Coronary Artery Disease

Association of Body Mass Index and Clinical Outcomes in Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

Ting-Yu Lin[1,2,3] and Hsin-Bang Leu[1,2,4,5]

Background: The obesity paradox refers to lower mortality rates among overweight or obese individuals within certain populations. However, whether this paradox is applicable to patients undergoing percutaneous coronary intervention (PCI) remains unclear.

Methods: A total of 5,427 patients with coronary artery disease (CAD) who underwent successful PCI between 2005 and 2015 were enrolled. The association between body mass index (BMI) and future adverse cardiovascular events post PCI was analyzed. The study endpoints encompassed total cardiovascular (CV) events, including cardiac death, nonfatal myocardial infarction (MI), ischemic stroke, and hospitalization for congestive heart failure (CHF).

Results: Over an average follow-up period of 65.1 ± 32.1 months, 942 patients (17.4%) had CV events, including 200 CV deaths (3.7%), 294 acute MIs (5.4%), 111 ischemic strokes (2.0%), 469 CHF hospitalizations (8.6%), and 1,098 revascularizations (20.2%). A J-shaped relationship between BMI and future adverse events was observed, in which individuals with a BMI of 25.0-29.9 kg/m² had significantly lower risks of CV events [hazard ratio (HR) = 0.84, 95% confidence interval (CI) = 0.72-0.98], major adverse cardiovascular events (HR = 0.76, 95% CI = 0.63-0.93), acute MI (HR = 0.76, 95% CI = 0.58-1.00), and ischemic stroke (HR = 0.61, 95% CI = 0.39-0.95), compared to those with a BMI of 22.0-24.9 kg/m².

Conclusion: We found a J-shaped relationship between baseline BMI and future adverse events in CAD patients undergoing PCI. Overweight individuals (BMI 25.0-29.9 kg/m²) had the lowest future risk of total CV events compared to those with a normal BMI (22.0-24.9 kg/m²).

INTRODUCTION

Most of the world's population lives in countries where overweight status and obesity pose greater risks of morbidity and mortality compared to underweight status. According to the World Health Organization (WHO), 39.0% of adults aged 18 and over are overweight, with 13.0% categorized as obese.[1] Body mass index (BMI) is frequently used to assess excess body fat and obesity. According to the WHO's definition, overweight is defined as a BMI of 25.0-29.9 kg/m², and obesity as a BMI $\geq$ 30.0 kg/m². Both overweight and obesity status are documented risk factors for chronic illnesses, including hypertension, dyslipidemia, fatty liver, sleep apnea, type 2 diabetes, symptomatic osteoarthritis, and coronary artery disease.[2,3] Consequently, weight loss interventions

Abbreviation	
ACEi	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
AMI	Acute myocardial infarction
ARB	Angiotensinogen receptor blocker
BMI	Body mass index
BMS	Bare-metal stent
CAD	Coronary artery disease
CCB	Calcium channel blocker
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
DVD	Double vessel disease
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
LDL-C	Low-density lipoprotein cholesterol
LVEF	Left ventricular ejection fraction
MACEs	Major adverse cardiovascular events
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
PDAY	Pathobiological Determinants of Atherosclerosis in Youth
SVD	Single vessel disease
TVD	Triple vessel disease
WHO	World Health Organization
WHR	Waist-to-hip ratio

are typically recommended for individuals with a BMI of 25.0 or higher to prevent or reverse complications associated with excess weight. According to the WHO, mortality increases as the BMI rises above 25.0 kg/m^2, with the lowest mortality rates found among individuals in the ideal weight range (BMI of 18.5 to 24.9 kg/m^2).[4]

Even though overweight and obesity are generally considered risk factors for premature mortality, some scientific evidence supports that overweight might be associated with reduced comorbidities and longer survival in patients with chronic kidney disease (CKD), cancer, and among the elderly.[11] It is also not uncommon for overweight or obese individuals to have few metabolic abnormalities.[5,6] One theory suggests that the adverse health effects of obesity often take many years to manifest.[7] Additionally, individuals with the same BMI do not necessarily have the same body fat distribution. Pischon et al. noted that excessive abdominal fat accumulation is the primary contributor to cardiometabolic

abnormalities, which can lead to cardiovascular disease (CVD).[8] In addition, the "obesity paradox" has been observed among patients with congestive heart failure (CHF) and atrial fibrillation (AF).[9,10] Studies have indicated a lower future risk of adverse events in overweight individuals compared to those with a normal BMI, suggesting a 'J-shaped' curve between BMI and mortality in patients with cardiovascular conditions.

Advances in percutaneous coronary intervention (PCI) techniques have significantly improved clinical outcomes in patients with coronary artery disease (CAD). However, whether the obesity paradox exists in CAD patients following successful coronary interventions remains unclear. In addition, there is limited information regarding the obesity paradox in relation to specific future cardiovascular events, such as ischemic stroke, myocardial ischemia, or cardiovascular death. Therefore, this cohort study aimed to investigate the association between baseline BMI and the risk of future adverse events in CAD patients following successful PCI.

METHODS

Study population

This single-center retrospective study recruited patients between 2005 and 2015 who had established CAD following PCI, including coronary stenting or balloon angioplasty. All CAD patients who underwent coronary interventions were enrolled for analysis. CAD was diagnosed if the patient met at least one of the following criteria: (1) ischemic change in 12-lead electrocardiography (ECG), elevated cardiac enzymes, and a diagnosis of myocardial infarction (MI) on medical records; or (2) symptoms of angina with ischemic change in 12-lead ECG or positive stress test. Patients were enrolled if they (1) had a history of at least one previously successful PCI with either coronary stenting or balloon angioplasty, and (2) were stable on medical treatment for at least 1 month before enrollment. The exclusion criteria were: (1) hospitalization for any CV event within the last 3 months, (2) significant malignancy requiring hospitalization or surgery, (3) other major systemic diseases necessitating hospitalization or surgery, (4) life expectancy of less than 6 months, (5) treatment with immunosuppressive agents, or (6) inability or unwillingness to be followed up for 1

year. The study adhered to the principles of the Declaration of Helsinki, and approval was obtained from the Ethics Committees and Independent Review Boards at Taipei Veterans General Hospital.

