

# Body Mass Index and Sudden Cardiac Death in Japanese Patients After Acute Myocardial Infarction: Data From the JCAD Study and HIJAMI-II Registry

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**Background**—Although an “obesity paradox” exists in patients after myocardial infarction, the association between obesity and the risk of sudden cardiac death (SCD) is limited. The aim of this study was to determine whether obesity is associated with an increased risk of SCD in Japanese survivors of acute myocardial infarction.

**Methods and Results**—Pooled data from 2 cohort studies in Japan, JCAD (Japanese Coronary Artery Disease) study and the Heart Institute of Japan Acute Myocardial Infarction-II (HIJAMI-II) registry, comprising of 6216 patients (mean age  $65 \pm 11$  years, 75.2% male) with acute myocardial infarction who were discharged alive, were studied. The patients were categorized into the following body mass index (BMI) groups at baseline according to the World Health Organization classification for Asian populations: BMI  $< 18.5$  kg/m<sup>2</sup> (n=335), 18.5 to 23 kg/m<sup>2</sup> (n=2371), 23 to 27.5 kg/m<sup>2</sup> (n=2823), and  $\geq 27.5$  kg/m<sup>2</sup> (n=687). The main outcomes were all-cause mortality and SCD. During an average follow-up period of  $3.6 \pm 1.4$  years, all-cause mortality was 10.1%, and SCD was 1.2%. Patients with BMI  $< 18.5$  kg/m<sup>2</sup> had the highest rate of all-cause mortality (adjusted hazard ratio, 1.61; 95% confidence interval, 1.20–2.16), but high BMI ( $\geq 27.5$  kg/m<sup>2</sup>) was not associated with mortality compared with patients in the group with BMI  $\geq 18.5$  and  $< 23$  kg/m<sup>2</sup>. However, the long-term risk of SCD was increased in the group with BMI  $\geq 27.5$  kg/m<sup>2</sup> (adjusted hazard ratio, 2.97; 95% confidence interval, 1.24–7.15). Multivariate analysis revealed that BMI  $\geq 27.5$  kg/m<sup>2</sup> was associated with an increased risk of SCD (hazard ratio, 2.78; 95% confidence interval, 1.35–5.74).

**Conclusions**—Obesity (BMI  $\geq 27.5$  kg/m<sup>2</sup>) was associated with the risk of SCD in Japanese patients after myocardial infarction, although an obesity paradox was found for all-cause mortality. (*J Am Heart Assoc.* 2018;7:e008633. DOI: 10.1161/JAHA.118.008633.)

**Key Words:** body mass index • left ventricular ejection fraction • myocardial infarction • obesity • sudden cardiac death

Obesity is an important predictor of myocardial infarction (MI) and mortality in the general population.<sup>1,2</sup> However, several studies have revealed an obesity paradox in patients after MI: low body mass index (BMI) is associated with

mortality in high-risk patients with MI in the primary percutaneous coronary intervention era.<sup>3–5</sup> Sudden cardiac death (SCD) is one of the major causes of death in patients with coronary artery disease (CAD) and MI.<sup>6</sup> Recent large population-based cohort studies have reported that higher BMI is associated with an increased risk of SCD, although these findings are controversial.<sup>7,8</sup> Data on the association between obesity and the risk of SCD and ventricular tachyarrhythmias in patients with MI are limited.<sup>9–11</sup> Moreover, whether obese patients who survive an acute MI have a long-term risk of SCD is unclear.

The World Health Organization (WHO) expert consultation recommended that the cutoff point for obesity be 27.5 kg/m<sup>2</sup> or higher for the Asian population because Asian individuals have different associations between BMI, body fat, and health risks than individuals in the United States and Europe.<sup>12</sup> The NIPPON DATA 80 study group and Asia Cohort Consortium BMI Project also support the World Health Organization

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## Clinical Perspective

### What Is New?

- Our study demonstrated a U-shaped relationship between body mass index and risk of sudden cardiac death in Japanese patients after acute myocardial infarction, although an “obesity paradox” existed for all-cause mortality.
- In addition, our study showed obese patients (body mass index  $\geq 27.5$  kg/m<sup>2</sup>) exhibited an increased long-term risk of sudden cardiac death.

