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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

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ABSTRACT

OBJECTIVES This study sought to investigate the effect of different body mass index (BMI) categories on clinical outcomes in female patients treated with percutaneous coronary intervention (PCI) and drug-eluting stents.

BACKGROUND Patients with higher BMI might, paradoxically, have better long-term clinical outcomes after acute coronary syndrome treated with PCI.

METHODS We pooled patient-level data for female participants from 26 randomized trials on PCI with drug-eluting stents. Patients were stratified into underweight (BMI, <18.5), normoweight (BMI, 18.5 to 24.9), overweight (BMI, 25 to 29.9), obese (BMI, 30 to 34.9), or morbidly obese (BMI, ≥35). The primary endpoint was major adverse cardiac events, a composite of death, myocardial infarction, or target lesion revascularization at 3 years.

RESULTS Among 11,557 female patients included in the pooled database, 9,420 were treated with a drug-eluting stent and had BMI data available. Patients with higher BMI were significantly younger and with more cardiovascular risk factors. Only 139 patients were underweight and had significantly higher adjusted rates of cardiac mortality and all-cause mortality than the rest of the population (hazard ratio: 2.20 [1.31 to 3.71] compared with normoweight). There was a significantly lower frequency of unadjusted 3-year all-cause mortality in overweight, obese, and severely obese patients compared with normoweight. However, following multivariable analysis, a trend toward increased risk of death in severely obese patients was observed, describing an inverse "J"-shaped relation between BMI and 3-year mortality. Conversely, the relationship between BMI and other outcomes, such as major adverse cardiac events, was flat for normoweight and higher BMI.

CONCLUSIONS The risk of 3-year adjusted cardiac events did not differ across BMI groups, whereas the risk of all-cause mortality compared with normoweight was significantly higher in underweight patients and lower in overweight patients with a trend toward increased risk in the severely obese population. (J Am Coll Cardiol Intv 2017;■:■–■)

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAD = coronary artery disease

DES = drug-eluting stent(s)

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

TLR = target lesion revascularization

Obesity represents a growing public health issue. It is estimated that more than two-thirds of U.S. adults are overweight with consequences on general and cardiovascular health and health care costs (1). Body mass index (BMI) is an indicator of relative weight for height and is frequently used as a surrogate for the assessment of excess body fat and obesity. A prospective study on more than 1.4 million white adults has shown that the risk of all-cause mortality in the general population has a "J" shape association with BMI with the lower mortality rate for a BMI of 25 kg/m^2. A progressive increase in mortality is observed for BMI values higher and lower than 25 kg/m^2 (2).

Nevertheless, a growing body of evidence in the past decade has shown that among patients with chronic diseases, higher, instead of lower BMIs, are associated with better prognosis (3–6). This phenomenon is called "obesity paradox" or "reverse epidemiology." An inverse relation between BMI and cardiovascular outcomes has also been described after percutaneous coronary intervention (PCI), supporting the existence of the obesity paradox (7–18). Yet, evidence of this phenomenon in female patients undergoing contemporary PCI is very limited. In several reports on the obesity paradox in PCI patients, female patients accounted for less than 30% of the study population (19,20). In addition, it has been suggested that overweight and obese female patients might have a higher mortality rate than male counterparts after PCI. Although these data need to be interpreted with caution because of the small sample size and the observational nature of the study, they are certainly provocative and hypothesis generating (19). Therefore, we sought to carefully evaluate the relation between BMI and risks of major cardiovascular events and mortality after PCI with drug-eluting stent (DES) in female patients using patient-level data from 26 randomized clinical trials.

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METHODS

PATIENT POPULATION. Principal investigators and device manufacturers participating in the Gender Data Forum (convened on September 24, 2012, in Washington, DC) were contacted to obtain patient-level data for female participants from randomized trials on DES. The design and rationale of the patient-level pooled database have been previously reported (21). Briefly, we pooled in our dataset patient-level data for female participants of 26 randomized clinical trials, designed to study PCI outcomes, performed between 2002 and 2013. The list of included studies in the database and their characteristics are described in Online Tables 1 and 2. All trials included in our analysis complied with the provisions of the Declaration of Helsinki, and were approved by the institutional review boards. Patients provided written informed consent for participation in each study.