Baseline data collection

All baseline characteristics were retrieved from the web-based electronic medical record system at Taipei Veterans General Hospital by physicians or trained assistants. These characteristics included age, sex, BMI, laboratory data, and comorbidities such as diabetes, hypertension, hyperlipidemia, heart failure, CKD, chronic obstructive pulmonary disease, stroke, CAD, or acute coronary syndrome at enrollment.

Body weight assessment

Baseline body weight was obtained from hospital medical records. BMI, calculated as the ratio of body weight to height squared, was used as an indicator of obesity. According to the WHO definition published in 2000,[11,12] BMI values are classified as underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5-24.9 kg/m^2), overweight (BMI = 25.0-29.9 kg/m^2), grade 1 obesity (BMI = 30.0-34.9 kg/m^2), grade 2 obesity (BMI = 35.0-39.9 kg/m^2), or grade 3 obesity (BMI $\geq$ 40.0 kg/m^2). Given the low prevalence of underweight individuals in our population, we categorized BMI < 22.0 kg/m^2 as low BMI and a BMI of 22.0-24.9 kg/m^2 as the reference group for normal weight, consistent with previous studies.[13] Although the WHO has recommended lower BMI thresholds for Asian populations (overweight: BMI = 23.0-24.9 kg/m^2; obesity: BMI $\geq$ 25.0 kg/m^2) due to the higher risk of cardiovascular diseases and metabolic disorders at lower BMI levels, we chose to use the global WHO definitions. This decision allows for easier comparison and integration of our findings with other studies, as the global WHO criteria are widely used in international research. Additionally, using the WHO criteria enabled us to assess the impact of overweight and obesity based on a more universally recognized standard. We also analyzed the association between BMI and future events. All BMI categories were analyzed, and the association was not affected by different cutoff values.

Outcomes

The primary outcome was the first occurrence of total cardiovascular (CV) events, defined as the combination of CV death, nonfatal MI, nonfatal stroke, and heart failure hospitalization. We recorded the time to the first occurrence of any of these events. Additionally, individual outcomes including CV death, nonfatal MI, nonfatal stroke, revascularization, heart failure hospitalization, and major adverse cardiovascular events (MACEs) were analyzed. MACEs encompassed CV death, nonfatal MI, and ischemic stroke. MI was defined as elevated serum cardiac enzyme levels accompanied by characteristic ECG changes, while ischemic stroke was defined as reduced blood flow to part or all of the brain, supported by evidence from brain imaging studies such as computed tomography or magnetic resonance imaging. CV death was defined as death from CV causes such as MI, heart failure, stroke, CV-related hemorrhage, procedure-related death, or sudden cardiac death. The last follow-up date for the study was December 31, 2019. Similar event definitions were also reported in our previous studies.[13-15]

Statistical analysis

Baseline patient characteristics were compared across BMI subgroups. Quantitative variables were expressed as means with standard deviations for normally distributed data, while qualitative variables were presented as absolute frequencies (number of patients) and relative frequencies (percentages). Continuous variables between groups were compared using ANOVA, while categorical variables were compared using the χ^2 test or Fisher's exact test. All outcomes were reported as the number of patients and corresponding percentages. Event-free survival rates for the BMI subgroups were calculated using the Kaplan-Meier method, with significance evaluated by log-rank tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome by BMI group were calculated using Cox proportional hazard regression analysis, adjusted for age, sex, and comorbidities, with a BMI of 22.0-24.9 kg/m^2 serving as the reference group.

RESULTS

Baseline characteristics

A total of 5,427 patients who underwent PCI were enrolled in this study. The distribution of BMI in our study population is shown in Figure 1. In this cohort, 29.5% had a normal BMI (22.0-24.9 kg/m^2), while the majority
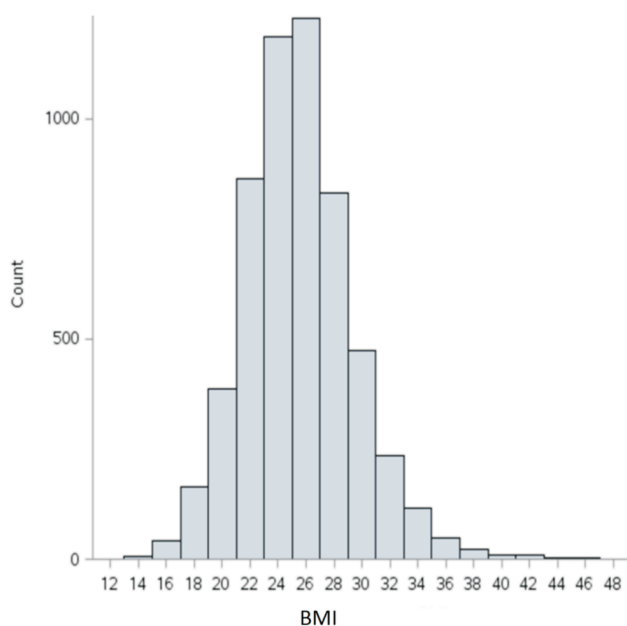
Figure 1. *Distribution of body mass index in the study population. BMI, body mass index.*

(41.1%) were overweight (BMI = 25.0-29.9 kg/m^2). The baseline characteristics of the participants by BMI subgroups are presented in Table 1. The mean age was 69.2 ± 13.3 years, and 73.9% of the patients were male. The mean BMI was 25.5 ± 4.2 kg/m^2. There were no significant differences in the angiographic severity of CAD across BMI groups. However, the patients with a higher BMI were younger than those with a lower BMI. The patients with a higher BMI had a higher prevalence of hypertension, hyperlipidemia, and diabetes, and were more frequently receiving medication therapy for these conditions. In contrast, the patients with a BMI < 22.0 kg/m^2 had a higher prevalence of heart failure (17.6%), CKD (9.9%), stroke (6.9%), and were more likely to present with acute coronary syndrome (49.5%) at enrollment.