### What Are the Clinical Implications?

- Our findings suggest that a substantial reassessment is needed of the importance of obesity for sudden cardiac death prevention in patients after myocardial infarction and that obese patients with myocardial infarction should be encouraged to pursue weight-loss strategies.

proposal that the BMI cutoff for obesity should be  $\geq 27.5$  kg/m<sup>2</sup> for the Asian population.<sup>13,14</sup>

The aim of this study was to evaluate whether obesity, as defined by BMI  $\geq 27.5$  kg/m<sup>2</sup>, is associated with an increased risk of SCD in Japanese survivors of MI using data from the combined cohorts of the JCAD (Japanese Coronary Artery Disease) study and the Heart Institute of Japan Acute Myocardial Infarction-II (HIJAMI-II) registry.

## Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

## Study Population

Pooled patient data were obtained from the JCAD study and HIJAMI-II registry. The JCAD study is an observational cohort study designed to investigate the risk factors and status of the medical management of Japanese CAD patients. The study design, objectives, and criteria for the eligibility and exclusion of patients are described in detail elsewhere.<sup>15</sup> Briefly, 13 812 consecutive patients undergoing coronary angiography who were diagnosed as having 75% or higher stenosis in at least 1 branch of the coronary arteries, according to the American Heart Association classification, were enrolled from 217 participating hospitals in Japan between 2000 and 2001 and were followed up for a mean period of 2.7 years.<sup>16</sup> The HIJAMI-II registry is an observational cohort study designed to determine the incidence of SCD according to the left

ventricular ejection fraction (LVEF) in Japanese survivors of MI. The study design, objectives, and recruitment of study participants are described in detail elsewhere.<sup>17</sup> Briefly, 4122 patients with acute MI who were discharged alive from 18 participating hospitals in Japan between 1999 and 2002 were enrolled immediately and were followed up for a mean period of 4.1 years. The JCAD protocol was approved by the Central Institutional Review Board of the University of Tokyo. The HIJAMI-II registry protocols were approved by the institutional review boards of each participating hospital. Written informed consent was obtained from each study participant.

In the JCAD study, 2955 of the 13 812 enrolled patients had suffered an acute MI at the time of registration. After data were combined, the total population of the 2 studies comprised 7077 patients. Of 2955 JCAD patients with acute MI, the LVEF measurement was not available for 834 (28%) patients. Data on the clinical and angiographic characteristics were not available for 27 (0.7%) of the 4122 HIJAMI-II patients. The total population of the 2 studies comprised 6216 patients.

## Exposure Assessment

In these studies, the baseline demographic values, weights, and heights of all patients were recorded to calculate BMI as weight in kilograms divided by height in meters squared (kg/m<sup>2</sup>). Patients were divided into 4 prespecified BMI groups using the World Health Organization classification for Asian populations: BMI  $< 18.5$  kg/m<sup>2</sup> denoted underweight, 18.5 to 23 kg/m<sup>2</sup> denoted an increasing but acceptable risk, 23 to 27.5 kg/m<sup>2</sup> denoted an increased risk, and  $\geq 27.5$  kg/m<sup>2</sup> denoted a high risk.<sup>12</sup>

LVEF was obtained from the baseline database of both studies containing the results of ventriculography, echocardiography, or radionuclide ventriculography, performed before hospital discharge.<sup>15,17</sup>

## Outcome Assessment

The prespecified outcomes in this study were all-cause mortality and SCD. To standardize the definition of SCD in this analysis of the combined studies, all fatal cases were reviewed and adjudicated by a committee of investigators (H.Y., T.K., T.S., and K.A.). Definite SCD was defined as sudden, unexpected death attributable to a cardiac cause such as a sudden cardiac arrest in a previously stable individual. Possible SCD was defined as unexpected, endogenous death within 24 hours after last having been seen alive that was not related to a specific cause of circulatory failure or a cause other than the heart. In this study, definite SCD and possible out-of-hospital SCD were included as SCD.

## Determination of LVEF

LVEF was calculated from the results of ventriculography, echocardiography, or radionuclide ventriculography performed during hospitalization due to acute MI. All LVEF determinations were performed by independent investigators (T.K. and A.S.) who were blinded to the patients' data.