Among all studies included, we calculated the baseline BMI with the use of weight and height measured at the time of enrollment. We identified 10,449 patients receiving a DES of which 9,420 had BMI data available and were used for this analysis. We stratified patients according to a modified World Health Organization BMI classification where class II and class III obesity were combined to maintain an adequate number of patients in each study group with increased BMI. Patients were stratified as follows: BMI <18.5 (underweight), between 18.5 and 24.9 (normal weight), between 25 and 29.9 (overweight), between 30 and 34.9 (obese), or ≥35 (severely obese). We described clinical, demographic, angiographic, and procedural characteristics for each group according to BMI categories.

STUDY ENDPOINTS. The primary endpoint was occurrence of major adverse cardiac events (MACE) during follow-up. MACE was defined as the composite of death, myocardial infarction (MI), target-lesion revascularization (TLR), or definite/probable stent thrombosis (ST). Secondary endpoints were individual rates of all-cause mortality, cardiac death, MI, TLR, and definite/probable ST. The follow-up time lasted for up to 3 years after index PCI, or until the last follow-up available. For purposes of this analysis we considered as lost those patients without any event and no follow-up data beyond 30 days from index PCI (n = 56; 0.56%). The number of patients lost at follow-up in each trial included in this study is reported in Online Table 1.

STATISTICAL ANALYSIS. We used Cox proportional hazards regression models to analyze the association between BMI and MACE and between BMI and secondary endpoints with a categorical representation of BMI as the predictor variable. The model included a frailty term (γ) to assess random effects in the trials. Using the normal weight group as the referent category, we estimated hazard ratios and 95% confidence interval for the other BMI groups. A multivariable model was used to adjust for potentially confounding factors comprising age, diabetes, hypertension, smoking habit, hypercholesterolemia, family history of coronary artery disease (CAD), presentation (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, unstable angina, stable CAD), number of stents implanted, stent length, and B2/C lesions. The percentages of missing values for the covariates used in the model are the following: <0.2% for age, diabetes, hypertension, smoking habit, and hypercholesterolemia; <5% for family history of CAD, presentation, and number of stents implanted; and 15% for stent length and B2/C lesion. Patients with missing covariate data were excluded from the analysis. Survival curves from Kaplan-Meier estimates were compared using log-rank test. Patients lost at follow-up were censored for the purpose of this analysis. We reported 2-sided p values, and considered p values of <0.05 to be significant. All analyses were done with SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

A total of 11,557 female participants were pooled from 26 clinical trials on patients with CAD undergoing PCI. Of the 10,449 patients receiving a DES, 9,420 had BMI data available and were used for this study. The mean ± SD BMI for the study population was 28.0 ± 5.8. When subdivided by the predefined BMI categories, 139 (1.0%) were underweight, 2,740 (29.0%) were normal weight, 3,430 (36.4%) were overweight, 1,920 (20.4%) were obese, and 1,191 (12.6%) were severely obese. Baseline clinical and angiographic characteristics across the BMI categories are described in **Tables 1 and 2**. Females with higher BMI were significantly younger but they were more likely to have hypertension, hyperlipidemia, diabetes mellitus, and family history of CAD. Rates of prior MI and PCI were unchanged among BMI groups, whereas history of coronary artery bypass graft was more common in patients with high BMI. At presentation, acute coronary syndromes were more frequent among lower BMIs, underweight, normoweight, and overweight, whereas stable angina was more prevalent in obese and severely obese patients. In addition, obese female patients had lower prevalence of multivessel