Association between BMI groups and CV outcomes after PCI

Clinical follow-up was conducted for a mean period of 65.6 ± 32.1 months. The incidence rates of outcomes in the BMI subgroups are shown in Table 2. During the entire cohort study, there were 942 patients (17.4%) having CV events: 569 MACEs (10.5%), 200 CV deaths (3.7%), 294 acute MIs (5.4%), 111 ischemic strokes (2.0%), 469 heart failure hospitalizations (8.6%), and 1,098 revascularizations (20.2%). During the follow-up period, the underweight group (BMI < 22.0 kg/m^2) had the highest incidence of total CV events and MACEs. Specifically, this group had a higher rate of heart failure hospitalizations and revascularizations compared to the other groups. Conversely, in the highest BMI category (BMI ≥ 35.0 kg/m^2), the risks of total CV events, heart failure hospitalizations, and revascularizations were significantly elevated, consistent with the increased risks associated with traditional obesity-related complications. Statistical analysis across the groups confirmed significant differences in outcomes such as total CV events, MACEs, heart failure hospitalizations, and revascularizations, demonstrating that both lower and higher BMI extremes were associated with increased adverse events, while the lowest incidence was observed in the overweight BMI category (25.0-29.9 kg/m^2). Kaplan-Meier survival analysis of all outcomes by BMI subgroups is shown in Figure 2. The results revealed that patients in the BMI 25.0-29.9 kg/m^2 group had lower rates of adverse clinical outcomes, while those in the BMI < 22 kg/m^2 group tended to have the worst clinical outcomes. The log-rank test substantiated these differences, confirming statistical significance in total CV events (p < 0.001), MACEs (p < 0.001), acute MI (p = 0.029), and heart failure hospitalization (p < 0.001).

Predictive value of BMI for future CV risk after PCI

HRs for all outcomes by BMI subgroup are shown in Table 3. Using BMI 22.0-24.9 kg/m^2 as the reference, the unadjusted risk model revealed that the overweight group (BMI = 25.0-29.9 kg/m^2) had significantly lower HRs for total CV events, MACEs, acute MI, and ischemic stroke compared to the reference group. Conversely, the underweight group (BMI < 22.0 kg/m^2) had significantly higher risks of total CV events and heart failure hospitalization. After adjusting for age, sex, and comorbidities, a "J-shaped" association between BMI categories and future adverse CV events remained. The overweight group (BMI = 25.0-29.9 kg/m^2) was associated with a significantly lower risk of total CV events [hazard ratio (HR) = 0.84, 95% confidence interval (CI) = 0.72-0.98, p = 0.031], MACEs (HR = 0.76, 95% CI = 0.63-0.93, p = 0.008), acute MI (HR = 0.76, 95% CI = 0.58-1.00, p = 0.048), and ischemic stroke (HR = 0.61, 95% CI = 0.39-0.95, p = 0.030) (Table 3) (Figure 3). The underweight and obese groups continued to show a higher future risk, particularly for total CV events, MACEs, and heart failure.

Table 1. Baseline characteristics of study participants in body mass index categories

Characteristics	BMI < 22 (n = 934)	BMI = 22-24.9 (n = 1601)	BMI = 25-29.9 (n = 2263)	BMI = 30-34.9 (n = 530)	BMI > 35 (n = 99)	p value
Age (years)	73.7 ± 11.67	70.2 ± 12.62	67.1 ± 12.95	62.7 ± 13.96	59.2 ± 14.21	< .0001
Weight (Kg)	52.8 ± 6.82	62.5 ± 6.95	72.8 ± 8.66	84.3 ± 10.59	100.2 ± 20.16	< .0001
Height (cm)	161.7 ± 8.35	162.6 ± 8.49	163.8 ± 8.77	162.6 ± 9.73	160 ± 11.70	< .0001
BMI (Kg/m^2)	20.1 ± 1.57	23.5 ± 0.85	27 ± 1.36	31.7 ± 1.36	38.9 ± 5.34	< .0001
Males	633 (67.77)	1188 (74.2)	1757 (77.64)	379 (71.51)	56 (56.57)	< .0001
Underlying diseases						
Hypertension	492 (52.68)	960 (59.96)	1484 (65.58)	382 (72.08)	80 (80.81)	< .0001
Diabetes	257 (27.52)	553 (34.54)	800 (35.35)	241 (45.47)	58 (58.59)	< .0001
Hyperlipidemia	167 (17.88)	438 (27.36)	785 (34.69)	202 (38.11)	38 (38.38)	< .0001
Heart failure	164 (17.56)	228 (14.24)	246 (10.87)	70 (13.21)	12 (12.12)	< .0001
CKD	92 (9.85)	129 (8.06)	101 (4.46)	27 (5.09)	4 (4.04)	< .0001
Stroke	64 (6.85)	95 (5.93)	121 (5.35)	24 (4.53)	1 (1.01)	0.0765
ACS at enrollment	462 (49.46)	665 (41.54)	832 (36.77)	196 (36.98)	33 (33.33)	< .0001
Lab data						
HbA1c (%)	6.7 ± 1.35	6.9 ± 1.42	7 ± 1.35	7.4 ± 1.38	7.6 ± 1.68	< .0001
LDL-C (mmol/L)	99.2 ± 33.31	104.1 ± 33.82	108.4 ± 34.33	108.9 ± 37.25	108.5 ± 35.45	< .0001
HDL-C (mmol/L)	45.4 ± 13.71	43.4 ± 12.36	41.4 ± 10.90	39.3 ± 10.17	40.5 ± 10.82	< .0001
eGFR (mL/min/1.73 m^2)	58 ± 29.34	62.3 ± 28.79	64.3 ± 25.57	64.6 ± 27.16	60.5 ± 27.75	< .0001
LVEF (%)	48 ± 12.30	51.2 ± 11.78	52.6 ± 10.39	52.9 ± 9.59	52.7 ± 9.96	< .0001
Angiographic features						
SVD	254 (27.19)	438 (27.36)	688 (30.4)	163 (30.75)	34 (34.34)	0.096
DVD	304 (32.55)	492 (30.73)	715 (31.6)	175 (33.02)	34 (34.34)	0.7795
TVD	367 (39.29)	666 (41.6)	853 (37.69)	187 (35.28)	31 (31.31)	0.0202
Medication use						
ACEi	185 (19.81)	312 (19.49)	507 (22.4)	109 (20.57)	18 (18.18)	0.186
ARB	271 (29.01)	556 (34.73)	913 (40.34)	244 (46.04)	44 (44.44)	< .0001
Beta-blockers	398 (42.61)	742 (46.35)	1132 (50.02)	284 (53.58)	54 (54.55)	< .0001
CCB	235 (25.16)	533 (33.29)	839 (37.07)	219 (41.32)	44 (44.44)	< .0001
Statin	461 (49.36)	897 (56.03)	1369 (60.49)	336 (63.4)	63 (63.64)	< .0001
Thiazide diuretics	69 (7.39)	153 (9.56)	244 (10.78)	80 (15.09)	8 (8.08)	< .0001