## Statistical Analysis

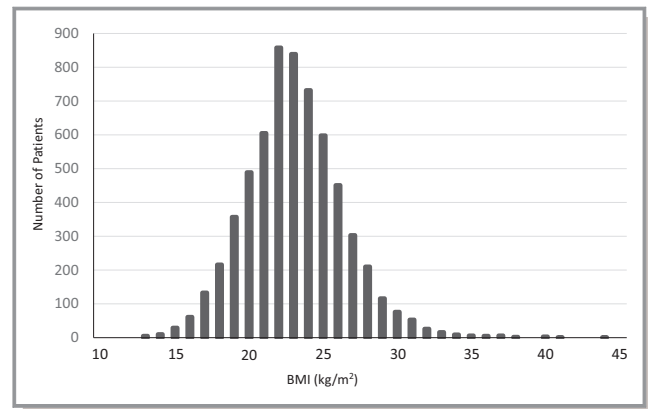
Data are presented as the mean±standard deviation and median with the interquartile range or frequency. One-way ANOVA was used to compare groups with respect to normally distributed continuous variables, and the Kruskal-Wallis test was used for other variables. Categorical variables were subjected to chi-squared analysis. Cumulative probabilities of all-cause mortality and SCD were estimated with the Kaplan-Meier method from enrollment data and by means of a comparison of cumulative events based on BMI with the log-rank test. To evaluate the influence of BMI on subsequent death events, unadjusted and adjusted Cox proportional hazards models were evaluated according to BMI group: BMI <18.5, 18.5 to 23, 23 to 27.5, and ≥27.5 kg/m<sup>2</sup>. The Cox model was adjusted for age, sex, risk factors, LVEF, and medications. The proportionality assumption was checked by inspection of the log-log plots. Univariate and multivariate analyses using the Cox model were performed to determine the relationships between the BMI group and SCD, independent of the following confounders: age, sex, each coronary risk factor, LVEF, coronary revascularization, and each medication. A forward stepwise method was used for the multivariate analyses, with entry or removal based on a  $P<0.10$ .

Two-tailed  $P<0.05$  were considered to indicate a statistically significant difference. Data analyses were performed using SPSS statistical software (version 11.01, SPSS Inc, Chicago, IL, USA).

## Results

Of 6216 MI survivors, 86.4% received coronary revascularization during their hospitalization. During an average follow-up of  $3.6\pm 1.4$  years, the rate of all-cause mortality was 10.1% and the rate of SCD was 1.2%. In this study, the mean BMI was  $23.6\pm 3.3$  kg/m<sup>2</sup>, and the median BMI was 23.4 kg/m<sup>2</sup> (interquartile range, 21.5–25.6) (Figure 1). The patient distribution according to BMI was as follows: 5.4% had a BMI of <18.5 kg/m<sup>2</sup>, 38.1% had a BMI of 18.5 to 23 kg/m<sup>2</sup>, 45.4% had a BMI of 23 to 27.5 kg/m<sup>2</sup>, and 11.1% had a BMI of ≥27.5 kg/m<sup>2</sup>.

The patients' baseline characteristics are shown in Table 1. Patients with a BMI of ≥27.5 kg/m<sup>2</sup> were younger and had higher LVEF and systolic and diastolic blood pressure values.



**Figure 1.** Distribution of body mass index (BMI) among 6216 patients with acute myocardial infarction who were discharged alive.

The incidences of complicated coronary risk factors such as hypertension, dyslipidemia, diabetes mellitus, smoking, and a family history of CAD were higher in this group of patients. With regard to medications at discharge, use of aspirin, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers,  $\beta$ -blockers, statins, and calcium channel blockers were more frequent in this group.

Kaplan-Meier curves for all-cause mortality in the 4 groups are shown in Figure 2. There was a significantly lower incidence of all-cause mortality in patients with a BMI of 23.5 to 27.5 kg/m<sup>2</sup> and ≥27.5 kg/m<sup>2</sup> compared with the others ( $P<0.001$ ). Kaplan-Meier curves for SCD-free status in the 4 groups are shown in Figure 3. There was a significantly higher incidence of SCD in patients with a combined BMI <18.5 and ≥27.5 kg/m<sup>2</sup> compared with the others ( $P=0.005$ ).

The unadjusted Cox proportional hazards model demonstrated an increased risk of 3-year all-cause death in the lowest BMI group (BMI <18.5 kg/m<sup>2</sup>) and a U-shaped relationship between BMI and the risk of 3-year SCD, with an increased risk in both patients with a BMI of <18.5 kg/m<sup>2</sup> and those with a BMI of ≥27.5 kg/m<sup>2</sup> (Table 2). After adjusting for age, sex, risk factors, LVEF, and medications, the risk of SCD was significantly higher in patients with a BMI of ≥27.5 kg/m<sup>2</sup> (adjusted hazard ratio, 2.97, 95% confidence interval, 1.24–7.15) compared with those with a BMI of 18.5 to 23 kg/m<sup>2</sup> (Table 2).