TABLE 1 Baseline Characteristics

	Underweight, 139 (1.0%)	Normal Weight, 2,740 (29.0%)	Overweight, 3,430 (36.0%)	Obese, 1,920 (20.0%)	Severely Obese, 1,191 (13.0%)	p Value
Age, yrs	69.76 ± 12.20	68.75 ± 10.68	67.86 ± 10.27	66.23 ± 10.60	63.45 ± 10.16	<0.0001
Weight, kg	43.17 ± 6.62	56.83 ± 7.49	69.45 ± 7.91	81.68 ± 8.36	100.14 ± 13.89	<0.0001
Height, cm	157.67 ± 11.45	158.98 ± 8.54	160.27 ± 7.97	160.05 ± 7.28	159.92 ± 7.36	<0.0001
BMI, kg/m^2	17.26 ± 1.08	22.42 ± 1.53	27.01 ± 1.44	31.83 ± 1.42	38.99 ± 4.24	<0.0001
Median, IQR	18.00 (17.00–18.00)	23.00 (21.00–24.00)	27.00 (26.00–28.00)	32.00 (30.80–33.00)	37.98 (36.00–40.97)	
Risk factors						
Diabetes mellitus	24 (17.3)	606 (22.1)	1,022 (29.8)	733 (38.2)	657 (55.2)	<0.0001
Hypertension	91 (65.5)	1,842 (67.2)	2,617 (76.3)	1,548 (80.6)	1,035 (86.9)	<0.0001
Hypercholesterolemia	68 (48.9)	1,676 (61.2)	2,337 (68.3)	1,396 (72.9)	855 (72.1)	<0.0001
Serum creatinine, mg/dl	1.07 ± 1.11	0.95 ± 0.91	0.91 ± 0.64	0.93 ± 0.65	0.93 ± 0.393	0.22
Smoking	45 (32.4)	721 (26.3)	872 (25.5)	553 (28.9)	334 (28.2)	0.03
Family history of CAD	34 (26.0)	918 (35.0)	1,239 (37.8)	783 (42.9)	535 (48.1)	<0.0001
Clinical history						
Previous MI	27 (19.4)	479 (17.6)	622 (18.2)	373 (19.5)	227 (19.3)	0.46
Previous PCI	35 (25.4)	578 (21.1)	723 (21.1)	440 (22.9)	264 (22.2)	0.37
Previous CABG	5 (3.6)	116 (4.2)	172 (5.0)	126 (6.6)	75 (6.3)	<0.01
LVEF, %	55.2 ± 13.7	55.2 ± 17.9	55.0 ± 18.4	54.9 ± 17.8	54.6 ± 16.9	0.97

Values are mean ±SD, median (interquartile range) or n(%).

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

disease and fewer type B2/C lesions according to the American Heart Association classification but frequently had more bifurcation lesions and moderate or severe calcifications. Conversely, underweight patients were more likely to be current or past smokers, have B2/C lesions, and require longer stent lengths. Both extremes of the BMI spectrum, underweight and severely obese patients, were more often treated with early generation DES compared with normoweight, overweight, and obese counterparts.

During the 3-year follow-up, a total of 1,285 MACE (composite of death, MI, TLR, or definite or probable ST) and 440 deaths were reported. Rates of all clinical primary and secondary endpoints at 1 and 3 years after index PCI are reported in Online Table 3. At 3 years, unadjusted risk of MACE, all-cause mortality, and