Data are mean $\pm$ SD or n (%).
ACEi, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensinogen receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease; DVD, double vessel disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricle ejection fraction; SD, standard deviation; SVD, single vessel disease; TVD, triple vessel disease.

**Table 2.** Incidence of outcomes in BMI categories

Outcomes	BMI < 22 (n = 934)	BMI = 22-24.9 (n = 1601)	BMI = 25-29.9 (n = 2263)	BMI = 30-34.9 (n = 530)	BMI > 35 (n = 99)	p value
Total CV events*	199 (21.31)	300 (18.74)	345 (15.25)	81 (15.28)	17 (17.17)	0.0003
MACE[#]	116 (12.42)	190 (11.87)	205 (9.06)	48 (9.06)	10 (10.1)	0.011
CV death	43 (4.6)	66 (4.12)	71 (3.14)	17 (3.21)	3 (3.03)	0.2436
Acute MI	57 (6.1)	98 (6.12)	111 (4.9)	23 (4.34)	5 (5.05)	0.3094
Ischemic stroke	19 (2.03)	42 (2.62)	37 (1.63)	11 (2.08)	2 (2.02)	0.3337
HF hospitalization	103 (11.03)	147 (9.18)	175 (7.73)	37 (6.98)	7 (7.07)	0.0185
Revascularization[†]	146 (15.63)	316 (19.74)	506 (22.36)	113 (21.32)	17 (17.17)	0.0005

Data are n (%).
BMI, body mass index; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction.
* Include MACE + HF hospitalization; [#] Include acute myocardial infarction, ischemic stroke, cardiovascular death; [†] Include coronary stenting and bypass surgery.
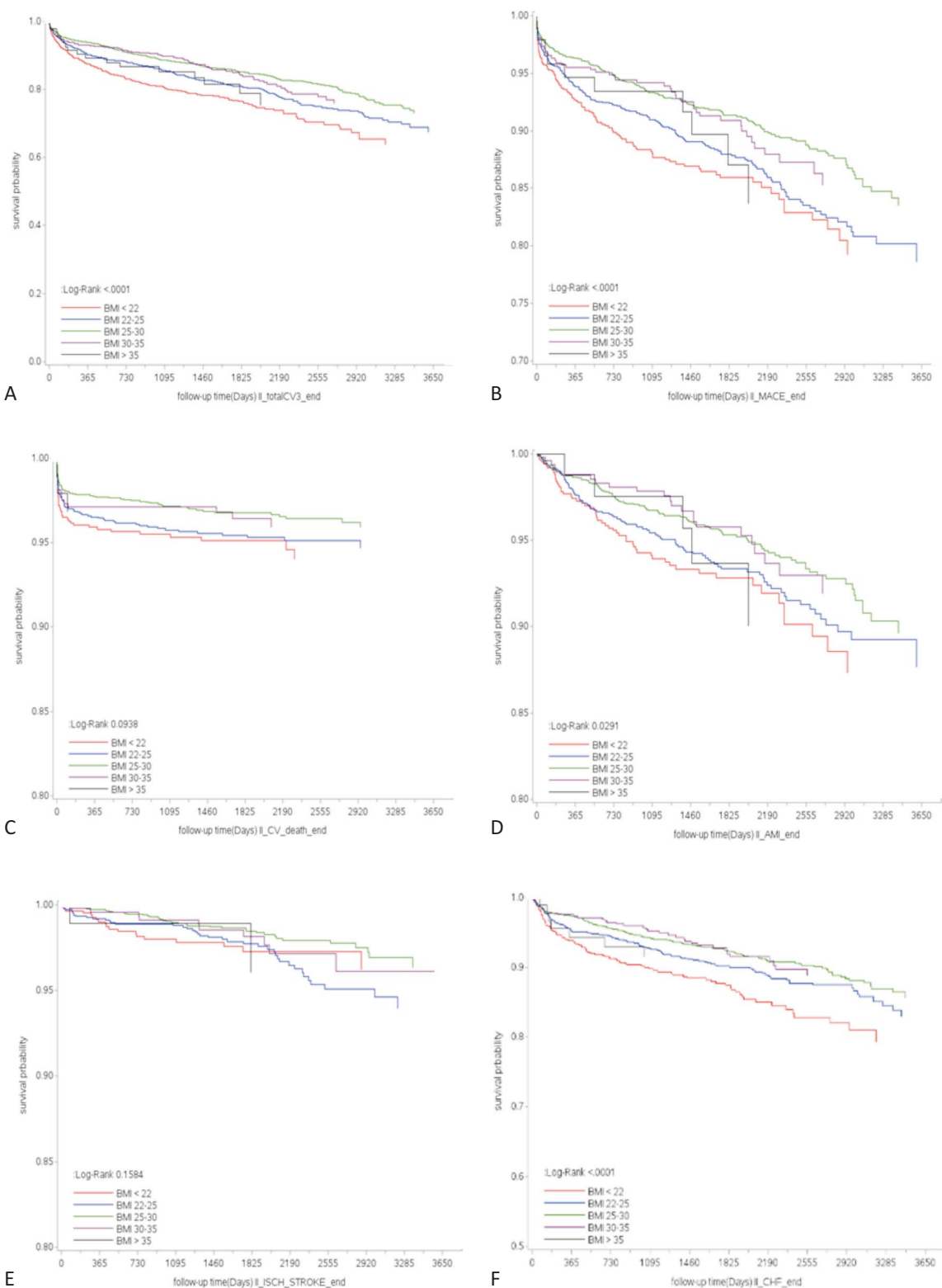
Figure 2. *Time to event curves of individual outcomes in BMI categories. (A) Total CV events, (B) MACE, (C) CV mortality, (D) Acute myocardial infarction, (E) Ischemic stroke, (F) Acute decompensate heart failure hospitalization. BMI, body mass index; CV, cardiovascular; MACE, major adverse cardiovascular event.*

