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Association between body mass index and clinical outcomes after new-generation drug-eluting stent implantation: Korean multi-center registry data

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HIGHLIGHTS

- Lower BMI was linked to worse outcomes after new-generation DES implantation.
- This result was driven by not only mortality but also ischemic adverse events.
- A BMI below 24 kg/m^2 was an independent predictor of MACCEs.
- Patients with low BMI might have more atherosclerotic burden than those with high BMI.
- Physicians should identify other risk factors and comorbidities in patients with low BMI.

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ABSTRACT

Background and aims: It is unclear whether the obesity paradox is still apparent in the new-generation drug-eluting stent (DES) era. Therefore, we assessed the impact of body mass index (BMI) on clinical outcome after percutaneous coronary intervention (PCI) with new-generation DESs.

Methods: A total of 5264 consecutive patients from 4 new-generation DES registries were divided into 4 categories according to BMI: 1) underweight (BMI < 18.5 kg/m^2, n = 130), 2) normal weight (18.5 ≤ BMI < 25 kg/m^2, n = 2943), 3) overweight (25 ≤ BMI < 30 kg/m^2, n = 1932), and 4) obese (BMI ≥ 30 kg/m^2, n = 259). The primary endpoint was the occurrence of major adverse cardiac and cerebrovascular event (MACCE) at 12 months, including all-cause mortality, nonfatal myocardial infarction, stroke, and target-vessel revascularization.

Results: The 12-month MACCE rates decreased according to increasing BMI categories. (underweight, 13.1%; normal, 6.0%; overweight, 4.8%; obese, 4.2%; $p < 0.001$). After adjustment for other confounders, the underweight group had significantly higher MACCE rates than the normal-weight (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.33–0.99; $p = 0.049$), overweight (HR, 0.49; 95% CI, 0.27–0.88; $p = 0.017$), and obese (HR, 0.41; 95% CI, 0.18–0.98; $p = 0.044$) groups. These differences were mainly driven by all-cause mortality and target-vessel revascularization. When BMI was treated as a continuous variable, BMI per 1 kg/m^2 was also an independent predictor for MACCE (HR, 0.95; 95% CI, 0.91–0.99; $p = 0.008$) and a MACE increase began below a BMI of 24 kg/m^2.

Conclusions: Lower BMI was significantly associated with higher rates of MACCE and all-cause mortality after PCI. The obesity paradox is manifested in Korean patients in the new-generation DES era.

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1. Introduction

In the general population, it is well known that obesity is an independent risk factor of cardiovascular diseases [1] and is related to adverse clinical outcomes [2]. In the population with established coronary artery disease (CAD), however, several studies have reported that obese patients have better outcomes than non-obese patients after percutaneous coronary intervention (PCI) [3–6]. This peculiar phenomenon, known as the obesity paradox, has been replicated in Western populations [3,5] as well as in Eastern populations [4,6], although there is still an ongoing debate regarding its uncertain mechanism and the possibility of misconception owing to some bias. Recently, new-generation drug-eluting stents (DES), characterized by thinner stent struts, biocompatible durable or biodegradable polymers, and limus-based antiproliferative agents, have been widely used and have demonstrated superior clinical outcomes in various high-risk patients and lesions over the first-generation DES [7]. However, there is a paucity of data on whether body mass index (BMI) still has a prognostic impact on clinical outcomes in patients treated with new-generation DES. Therefore, this study, using data from Korean multicenter registries, aimed to evaluate the association between BMI and the clinical outcomes of CAD patients who underwent PCI with a new-generation DES.