Multivariate analysis revealed that a BMI of ≥27.5 kg/m<sup>2</sup> was associated with an increased risk of SCD (hazard ratio 2.78, 95% confidence interval, 1.35–5.74;  $P=0.006$ ), which was independent of LVEF ≤30% and multivessel disease (Table 3).

## Discussion

Our study revealed an obesity paradox in Japanese patients who survived an acute MI, whereby low BMI (<18.5 kg/m<sup>2</sup>)

**Table 1.** Baseline Patient Characteristics by BMI Category

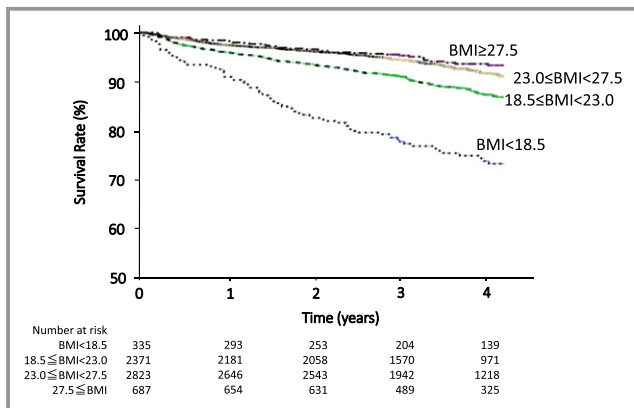
	BMI <18.5 (n=335)	BMI 18.5 to 22.9 (n=2371)	BMI 23.0 to 27.4 (n=2823)	BMI ≥27.5 (n=687)	P Value
BMI, kg/m <sup>2</sup>	17.3±1.1	21.2±1.2	24.8±1.2	29.6±2.3	<0.0001
Age, y	73±11	68±11	64±11	59±12	<0.0001
Male	182 (54)	1724 (73)	2239 (79)	530 (77)	<0.0001
Smoker	160 (48)	1276 (54)	1673 (59)	411 (60)	<0.0001
Hypertension	165 (49)	1178 (50)	1629 (58)	465 (68)	<0.0001
Diabetes mellitus	98 (29)	781 (33)	1042 (37)	310 (45)	<0.0001
Dyslipidemia	81 (24)	900 (38)	1351 (48)	418 (61)	<0.0001
Family history of CAD	42 (13)	337 (14)	480 (17)	134 (20)	0.0007
Systolic BP, mm Hg	128±25	129±24	131±25	136±24	<0.0001
Diastolic BP, mm Hg	72±14	74±15	76±15	80±15	<0.0001
LVEF, %	51±14	52±13	53±13	53±12	0.0168
Multivessel disease	153 (46)	1103 (47)	1273 (45)	297 (43)	0.5059
Left main lesion	7 (2)	54 (2)	51 (2)	6 (1)	0.1123
Coronary revascularization	264 (79)	2031 (86)	2483 (89)	597 (87)	<0.0001
<b>Medications at discharge</b>					
Aspirin	295 (88)	2137 (90)	2574 (91)	687 (100)	0.0664
ACE inhibitors/ARBs	183 (55)	1539 (65)	2016 (71)	500 (73)	<0.0001
β-Blockers	108 (32)	780 (33)	1045 (37)	290 (42)	<0.0001
Statins	53 (16)	618 (26)	927 (33)	268 (39)	<0.0001
Calcium channel blockers	97 (29)	673 (28)	844 (30)	265 (39)	<0.0001
Nitrates	207 (62)	1318 (56)	1583 (56)	384 (56)	0.2018

Values are mean±SD or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; LVEF, left ventricular ejection fraction.

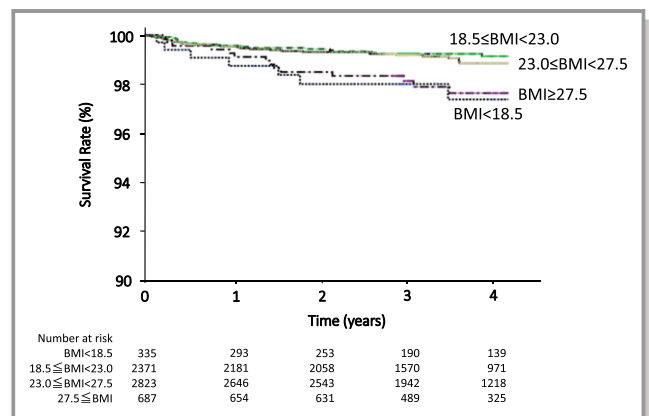
was associated with the highest rate of all-cause mortality and high BMI (≥27.5 kg/m<sup>2</sup>) was not associated with mortality. A U-shaped relationship between BMI and the risk of SCD exists in Japanese patients after acute MI. After a multivariable adjustment, patients with high BMI (≥27.5 kg/m<sup>2</sup>) had an

increased risk of SCD compared with those with a BMI of 18.5 to 23 kg/m<sup>2</sup>. Furthermore, our results suggested that high BMI is a risk factor of SCD independent of LVEF.