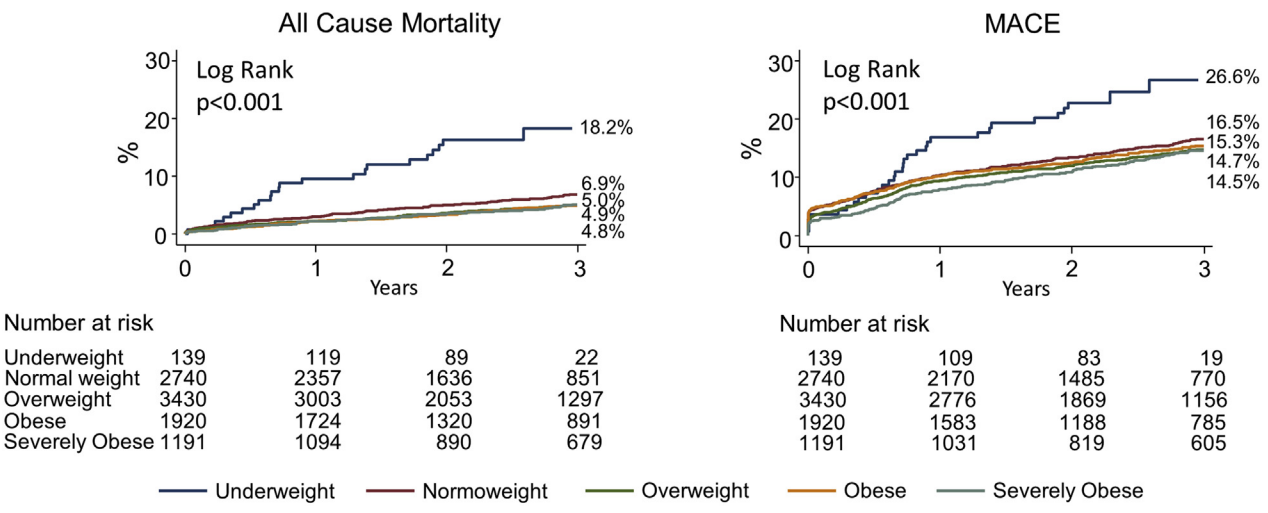
TABLE 2 Procedural Characteristics

	Underweight, 139 (1.0%)	Normal Weight, 2,740 (29.0%)	Overweight, 3,430 (36.0%)	Obese, 1,920 (20.0%)	Severely Obese, 1,191 (13.0%)	p Value
Presentation						<0.0001
NSTEMI	19 (14.0)	394 (14.6)	510 (15.1)	255 (13.5)	125 (11.0)	
STEMI	11 (8.1)	257 (9.5)	242 (7.2)	92 (4.9)	52 (4.6)	
Stable angina	75 (55.1)	1,456 (53.8)	1,882 (55.6)	1,136 (60.0)	732 (64.2)	
Unstable angina	31 (22.8)	598 (22.1)	748 (22.1)	409 (21.6)	232 (20.3)	
Angiographic characteristics						
Multivessel disease	45 (38.8)	704 (29.9)	867 (29.0)	491 (28.8)	286 (25.7)	0.02
Lesions treated	1.30 ± 0.53	1.27 ± 0.57	1.32 ± 0.65	1.31 ± 0.62	1.25 ± 0.55	<0.001
Stents implanted	1.59 ± 1.01	1.55 ± 0.92	1.56 ± 0.95	1.56 ± 0.95	1.46 ± 0.83	0.02
Mean stent diameter, mm	2.92 ± 0.39	2.94 ± 0.38	2.95 ± 0.38	2.96 ± 0.39	2.97 ± 0.39	0.55
Total stent length, mm	32.51 ± 21.85	30.39 ± 19.50	30.49 ± 19.87	29.60 ± 19.45	27.93 ± 16.79	<0.01
Type B2/C lesion	89 (75.4)	1,495 (65.1)	1,796 (63.5)	972 (59.7)	625 (58.7)	<0.0001
Moderate/severe calcifications	15 (15.0)	465 (25.1)	560 (26.5)	308 (27.2)	166 (26.6)	0.08
Bifurcation lesion	18 (22.5)	253 (20.1)	289 (20.3)	175 (22.1)	166 (27.8)	<0.01
Stent type implanted						0.01
Early generation DES	65 (46.8)	1,051 (38.4)	1,339 (39.0)	710 (37.0)	505 (42.4)	
New-generation DES	74 (53.2)	1,689 (61.6)	2,091 (61.0)	1,210 (63.0)	686 (57.6)	

Values are n(%) or mean ±SD.