2. Materials and methods

2.1. Study population

The study flow and reasons for exclusion are provided in Supplementary Fig. 1. The data in the present study were derived from 3 different prospective and 1 retrospective Korean multicenter DES registries (5712 patients): 1) REVOLUTE (registry to evaluate clinical outcomes following new-generation drug-eluting stents), a prospective, multicenter registry for patients who underwent PCI, evaluating clinical efficacy of new-generation DES, including sirolimus-eluting silicon carbide coating stent, novolimus-eluting stent, and biolimus-eluting abluminal biodegradable polymer stent; 2) NOBORI (*ClinicalTrial.gov* NCT01348360), a prospective, multicenter registry, investigating efficacy and safety of biolimus A9-eluting stent for coronary lesions in high-risk patients; 3) CONSTANT (clinical, optical coherence tomography, and angiographic outcomes following Resolute zotarolimus-eluting stent implantation for patients with or without diabetes mellitus; *ClinicalTrial.gov* NCT01869842), a prospective, multicenter registry, evaluating the impact of optical coherence tomography-guided percutaneous coronary intervention on the neointimal coverage and malapposition following zotarolimus-eluting stent implantation; and 4) PCI-CABG (clinical outcomes of PCI versus coronary artery bypass graft for multivessel disease from the Korean multicenter angioplasty team registry), a retrospective, multicenter observational registry, evaluating efficacy and safety of various DESs for complex coronary lesions and long-term clinical outcomes compared with coronary artery bypass graft surgery [8]. These registries included all eligible patients without specific inclusion or exclusion criteria, reflecting real-world practice. A detailed list of the participating institutes is given in Supplementary Data.

Among a total of 5712 patients, 186 patients without a new-generation DES, 151 patients with no data regarding stent type or BMI, and 111 patients without follow-up were excluded. Thus, a total of 5264 consecutive patients, who underwent PCI with new-generation DES in 26 centers of South Korea and fulfilled the study criteria, were finally included in these analyses. The enrolled patients were classified into 4 categories according to BMI status, according to the World Health Organization: 1) underweight (BMI $< 18.5\,kg/m^2$), 2) normal weight ($18.5 \leq$ BMI $< 25.0\,kg/m^2$), 3) overweight ($25.0 \leq$ BMI $< 30.0\,kg/m^2$), and 4) obese (BMI $\geq 30.0\,kg/m^2$) [9].

New-generation DESs included zotarolimus-eluting (Endeavor Resolute; Medtronic, Minneapolis, MN, USA), everolimus-eluting (Xience; Abbot Vascular, Santa Clara, CA, USA; and Promus; Boston Scientific, Marlborough, MA, USA), biolimus-eluting (BioMatrix; Biosensors International, Singapore; and Nobori; Terumo, Tokyo, Japan), novolimus-eluting (DESyne; Elixir Medical Corporation, Sunnyvale, CA, USA), and sirolimus-eluting (Orsiro; Biotronik, Bülach, Switzerland) stents. The study protocol was approved by the institutional review board at each participating site, and all participants provided written informed consent.

2.2. Endpoints and definitions

The primary endpoint was the occurrence of major adverse cardiac and cerebrovascular events (MACCE) at 12 months, including all-cause mortality, nonfatal myocardial infarction (MI), stroke, and target-vessel revascularization (TVR). The secondary endpoint was all-cause mortality at 12 months. The individual components of the primary endpoint were also evaluated.

Clinical events were defined according to the Academic Research Consortium [10]. All-cause mortality included any death after PCI. MI was defined as a creatine kinase muscle/brain fraction elevation above the upper limit of normal or troponin T/I > 99th percentile of the upper limit of normal, with concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia unrelated to an interventional procedure [10]. Stroke was defined as any occurrence of a focal neurological deficit confirmed by abnormal findings of brain imaging studies and a neurologist after PCI. Stent thrombosis was defined as definite or probable stent thrombosis [10]. Clinical follow-up was performed in-hospital, and after 1, 3, 6, and 12 months, either by a clinic visit or a telephone interview.