Obesity is a metabolic disorder and an important and well-established risk factor for cardiovascular disease, including



**Figure 2.** Kaplan-Meier curve for all-cause death in patients with myocardial infarction by body mass index (BMI) groups.



**Figure 3.** Kaplan-Meier curve for sudden cardiac death in patients with myocardial infarction by body mass index (BMI) groups.

**Table 2.** Unadjusted and Adjusted 3-Year All-Cause Mortality and Sudden Cardiac Death

	BMI <18.5 (n=335)	BMI 18.5 to 22.9 (n=2371)	BMI 23.0 to 27.4 (n=2823)	BMI ≥27.5 (n=687)
All-cause mortality (%)	69 (20.6)	202 (8.5)	149 (5.3)	30 (4.4)
Hazard ratio (95% CI)				
Unadjusted	2.60 (1.98–3.42)	1 (reference)	0.61 (0.49–0.75)	0.50 (0.34–0.73)
Adjusted*	1.61 (1.20–2.16)	1 (reference)	0.79 (0.63–0.99)	0.81 (0.54–1.23)
Sudden cardiac death (%)	6 (1.8)	17 (0.7)	22 (0.8)	11 (1.6)
Hazard ratio (95% CI)				
Unadjusted	2.65 (1.05–6.73)	1 (reference)	1.07 (0.57–2.01)	2.17 (1.02–4.63)
Adjusted*	2.45 (0.88–6.81)	1 (reference)	0.92 (0.45–1.85)	2.97 (1.24–7.15)

BMI indicates body mass index; CI, confidence interval.

\*Adjusted for age, sex, risk factors, left ventricular ejection fraction, and medications.

CAD, in the general population; obesity is also associated with increased cardiovascular and with all-cause morbidity and mortality.<sup>18</sup> Obese patients with acute MI are younger and have a higher incidence of risk factors and higher LVEF compared with nonobese patients.<sup>3,5,9,19</sup> For the primary prevention of CAD, obesity is recognized as a potent risk factor and an opportunity for therapeutic intervention to prevent cardiovascular disease. However, recent reports have shown that obesity (high BMI) itself does not present a mortality risk but is associated with a better prognosis (obesity paradox) in CAD patients receiving secondary care; these patients received appropriate therapy, including percutaneous coronary intervention and guideline-based medications, such as aspirin, β-blockers, and statins.<sup>3–5,18,19</sup> Our study also observed the obesity paradox, and patients with a BMI of ≥27.5 kg/m<sup>2</sup> also received several cardiovascular drugs.

Das et al<sup>19</sup> reported that extreme obesity is independently associated with higher in-hospital mortality in patients with ST-segment elevation MI as found through the analysis of a large registry. Romero-Corral et al<sup>4</sup> performed a meta-analysis of 40 cohort studies of patients with CAD and

reported that a U-shaped interaction existed between BMI and cardiovascular mortality but not total mortality and that mortality increased in patients who were extremely obese (BMI ≥35 kg/m<sup>2</sup>). These results indicate that obesity remains a risk factor for cardiovascular mortality, including SCD, in patients with CAD despite their younger ages, better LV function, and receipt of optimal therapy.

The reason obese patients have a risk of SCD after MI despite these advantages is not well understood. Recently, Eranti et al<sup>20</sup> reported that overweight and obese patients were at increased risk for SCD in a general population of 10 543 middle-aged subjects. Obesity itself may contribute to the development of arrhythmogenic substrates in the ventricle. Obesity is reported to be independently associated with LV hypertrophy, which leads to cardiac structural and functional remodeling.<sup>21</sup> An autopsy study of 28 obese patients (22 SCDs) revealed LV dilatation, severe coronary atherosclerosis, and concentric LV hypertrophy and histologically confirmed cardiomyocyte hypertrophy in these patients.<sup>22</sup> Some reports have shown QT prolongation or an increased late potential in obese patients.<sup>23–25</sup> An autonomic disturbance was reported in obese patients,<sup>26</sup> which may provoke arrhythmia.