DES = drug-eluting stent(s); NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

FIGURE 1 Kaplan-Meier Curves



Kaplan-Meier curves of 3-year mortality and MACE according to body mass index. MACE = major adverse cardiovascular event(s).

cardiac death were significantly higher in underweight patients compared with normal weight, whereas it was lower in overweight, obese, and severely obese subjects (Figure 1). After multivariable adjustment, the rate of MACE, MI, TLR, or definite/probable ST was not significantly different across the BMI groups (Table 3, Figure 2B), whereas the risk of all-cause mortality and cardiac death remained over 2-fold higher in underweight patients (Table 3). The risk was the lowest in overweight patients and tended to increase in obese and severely obese patients describing an inverse "J-shaped" curve (Figure 2A). The observed relationship between mortality and BMI was unchanged at a sensitivity analysis performed using, as reference, a narrower BMI range for normoweight patients, between 20 and 24.9 (Online Figure 1).

DISCUSSION

This is the largest study to date to evaluate the association between BMI and cardiovascular outcomes in a large female population with CAD treated with PCI and DES using pooled patient-level data from randomized trials. After adjusting for potential confounders, our results show that BMI affects all-cause mortality and cardiac death but has no clear relationship with other ischemic clinical outcomes. Unsurprisingly, underweight female patients had a higher rate of all-cause mortality and cardiac death than normal weight patients. However, the risk was lower in overweight and increased slightly in severely obese patients suggesting a significant advantage of overweight patients in terms of all-cause mortality.

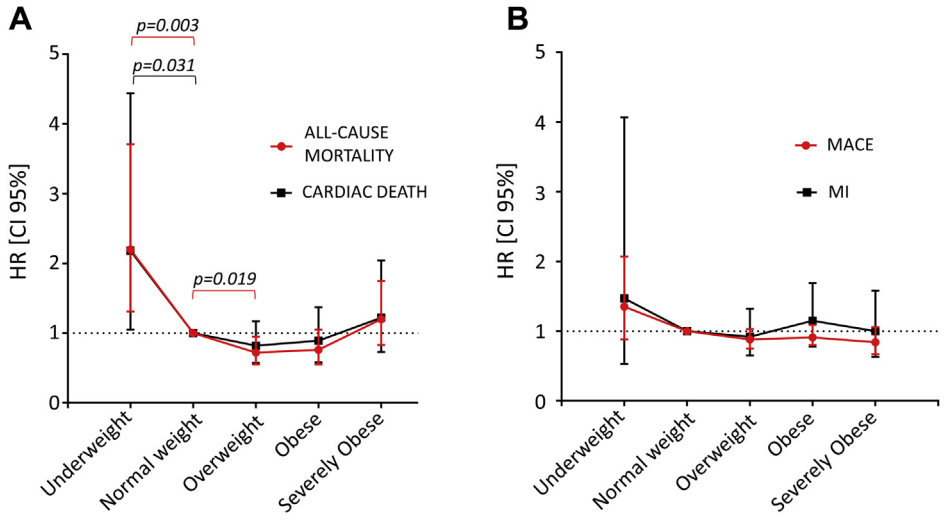
TABLE 3 Adjusted Risks of 3-Year Adverse Clinical Outcomes in All BMI Groups Compared With Normal Weight Subjects

	Underweight (n = 139) HR (95% CI)	Normal Weight (n = 2,740)	Overweight (n = 3,430) HR (95% CI)	Obese (n = 1,920) HR (95% CI)	Severely obese (n = 1,191) HR (95% CI)
MACE	1.35 (0.88-2.07), p = 0.17	1.00	0.88 (0.75-1.03), p = 0.11	0.91 (0.75-1.09), p = 0.31	0.84 (0.67-1.06), p = 0.14
Death	2.20 (1.31-3.71), p = 0.013	1.00	0.72 (0.55-0.94), p = 0.02	0.76 (0.55-1.05), p = 0.10	1.20 (0.83-1.75), p = 0.33
Cardiac death	2.18 (1.07-4.44), p = 0.03	1.00	0.82 (0.57-1.17), p = 0.28	0.89 (0.58-1.37), p = 0.60	1.22 (0.73-2.04), p = 0.45
MI	1.06 (0.25-4.43), p = 0.94	1.00	0.99 (0.64-1.52), p = 0.95	1.23 (0.77-1.98), p = 0.39	1.03 (0.58-1.81), p = 0.93
TLR	1.22 (0.56-2.63), p = 0.61	1.00	1.23 (0.96-1.57), p = 0.09	1.00 (0.74-1.33), p = 0.98	0.86 (0.61-1.21), p = 0.38
Definite/probable ST	2.00 (0.47-8.54), p = 0.35	1.00	1.11 (0.64-1.90), p = 0.71	1.47 (0.83-2.62), p = 0.18	0.83 (0.39-1.77), p = 0.63