2.3. Procedures and clinical data

Stent implantation was performed according to current standard techniques and medical guidelines. Intravenous heparin was given at the start of the procedure (8000 to 10,000 IU bolus) to maintain an activated clotting time of 220–300 s. All patients were administered 300 mg of aspirin and clopidogrel 300–600 mg before procedure and maintained 100 mg of aspirin and 75 mg of clopidogrel after PCI. Details of the intervention, such as lesion predilation, post-stent dilation, and the application of mechanical support or concomitant medication, were left to the discretion of the operator.

Baseline data including age, sex, BMI, blood chemistries, smoking status, medication use, comorbidities, and echocardiographic, angiographic, and procedural findings were collected. Chronic renal failure was defined as a baseline estimated glomerular filtration rate $< 60\,ml/min/1.73\,m^2$. Severe calcification was defined as calcification noted without cardiac motion before contrast injection and generally involving both sides of the arterial wall [11].

2.4. Statistical analysis

Continuous variables are reported as mean ± standard deviation, and categorical variables as actual number and percentage. Baseline and procedural characteristics among groups were compared using 1-way analysis of variance or Mann-Whitney *U* test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables. Hazard ratios (HR) for the primary endpoint and for all endpoints were calculated with multivariable analyses using a Cox proportional hazards model and shown with the 95% confidence interval (CI). To determine the predictors for the occurrence of MACCE, multivariate regression analysis was performed; all variables with a p value of < 0.10, age, and sex were entered into the model. Kaplan-Meier survival analysis using the log-rank test was used to compare cumulative incidence of all-cause mortality and MACCE among groups.

To examine the relationship between BMI as the continuous variables and MACCE, restricted cubic splines were plotted to explore

potential nonlinear relationships [12]. The cutoff value that begins an increase of MACCE was determined from the cubic spline analysis plotting. Based on this cutoff value, low- and high-BMI groups were categorized. Subgroup analyses were performed by including an interaction term in the proportional hazards model. All tests were 2-sided, and the results were considered statistically significant at $p < 0.05$. All statistical analyses were carried out using SAS (version 9.4, SAS Inc., Cary, North Carolina).

3. Results

3.1. Baseline characteristics

The distribution of BMI values for all subjects is shown in Supplementary Fig. 2. The mean BMI of this cohort was 24.5 ± 3.3 kg/m^2. The baseline clinical characteristics of the patients according to BMI categories are summarized in Table 1. Compared with the normal weight and underweight groups, the obese and overweight groups were younger and had more frequent diagnoses of hypertension, diabetes,

Table 1
Baseline characteristics according to BMI categories.