Table 3. Association between BMI and future adverse events following PCI

Outcome	BMI category	Crude HR		Adjusted HR	
		HR (95% CI)	p value	HR (95% CI)	p value
Total CV events	BMI < 22	1.31 (1.09-1.57)	0.003	1.17 (0.98-1.40)	0.086
	BMI = 22-25	1.00 (1.00-1.00)	Reference	1.00 (1.00-1.00)	Reference
	BMI = 25-30	0.77 (0.66-0.89)	0.001	0.84 (0.72-0.98)	0.031
	BMI = 30-35	0.79 (0.62-1.01)	0.064	1.00 (0.78-1.28)	0.977
	BMI > 35	1.01 (0.62-1.65)	0.954	1.49 (0.91-2.44)	0.114
MACE	BMI < 22	1.19 (0.94-1.50)	0.145	1.10 (0.87-1.39)	0.411
	BMI = 22-25	1.00 (1.00-1.00)	Reference	1.00 (1.00-1.00)	Reference
	BMI = 25-30	0.72 (0.59-0.88)	0.001	0.76 (0.63-0.93)	0.008
	BMI = 30-35	0.75 (0.54-1.02)	0.069	0.86 (0.63-1.19)	0.366
	BMI > 35	0.92 (0.49-1.74)	0.799	1.15 (0.61-2.19)	0.669
CV death	BMI < 22	1.18 (0.80-1.73)	0.402	1.01 (0.69-1.49)	0.944
	BMI = 22-25	1.00 (1.00-1.00)	Reference	1.00 (1.00-1.00)	Reference
	BMI = 25-30	0.75 (0.54-1.05)	0.091	0.86 (0.61-1.20)	0.378
	BMI = 30-35	0.77 (0.45-1.32)	0.342	1.01 (0.59-1.72)	0.979
	BMI > 35	0.76 (0.24-2.43)	0.647	1.09 (0.34-3.49)	0.887
Acute MI	BMI < 22	1.17 (0.85-1.63)	0.339	1.14 (0.82-1.59)	0.421
	BMI = 22-25	1.00 (1.00-1.00)	Reference	1.00 (1.00-1.00)	Reference
	BMI = 25-30	0.74 (0.57-0.98)	0.034	0.76 (0.58-1.00)	0.048
	BMI = 30-35	0.69 (0.44-1.09)	0.110	0.73 (0.46-1.15)	0.175
	BMI > 35	0.91 (0.37-2.25)	0.846	1.00 (0.40-2.47)	0.995
Ischemic stroke	BMI < 22	0.92 (0.54-1.59)	0.775	0.86 (0.50-1.48)	0.585
	BMI = 22-25	1.00 (1.00-1.00)	Reference	1.00 (1.00-1.00)	Reference
	BMI = 25-30	0.58 (0.37-0.90)	0.015	0.61 (0.39-0.95)	0.030
	BMI = 30-35	0.78 (0.40-1.52)	0.465	0.92 (0.47-1.80)	0.805
	BMI > 35	0.87 (0.21-3.59)	0.846	1.15 (0.27-4.81)	0.852
HF hospitalization	BMI < 22	1.39 (1.08-1.79)	0.010	1.18 (0.92-1.52)	0.191
	BMI = 22-25	1.00 (1.00-1.00)	Reference	1.00 (1.00-1.00)	Reference
	BMI = 25-30	0.79 (0.64-0.99)	0.040	0.92 (0.74-1.14)	0.445
	BMI = 30-35	0.75 (0.52-1.07)	0.110	1.04 (0.73-1.50)	0.816
	BMI > 35	0.86 (0.40-1.83)	0.695	1.56 (0.73-3.36)	0.255
Revascularization	BMI < 22	0.88 (0.73-1.08)	0.221	0.93 (0.76-1.13)	0.479
	BMI = 22-25	1.00 (1.00-1.00)	Reference	1.00 (1.00-1.00)	Reference
	BMI = 25-30	1.07 (0.93-1.23)	0.335	1.03 (0.90-1.19)	0.655
	BMI = 30-35	1.06 (0.85-1.31)	0.623	0.99 (0.80-1.23)	0.949
	BMI > 35	0.92 (0.56-1.49)	0.723	0.86 (0.53-1.41)	0.553

BMI, body mass index; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Total CV event include MACE + HF hospitalization; MACE includes acute myocardial infarction, ischemic stroke, cardiovascular death; Revascularization includes coronary stenting and bypass surgery.

DISCUSSION

The present study demonstrated a J-shape relationship between baseline BMI and future adverse CV risk in CAD patients after coronary intervention. Overweight status (BMI = 25.0-29.9 kg/m^2) was associated with the lowest risk of total CV events, supporting the existence of the obesity paradox in CAD patients following coronary intervention.