Multivariable model based on age, diabetes, hypertension, smoking habit, hypercholesterolemia, family history of CAD, presentation (STEMI, NSTEMI, unstable angina, stable CAD), number of stents implanted, stent length, and B2/C lesions.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event(s); ST = stent thrombosis; TLR = target lesion revascularization; other abbreviations as in Tables 1 and 2.

FIGURE 2 Adjusted Risk of All-Cause Mortality and Cardiac Death, and MACE and Myocardial Infarction According to Body Mass Index



Adjusted risk of **(A)** all-cause mortality and cardiac death, and **(B)** MACE and myocardial infarction according to body mass index. Normoweight is used as reference. CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; other abbreviation as in Figure 1.

Findings of excess risk at the lowest levels of BMI may be attributable to several reasons. First, underweight female patients are usually more fragile and present with multiple noncardiovascular comorbidities, such as cancer, autoimmune disorders, and psychiatric diseases, which can influence clinical outcomes (22). Such patients are also less responsive to supportive therapies and require longer and more frequent rehospitalization (23). It has been previously reported that underweight female patiets with angiographic evidence of CAD have a 2-fold higher risk of death than normal weight counterparts (24). Our results are consistent with these prior reports because rates of all-cause and cardiac mortality were 2-fold higher compared with normal weight patients. Low BMI patients also presented more frequently with acute coronary syndrome and had complex lesions that required significantly longer stent implantation. Despite this higher risk clinical and angiographic phenotype, the rates of spontaneous MI, TLR, and definite/probable ST were not increased in underweight patients, highlighting the importance of nonvascular or even noncardiac mechanisms contributing to excess mortality. In elderly populations, for example, a very low BMI has been interpreted as a surrogate of the malnutrition-inflammation complex syndrome and is associated with a worse prognosis in patients with chronic diseases (25). Therefore, clinicians treating underweight or severely obese female patients after PCI should not only start a treatment for the secondary prevention of cardiovascular events but also manage underlying comorbidities and risk factors that could affect long-term survival.

Rates of all-cause death were lowest among overweight and obese female patients with adjusted hazard ratios demonstrating 28% and 24% lower risks for death at 3 years, respectively, compared with their normal weight counterparts. Results for cardiac death were numerically concordant, albeit not statistically significant. Our findings are largely consistent with and extend prior reports of an "obesity paradox" in the setting of CAD in a large female cohort. As suggested by others, the apparent protective effect of higher obesity on mortality risk may be caused by residual confounding or reflect the imprecision of BMI as a discriminator for lean mass versus central obesity (26,27). Other measures, such as waist circumference and waist-to-height ratio, although less common, can quantify central adiposity and might be better predictors of outcomes in patients with CAD. Coutinho et al. (28), for example, have shown that central obesity was directly associated with mortality (hazard ratio: 1.70; 95% confidence interval: 1.58 to 1.83), whereas BMI had an inverse relationship with mortality rate in CAD patients. Consistent with this

observation, other groups have reported in non-CAD patients, that after adjustment for lean body mass, the obesity paradox disappeared highlighting the importance of confounding by lean mass on the inverse association between BMI and mortality (29).