	Underweight (n = 130)	Normal weight (n = 2943)	Overweight (n = 1932)	Obese (n = 259)	*p* value
Mean BMI (kg/m^2)	17.3 ± 1.1	22.7 ± 1.6	26.8 ± 1.3	32.3 ± 2.9	< 0.001
Age (years)	72.3 ± 11.0	66.1 ± 11.0	63.3 ± 10.9	60.7 ± 12.2	< 0.001
Male, n (%)	82 (63.1)	2094 (71.3)	1412 (73.1)	157 (60.6)	< 0.001
Comorbidities, n (%)					
Hypertension	72 (55.8)	1794 (61.4)	1336 (69.4)	203 (79.0)	< 0.001
Diabetes	34 (26.2)	1090 (37.2)	763 (39.7)	123 (47.5)	0.016
Dyslipidemia	73 (56.6)	1982 (67.7)	1400 (72.7)	203 (78.7)	< 0.001
Current smoking	35 (26.9)	727 (24.7)	498 (25.8)	67 (25.9)	0.770
Previous smoking	23 (17.5)	642 (21.8)	439 (22.7)	52 (20.1)	0.446
Smoking status (pack-years)	35.1 ± 26.0	34.6 ± 21.2	33.4 ± 22.5	30.5 ± 21.5	0.122
Chronic renal failure	14 (10.9)	226 (7.7)	108 (5.6)	25 (9.7)	0.004
Previous PCI	21 (16.2)	602 (20.5)	419 (21.8)	62 (23.9)	0.231
Previous MI	9 (7.0)	218 (7.4)	149 (7.8)	23 (8.9)	0.838
Previous bypass surgery	2 (1.5)	59 (2.0)	42 (2.2)	7 (2.7)	0.828
Previous cerebrovascular accident	20 (15.0)	274 (11.0)	187 (9.7)	15 (5.8)	0.013
Clinical presentation, n (%)					
Stable angina	61 (46.9)	1439 (48.9)	1004 (52.0)	129 (49.8)	0.223
ACS	69 (53.1)	1504 (51.1)	928 (48.0)	130 (50.2)	0.223
Unstable angina	24 (18.5)	761 (25.9)	522 (27.0)	84 (32.4)	0.024
NSTEMI	28 (21.5)	393 (13.4)	213 (11.0)	27 (10.4)	0.003
STEMI	17 (13.1)	350 (11.9)	193 (10.0)	19 (7.3)	0.032
Laboratory data					
Hemoglobin (g/L)	11.9 ± 2.1	13.3 ± 2.0	13.7 ± 2.0	13.8 ± 2.1	< 0.001
White blood cell count (k/mm^3)	8.06 ± 3.49	8.01 ± 3.21	8.00 ± 3.00	8.03 ± 2.95	0.997
Low-density lipoprotein cholesterol (mg/dL)	95.5 ± 36.0	96.8 ± 36.1	98.2 ± 35.3	99.0 ± 38.2	0.548
High-density lipoprotein cholesterol (mg/dL)	46.2 ± 14.7	42.2 ± 11.3	40.6 ± 10.1	39.1 ± 9.6	< 0.001
Serum creatinine, mg/dL	1.3 ± 1.3	1.4 ± 3.0	1.3 ± 2.6	1.3 ± 1.5	0.835
C-reactive protein (mg/l)	5.0 ± 15.8	5.7 ± 20.0	5.6 ± 23.4	4.5 ± 13.4	0.970
Ejection fraction, %	48.6 ± 17.1	54.7 ± 17.5	56.1 ± 18.0	56.5 ± 17.6	< 0.001
Ejection fraction < 40%, n (%)	33 (25.7)	368 (12.5)	158 (8.2)	19 (7.3)	< 0.001
Medication at discharge, n (%)					
Statins	116 (89.2)	2622 (89.1)	1739 (90.0)	230 (88.8)	0.850
Beta blockers	82 (63.1)	1948 (66.2)	1250 (64.7)	174 (67.3)	0.647
Angiotensin converting enzyme or angiotensin receptor blockers	83 (63.8)	1898 (64.5)	1300 (67.3)	182 (70.3)	0.227
12-month dual antiplatelet therapy, n (%)	80 (61.5)	1625 (55.2)	1107 (57.3)	143 (55.2)	0.469
Angiographic characteristics					
Multivessel disease, n (%)	90 (69.2)	1975 (67.1)	1331 (68.9)	174 (67.3)	0.578
Severe calcification, n (%)	26 (20.0)	271 (9.2)	124 (6.4)	13 (5.0)	< 0.001
Bifurcation, n (%)	26 (20.0)	633 (21.5)	402 (20.8)	54 (20.8)	0.922
Thrombus, n (%)	8 (6.2)	333 (11.3)	226 (11.7)	30 (11.6)	0.476
Target vessel, n (%)					0.724
Left main	8 (6.2)	189 (6.4)	103 (5.3)	10 (3.9)	
Left descending artery	73 (56.2)	1605 (54.5)	1063 (55.0)	145 (56.0)	
Left circumflex artery	28 (21.5)	710 (24.1)	512 (26.5)	72 (27.8)	
Right coronary artery	46 (35.4)	1009 (34.3)	690 (35.7)	92 (35.5)	
Saphenous vein graft	0	8 (0.3)	9 (0.5)	2 (0.8)	
Procedure characteristics					
Vascular access, n (%)					0.282
Radial approach	45 (34.6)	1218 (41.4)	844 (43.7)	99 (38.2)	
Femoral approach	85 (65.4)	1725 (58.6)	1088 (56.3)	160 (61.8)	
Number of vessels treated, n (%)					0.084
1 or 2	127 (97.7)	2891 (98.2)	1906 (98.7)	250 (96.5)	
3	3 (2.3)	52 (1.8)	26 (1.3)	9 (3.5)	
Total number of stents implanted, n	1.4 ± 0.6	1.4 ± 0.6	1.5 ± 0.7	1.4 ± 0.6	0.034
Multiple stenting, n (%)	51 (39.2)	1084 (36.8)	773 (40.0)	96 (37.1)	0.159
Stent length (mm)	31.5 ± 15.0	32.8 ± 17.7	33.7 ± 18.5	33.0 ± 18.0	0.255
Stent diameter (mm)	3.0 ± 0.4	3.1 ± 0.8	3.1 ± 0.6	3.1 ± 0.7	0.407
Intra-aortic balloon pump (%)	7 (5.4)	68 (2.3)	42 (2.2)	3 (1.3)	0.203