Overweight status and obesity are independent risk factors for metabolic disorders and CVD. Most studies support the association between obesity with hyperten-
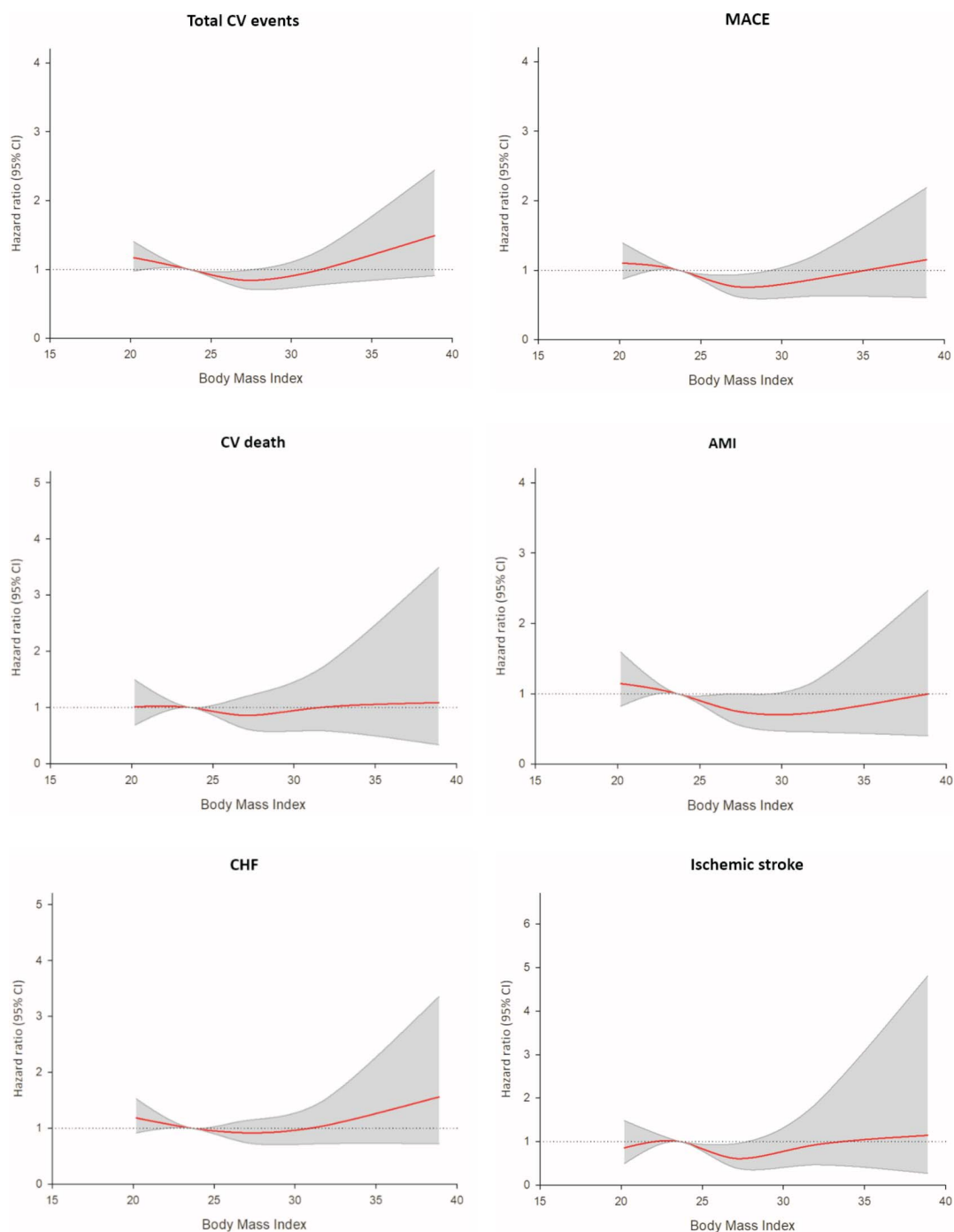
Figure 3. *Age-and-sex-adjusted hazard ratio of individual outcomes in BMI categories (BMI = 22.0-24.9 Kg/m² is used as reference category). AMI, acute myocardial infarction; BMI, body mass index; CHF, congestive heart failure; CV, cardiovascular; MACE, major adverse cardiovascular event.*

sion, hyperlipidemia, diabetes, insulin resistance and CAD, and lifestyle modification with weight control is strongly recommended as a treatment strategy to reduce future CV risk.[16] However, it is not rare for overweight or obese people to have better clinical outcomes.

Recently, the "BMI paradox" or "obesity paradox" has been widely discussed in cardiology, such as in studies concerning CHF and AF.[10] These studies have shown that patients who are overweight or obese tend to have a lower mortality rate, and that this protective effect ap-

pears to be especially pronounced in older patients.[17] Findings of the obesity paradox have been reported in several studies[18-21] as not a statistical error but a meaningful result which requires more investigation to be used in clinical practice. Our findings are consistent with the obesity paradox phenomenon, in that the overweight group was associated with better clinical outcomes. A meta-analysis revealed that among patients undergoing PCI, those classified as overweight or obese had lower short-term (30 days) and long-term (1-5 years) mortality rates compared to those with a normal BMI.[22] Furthermore, another meta-analysis confirmed the existence of a J-shaped relationship between BMI and total mortality in PCI patients with follow-up periods exceeding 5 years.[23] Notably, underweight patients had the highest mortality risk, while overweight patients had the lowest risk. In addition, a cohort study conducted in Eastern Taiwan (ET-CHD) also reported a J-shaped relationship between BMI and mortality in patients with obstructive CAD.[24] This study compared outcomes within and after a 5-year follow-up period. During the initial 5-year follow-up, underweight patients had elevated mortality risks, whereas obese patients had reduced mortality risks. However, after 5 years, the J-shaped pattern became more pronounced, with underweight and severely obese patients having higher mortality risks, and overweight patients having lower risks. In the present study, we analyzed data from over 5,000 patients from 2005 to 2015, with a mean follow-up period of approximately 7 years. The findings of our study further reinforce the notion that the obesity paradox is not merely a short-term phenomenon but also persists over the long term in patients undergoing PCI.