Reduced LVEF is the best available predictor of SCD in survivors of MI. In this study, a high BMI was a risk factor of SCD independent of LVEF. A subanalysis of the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) included high-risk patients with a previous MI and LVEF ≤30% and reported that an independent inverse association existed between the BMI values and risk of all-cause mortality and SCD.<sup>9</sup> In the MADIT-II, patients were randomized to receive a prophylactic implantable cardioverter-defibrillator or conventional medical therapy at a 3:2 ratio. In patients with an implantable cardioverter-defibrillator, however, obesity (BMI ≥30 kg/m<sup>2</sup>) was a significant risk factor for ventricular tachyarrhythmias requiring appropriate implantable

**Table 3.** Multivariate Risk Ratios for 3-Year Sudden Cardiac Death

	Risk Ratio (95% CI)	P Value
Age (1-year increase)	1.02 (0.99–1.05)	0.106
Family history of CAD	0.33 (0.10–1.08)	0.067
LVEF ≤30%	2.51 (1.06–5.96)	0.038
Multivessel disease	4.27 (2.11–8.64)	<0.001
BMI <18.5	1.65 (0.57–4.76)	0.353
BMI ≥27.5	2.78 (1.35–5.74)	0.006

BMI indicates body mass index; CAD, coronary artery disease; CI, confidence interval; LVEF, left ventricular ejection fraction.

cardioverter-defibrillator therapy.<sup>10</sup> From these results, obesity might contribute to the development of tachyarrhythmia, which can lead to SCD, in high-risk patients after MI. Multivessel disease was found to be an independent risk factor for SCD in this study. Multivessel disease is a well-known risk factor of mortality in patients with MI.<sup>27</sup> A small study showed that multivessel disease was not a predictor of long-term SCD in MI patients who received reperfusion therapy,<sup>28</sup> but there are few data on whether multivessel disease is a risk factor for SCD.

In this study, only 1.2% of patients experienced SCD after acute MI. Primary percutaneous coronary intervention in acute MI is central to optimal ST-elevation MI treatment and reduces infarct size, minimizes myocardial damage, preserves LV function, and decreases morbidity and mortality.<sup>29</sup> Early revascularization contributes to an improvement in LV function after acute MI, and this improvement will lead to better survival, including decreasing SCD. In our study, 86.4% of patients received early coronary revascularization during hospitalization due to acute MI. Currently, most patients with acute MI received early coronary revascularization, such as primary percutaneous coronary intervention, and a low incidence of SCD has been reported in patients with acute MI who receive primary percutaneous coronary intervention in the United States and Europe,<sup>29,30</sup> as well as in Japan.<sup>17</sup>

Our findings indicated that obese patients who survive an acute MI have a long-term risk of SCD. Although lifestyle modifications and medical therapies or implantable cardioverter-defibrillators may inhibit SCD, we could not determine whether intentional weight loss was effective in the prevention of SCD or in the reduction of risk in obese patients with MI. To make these determinations, further investigations are needed.

## Study Limitations

This study had some limitations. First, the present study used data from 2 past registries and thus could not account for confounders, such as frailty, cognitive impairment, chronic obstructive pulmonary disease, and peripheral artery disease, that were not contained in either database. In addition, analysis of the groups located at both ends of the distribution of BMI, low (<18.5 kg/m<sup>2</sup>) and high (≥27.5 kg/m<sup>2</sup>), was limited by the small number of subjects. However, the 2 confirmatory methods, Kaplan-Meier analysis and multivariate adjustment, that were employed in the present study consistently indicated an association between high BMI and risk of SCD in patients after MI in both cohorts. Second, longitudinal measurements of body weight and LVEF were not performed to evaluate the improvement in LV function after MI. Third, treatment bias existed because this was an observational study. β-Blocker use was limited in this study.

The original data were obtained between 1999 and 2002. Fourth, information about culprit and other vessels on coronary angiography was not fully available, so we could not assess the possible role of an organic coronary stenosis lesion in LVEF or subsequent death.

## Conclusions

Our study demonstrated a U-shaped relationship between BMI and risk of SCD in Japanese patients after acute MI, although an obesity paradox existed for all-cause mortality. Obese patients (BMI ≥27.5 kg/m<sup>2</sup>) exhibited an increased long-term risk of SCD. Our findings suggest that a substantial reassessment is needed of the importance of obesity for SCD prevention in patients after MI and that obese patients with MI should be encouraged to pursue weight-loss strategies.

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## Disclosures

None.

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