Data are presented as mean ± standard deviation or number (%).
ACS, acute coronary syndrome; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention.

and dyslipidemia. The proportion of patients with stable angina or acute coronary syndrome was similar between groups, but non-ST-elevation MI and ST-elevation MI were more frequent in the normal-weight and underweight groups than the obese and overweight groups. Left ventricular systolic dysfunction, defined as an ejection fraction < 40%, was more frequently observed in the underweight or normal-weight group. There were no significant differences among groups in the use of medication, including the rate of dual antiplatelet agents at 12 months.

Angiographic findings showed that the prevalence of multivessel disease, bifurcation lesions, and visible thrombus were comparable among the 4 groups, although severe calcific lesions were more frequently observed in the underweight group (Table 1). Other angiographic and procedural characteristics, including frequency of femoral access use, number and size of stents, did not differ among the groups.

3.2. Clinical outcomes according to BMI

Clinical outcomes according to BMI categories are summarized in Table 2. The primary endpoint, MACCE rate at 12 months, significantly differed among the BMI categories, with a gradual decrease according to the increasing BMI categories (underweight, 13.1%; normal weight, 6.0%; overweight, 4.8%; obese, 4.2%; $p < 0.001$, log-rank test) (Fig. 1A). After adjustment for age and sex (Model 1), the risk of MACCE remained significantly high in underweight patients (HR, 2.06; 95% CI, 1.25–3.41; $p = 0.005$ compared with normal weight) and decreased in overweight (HR, 0.81; 95% CI, 0.58–1.11; $p = 0.184$) and obese patients (HR, 0.72; 95% CI, 0.33–1.56; $p = 0.406$) without statistical significance. Furthermore, even after adjustment for other confounding variables (Model 2), the underweight group had a significantly higher MACCE rate than the other BMI groups, and the HR tended to gradually decrease according to increasing BMI categories (underweight 2.05, normal weight 1.0, overweight 0.81, obese 0.72) (Table 2). Our findings were consistent for the patients who received statin (n = 4707) (Supplementary Table 1), when we excluded those who did not receive statin. Significant differences of all-cause mortality and TVR across BMI groups were also noted. All-cause mortality rates at 12 months were significantly different among the 4 groups, with a gradual decrease according to the increasing BMI categories (underweight, 9.2%; normal, 2.8%; overweight, 1.9%; obese, 1.5%; $p < 0.001$, log-rank test), and the underweight group showed the highest mortality rate (Fig. 1B) (Table 2). Furthermore, with regard to TVR, the underweight group had a statistically significantly higher MACCE rate than did the normal-weight (HR, 3.04; 95% CI, 1.18–7.82; $p = 0.021$), and the overweight and obese groups showed a gradual decrease tendency compared with the normal weight group (overweight group, HR, 0.91; 95% CI, 0.58–1.43; $p = 0.678$, and obese group, HR, 0.74; 95% CI, 0.26–2.07; $p = 0.560$, respectively).