Regarding our results, the obesity paradox can be explained by several factors. First, catabolism is different between healthy people and diseased patients. Diseases such as CAD, HF, COPD, or CKD may increase catabolic state and decrease BMI levels, giving patients with overweight or grade 1 obesity more energy reserve to overcome this high catabolic state, along with a better prognosis during the post-PCI recovery phase. Second, there was a significant difference in age distribution in our study population (p < 0.001). The mean age of the BMI < 22.0 kg/m^2 group was 73.7 ± 11.7 years, which was the oldest group in our study; on the other hand, the patients with higher BMIs were younger. Thus, age may be

considered a confounding factor in the analysis of CV adverse events, in that older age may result in poorer CV outcomes. In the elderly, a lower BMI may indicate that the patient is involuntarily losing weight, is malnourished, or has sarcopenia,[25] which may also lead to higher mortality. Thus, a higher BMI in the elderly may provide survival benefits and result in the obesity paradox. Third, there was a significant difference between subgroups using standard CAD medications (p < 0.001). There appeared to be a trend that more patients in the high BMI groups were taking ARBs, beta-blockers, statins, or anti-platelet medications than those in the low BMI group. These medications are not only used to control hypertension or hyperlipidemia, but also used for cardiac remodeling and providing survival benefits in CAD or heart failure patients. Thus, patients receiving more adequate medication therapy in the higher BMI groups may have resulted in the obesity paradox. Fourth, the influence of obesity on health status is slow. In patients with visceral obesity, the fatty tissue releases inflammatory adipocytokines (e.g., tumor necrosis factor-alpha, interleukin-6, monocyte chemoattractant protein-1, leptin) which may induce endothelial dysfunction and systemic inflammation, facilitating the atherosclerosis process.[26] A compelling study, 'Pathobiological Determinants of Atherosclerosis in Youth' (PDAY),[27] found that obesity in adolescents and young adults could accelerate atherosclerosis progression decades before the appearance of clinical manifestations. It is believed that at least two decades of obesity is likely to be an independent risk factor for CAD. After the patient manifests with hypertension, hyperlipidemia, diabetes, myocardial ischemia, or heart failure, the benefits of starting medication therapy to control the disease outweigh the benefits of losing weight. Our study focused on CAD patients treated with PCI, in whom the prevalence of hypertension was 91.8%, hyperlipidemia 45.1%, and diabetes 42.9%. With these comorbidities, the negative influence of being obese may be offset by the advantage of high energy reserve, which may result in the obesity paradox.

Limitations

Our study has some limitations. First, the data were obtained from a single-center medical records system, with data collection spanning from October 2005 to July 2015, and more than 5,000 patients were enrolled. Due

to the low percentage of underweight patients (BMI < 18.5 kg/m^2) and those with grade 3 obesity (BMI $\geq$ 35.0 kg/m^2), sampling bias may be present. As a result, the findings should not be generalized to populations in countries with a higher prevalence of underweight or extremely obese individuals, given the epidemiological differences.

Second, BMI may not be the optimal indicator for assessing obesity and CVD risk. While BMI is simple to use, it does not differentiate between muscle mass and visceral fat distribution. Research has shown that excess abdominal visceral adipose tissue, regardless of BMI, is diabetogenic and atherogenic, increasing triglyceride and low-density lipoprotein levels while decreasing high-density lipoprotein levels, thereby elevating CVD risk.[28,29] According to the INTERHEART study, waist-to-hip ratio (WHR) and waist circumference (WC) are stronger predictors of MI than BMI alone.[30] A WHR above 0.9 in men or 0.85 in women, and a WC above 102 cm in men or 88 cm in women indicate central obesity, which carries a higher CV risk. Future studies could further investigate the obesity paradox using WHR or WC as alternative indicators of obesity.

Third, our study lacks data on weight loss interventions. Clinically, providing nutritional support to underweight patients and encouraging weight loss in overweight patients are logical strategies. Randomized trials have shown that reducing body weight through lifestyle changes lowers inflammatory biomarkers and insulin resistance, thereby decreasing the risk of adverse CV events.[31,32] In addition, small trials involving exercise and diet control in post-PCI cardiac rehabilitation programs have demonstrated reductions in revascularization rates.[33,34] However, less weight fluctuation in patients with CAD has also been associated with better CV outcomes.[35,36] Therefore, the impact of weight loss interventions on CAD patients post-PCI requires further investigation.

Fourth, several confounding factors may influence clinical outcomes in the post-PCI population. These include achieving functionally complete revascularization, using intravascular imaging guidance rather than angiography alone, and adhering to global consensus guidelines for pre- and post-stenting procedures: (1) selecting suitable patients, (2) pre-stenting balloon sizing, (3) stent sizing, (4) post-stenting balloon sizing, (5) ensuring complete apposition and adequate expansion (avoiding underexpansion or malapposition), and (6) preventing edge dissection. All of these factors could impact clinical outcomes.

As a retrospective study, our findings are subject to inherent biases including recall bias, selection bias, and the potential for incomplete data recording. Although we applied robust statistical methods to mitigate these biases, prospective, randomized controlled trials are necessary to validate our results. Given these limitations, our findings should be interpreted with caution. We emphasize the need for further research, including large-scale, multicenter, prospective studies with long-term follow-up.

CONCLUSION

Our study suggests a J-shaped relationship between baseline BMI and future CV risk in CAD patients following coronary intervention. Among the BMI categories, overweight individuals (BMI 25.0-29.9 kg/m^2) exhibited the lowest risk of total cardiovascular events.

DATA AVAILABILITY

Raw data were generated at Taipei Veterans General Hospital and obtained through Taiwan's National Health Insurance Research Database. The data supporting the findings of this study are available upon request from the corresponding author, Hsin-Bang Leu. These data are not publicly available due to privacy concerns regarding research participants.

FUNDING STATEMENT

ACKNOWLEDGEMENTS

lished in the online abstract supplement of the *European Heart Journal*, Volume 43, Issue Supplement_1, February 2022, ehab849.064.

DECLARATION OF CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

REFERENCES

1. WHO. Obesity and overweight. 2021, June 9.

2. Krauss RM, Winston M, Fletcher BJ, Grundy SM. Obesity: impact on cardiovascular disease. *Circulation* 1998;98:1472-6.

3. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 2003;290:1906-14.

4. Bhaskaran K, Dos-Santos-Silva I, Leon DA, et al. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol* 2018;6:944-53.

5. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol* 2013;1:152-62.

6. Iacobini C, Pugliese G, Blasetti Fantauzzi C, et al. Metabolically healthy versus metabolically unhealthy obesity. *Metabolism* 2019;92:51-60.

7. Deedwania P, Lavie CJ. Dangers and long-term outcomes in metabolically healthy obesity: the impact of the missing fitness component. *J Am Coll Cardiol* 2018;71:1866-8.

8. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;359:2105-20.

9. Chandramouli C, Tay WT, Bamadhaj NS, et al. Association of obesity with heart failure outcomes in 11 Asian regions: a cohort study. *PLoS Med* 2019;16:e1002916.

10. Lavie CJ, Pandey A, Lau DH, et al. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise. *J Am Coll Cardiol* 2017;70:2022-35.

11. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:i-xii, 1-253.

12. National Institutes of Health, National Heart, Lung, and Blood Institute, NHLBI Obesity Education Initiative, & North American Association for the Study of Obesity (2000). The practical guide: Identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, MD: National Institutes of Health, p. 1, Table 1.

13. Chen SC, Yang YL, Wu CH, et al. Association between preoperative nutritional status and clinical outcomes of patients with

14. Yang YL, Wu CH, Hsu PF, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. *Eur J Clin Invest* 2020;50:e13230.

15. Lim SS, Yang YL, Chen SC, et al. Association of variability in uric acid and future clinical outcomes of patient with coronary artery disease undergoing percutaneous coronary intervention. *Atherosclerosis* 2020;297:40-6.

16. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and The Obesity Society. *J Am Coll Cardiol* 2014;63:2985-3023.

17. Dwivedi AK, Dubey P, Cistola DP, Reddy SY. Association between obesity and cardiovascular outcomes: updated evidence from meta-analysis studies. *Curr Cardiol Rep* 2020;22:25.

18. Doehner W, Gerstein HC, Ried J, et al. Obesity and weight loss are inversely related to mortality and cardiovascular outcome in prediabetes and type 2 diabetes: data from the ORIGIN trial. *Eur Heart J* 2020;41:2668-77.

19. Forgie K, Bozso SJ, Hong Y, et al. The effects of body mass index on outcomes for patients undergoing surgical aortic valve replacement. *BMC Cardiovasc Disord* 2020;20:255.

20. Faggioni M, Baber U, Afshar AE, et al. Effects of body mass index on clinical outcomes in female patients undergoing percutaneous coronary intervention with drug-eluting stents: results from a patient-level pooled analysis of randomized controlled trials. *JACC Cardiovasc Interv* 2018;11:68-76.

21. Elagizi A, Kachur S, Lavie CJ, et al. An overview and update on obesity and the obesity paradox in cardiovascular diseases. *Prog Cardiovasc Dis* 2018;61:142-50.

22. Oreopoulos A, Padwal R, Norris CM, et al. Effect of obesity on short- and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity (Silver Spring)* 2008;16:442-50.

23. Li YH, Lin GM, Lin CL, et al. Relation of body mass index to mortality among patients with percutaneous coronary intervention longer than 5 years follow-up: a meta-analysis. *Int J Cardiol* 2013;168:4315-8.

24. Lin GM, Li YH, Lin CL, et al. Relation of body mass index to mortality among Asian patients with obstructive coronary artery disease during a 10-year follow-up: a report from the ET-CHD registry. *Int J Cardiol* 2013;168:616-20.

25. Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol (1985)* 2003;95:1851-60.

26. Vachharajani V, Granger DN. Adipose tissue: a motor for the inflammation associated with obesity. *IUBMB Life* 2009;61:424-30.

27. McMahan CA, Gidding SS, Malcom GT, et al. Pathobiological determinants of atherosclerosis in youth risk scores are associated with early and advanced atherosclerosis. *Pediatrics* 2006;118:1447-55.

28. Hwang YC, Fujimoto WY, Hayashi T, et al. Increased visceral adi-

coronary artery disease undergoing percutaneous coronary intervention. *Nutrients* 2020;12:1295.

pose tissue is an independent predictor for future development of atherogenic dyslipidemia. *J Clin Endocrinol Metab* 2016;101: 678-85.

29. Aparecida Silveira E, Vaseghi G, de Carvalho Santos AS, et al. Visceral obesity and its shared role in cancer and cardiovascular disease: a scoping review of the pathophysiology and pharmacological treatments. *Int J Mol Sci* 2020;21.

30. Rosengren A. Overweight, obesity...and BMI. The INTERHEART study shows that the BMI should probably be abolished--the waist-hip ratio is better. *Lakartidningen* 2006;103:628.

31. Porter Starr KN, Orenduff M, McDonald SR, et al. Influence of weight reduction and enhanced protein intake on biomarkers of inflammation in older adults with obesity. *J Nutr Gerontol Geriatr* 2019;38:33-49.

32. Garanty-Bogacka B, Syrenicz M, Goral J, et al. Changes in inflammatory biomarkers after successful lifestyle intervention in obese children. *Endokrynol Pol* 2011;62:499-505.

33. Pothineni NV, Gondi S, Kovelamudi S. Cardiac rehabilitation after percutaneous coronary intervention – evidence and barriers. *Heart and Mind* 2018;2:1-4.

34. Wallner S, Watzinger N, Lindschinger M, et al. Effects of intensified lifestyle modification on the need for further revascularization after coronary angioplasty. *Eur J Clin Invest* 1999;29:372-9.

35. Bangalore S, Fayyad R, Laskey R, et al. Body-weight fluctuations and outcomes in coronary disease. *N Engl J Med* 2017;376: 1332-40.

36. Lissner L, Odell PM, D'Agostino RB, et al. Variability of body weight and health outcomes in the Framingham population. *N Engl J Med* 1991;324:1839-44.