin therapy in ACS.

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## Disclosures

None.

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