Multivariate Cox regression analysis after adjustment for confounding factors showed that when BMI was entered as a continuous

Table 2
Clinical outcomes for 12 months after new-generation DES implantation according to BMI categories.

	No. of event	Event rate (%)	Unadjusted HR (95% CI)	*p* value	Model 1[a]		Model 2[b]	
					Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
MACCE								
Underweight	17	13.1	2.49 (1.51–4.10)	< 0.001	2.06 (1.25–3.41)	0.005	2.05 (1.11–3.78)	0.022
Normal weight	177	6.0	1	–	1	–	1	–
Overweight	92	4.8	0.85 (0.66–1.09)	0.197	0.84 (0.65–1.09)	0.183	0.81 (0.58–1.11)	0.184
Obese	11	4.2	0.76 (0.41–1.40)	0.373	0.83 (0.45–1.54)	0.561	0.72 (0.33–1.56)	0.406
All-cause death								
Underweight	12	9.2	3.57 (1.95–6.56)	< 0.001	2.22 (1.20–4.10)	0.011	2.10 (1.06–4.16)	0.033
Normal weight	82	2.8	1	–	1	–	1	–
Overweight	36	1.9	0.69 (0.47–1.03)	0.067	0.81 (0.55–1.20)	0.296	0.84 (0.54–1.28)	0.409
Obese	4	1.5	0.57 (0.21–1.55)	0.267	0.83 (0.30–2.29)	0.723	0.70 (0.22–2.22)	0.540
Cardiac death								
Underweight	6	4.6	3.78 (1.60–8.95)	0.003	2.28 (0.96–5.44)	0.063	2.36 (0.87–6.44)	0.093
Normal weight	43	1.5	1	–	1	–	1	–
Overweight	18	0.9	0.73 (0.41–1.27)	0.262	0.87 (0.50–1.53)	0.627	0.90 (0.43–1.85)	0.764
Obese	1	0.4	0.30 (0.04–2.18)	0.233	0.47 (0.07–3.47)	0.462	0.72 (0.10–5.41)	0.749
Non-fatal MI								
Underweight	1	0.8	1.02 (0.14–7.58)	0.983	0.93 (0.12–6.94)	0.940	1.01 (0.13–7.72)	0.990
Normal weight	24	0.8	1	–	1	–	1	–
Overweight	19	1.0	1.31 (0.71–2.42)	0.383	1.39 (0.75–2.57)	0.292	1.61 (0.77–3.39)	0.210
Obese	3	1.2	1.55 (0.47–5.18)	0.474	1.90 (0.56–6.41)	0.304	1.56 (0.35–7.03)	0.565
TVR								
Underweight	6	4.6	2.19 (0.95–5.06)	0.065	2.35 (1.01–5.45)	0.046	3.04 (1.18–7.82)	0.021
Normal weight	74	2.5	1	–	1	–	1	–
Overweight	48	2.5	1.06 (0.73–1.52)	0.773	0.94 (0.66–1.36)	0.759	0.91 (0.58–1.43)	0.678
Obese	7	2.7	1.17 (0.54–2.55)	0.689	1.00 (0.46–2.18)	0.993	0.74 (0.26–2.07)	0.560
Stroke								
Underweight	0	0	–	–	–	–	–	–
Normal weight	23	0.8	1	–	1	–	1	–
Overweight	8	0.4	0.53 (0.24–1.18)	0.117	0.59 (0.26–1.32)	0.195	0.67 (0.25–1.75)	0.410
Obese	0	0	–	–	–	–	–	–
Stent thrombosis								
Underweight	1	0.8	1.93 (0.25–14.82)	0.529	1.60 (0.20–12.52)	0.657	–	–
Normal weight	13	0.4	1	–	1	–	1	–
Overweight	5	0.3	0.63 (0.22–1.79)	0.387	0.70 (0.24–2.0)	0.503	0.39 (0.08–1.80)	0.225
Obese	1	0.4	0.95 (0.12–7.28)	0.957	1.34 (0.17–10.54)	0.779	–	–