Previous studies have suggested a "J shape" pattern of association between BMI and mortality wherein mortality risks at the extremes of BMI (i.e., ≥35) are increased. Although our adjusted point estimates for both mortality and cardiac mortality in this group were greater than 1, our findings did not reach statistical significance. This null result may reflect a type II error or alternatively suggest a different pattern of risk in female patients at the highest levels of BMI. Our results are consistent with previous findings in PCI patients treated with BMS where no significant difference was found in the 12-month rate of MI, target lesion, and target vessel revascularization among normal BMI, overweight, and obese patients (31% female patients) (7). There are several reasons that can explain the different relationship between BMI and mortality and BMI and cardiovascular ischemic outcomes. First, comorbidities and risk factors, potentially unaccounted for in cardiovascular studies, such as hypomobility, pulmonary embolism, chronic obstructive pulmonary disease, and cancer, might impact mortality without increasing the risk of ischemic outcomes. Second, it cannot be excluded that patients at the extremes of the BMI spectrum, underweight and severely obese patients, might undergo an accelerated worsening of comorbid conditions during the follow-up compared with other BMI strata and that might result in reduced survival in these patients. Finally, patients with a high BMI are more likely to seek medical contact at a younger age because of potential comorbid conditions. Therefore, they might be diagnosed and receive treatment for cardiovascular risk factors, such as diabetes and hypercholesterolemia, earlier in life compared with normoweight patients. In addition, because overweight and obese patients are considered at higher risk for cardiovascular diseases, physicians might treat them more aggressively, thus paradoxically reducing their cardiovascular risk more than that of normal BMI patients (30).

STUDY LIMITATIONS. An important strength of this study is that we, for the first time, studied a large sample of female patients treated with PCI and DES.

There are several limitations of our study, including the lack of information on variables comprising measures of fat distribution, fitness or physical activity level, serial BMI measures and chronic medical conditions, medical treatment for cardiovascular risk factors of comorbidities, and access site for the procedure. In the 26 randomized clinical trials pooled to obtain the dataset used for this analysis, patients were treated with a DES, differences in the obesity paradox in patients treated with BMS versus DES cannot be investigated. Although we adjusted for possible known confounding factors, unmeasured or unknown confounders associated with BMI might have biased the results. Information on the vessel treated (e.g., left main coronary artery interventions) was not available in our dataset. Similarly, we cannot report data on the quality of angiographic imaging that might have influenced the treatment choice. It has been reported that collider stratification bias caused by even 1 single unmeasured variable might change the relationship between BMI and outcomes in patients with cardiovascular diseases. Although we cannot exclude the possibility that collider bias may influence our observed associations between BMI and mortality, we are unable to quantify the magnitude of this bias because we only included women with CAD in our sample and a comparable cohort of women without CAD would be necessary to quantify the collider bias. In addition, it should be noted that this analysis is based on randomized clinical trials data, which usually exclude high-risk patients. Finally, our dataset does not contain information on men. Therefore, the influence of BMI on outcomes in men cannot be ascertained and a direct comparison between female and male patients to investigate sex differences in the effect of BMI on outcomes is not attainable.

CONCLUSIONS

Our results from an all-female pooled data analysis demonstrate no causal relationship between BMI and MACE risk. Conversely, mortality risk was the highest in underweight BMI and the lowest in overweight and obese female patients, thus refining the concept of an obesity paradox to a large female CAD cohort treated with DES. The apparent protective effect of higher BMI was no longer apparent, however, at extreme levels of obesity (>35). No significant associations were observed between low or high BMI and other cardiac outcomes, such as MI, TLR, and ST.

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PERSPECTIVES

WHAT IS KNOWN? Prior studies have suggested that among patients with chronic cardiovascular diseases, those with higher BMI paradoxically present a survival benefit compared with normoweight.

WHAT IS NEW? Our study has shown that in a contemporary female population treated with PCI with drug-eluting stents, all-cause mortality and cardiac death present a J-shaped relationship with BMI, whereas other clinical outcomes, such as myocardial infarction and target lesion revascularization, showed no causal relationship with BMI.

WHAT IS NEXT? Although physicians correctly target obesity, other risk factors and comorbidities with potentially higher impact on subsequent cardiovascular events after PCI should be identified and treated.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.