Event rates were calculated by Kaplan-Meier analysis.
BMI, body mass index; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; TVR = target-vessel revascularization.
[a] Model 1 was adjusted for age and sex.
[b] Model 2 was adjusted for age, sex, hypertension, diabetes, dyslipidemia, low-density lipoprotein cholesterol level, chronic renal failure, previous cerebrovascular accident, left ventricular systolic dysfunction, multivessel disease, and acute coronary syndrome.

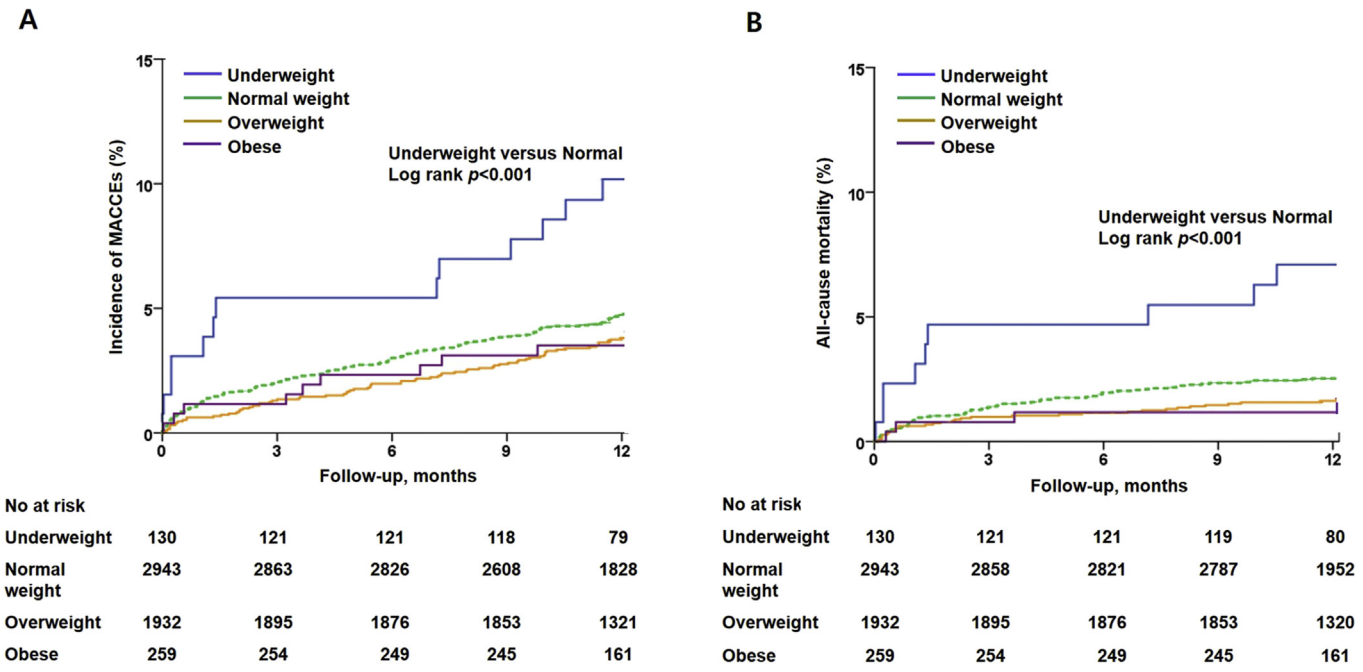

Fig. 1. Kaplan-Meier curves according to BMI categories.

Table 3
Predictors for 12-month MACCE and all-cause mortality after new-generation DES implantation.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
MACCE predictors				
Age ≥75 years	1.78 (1.39–2.27)	< 0.001	1.50 (1.13–2.00)	0.006
Male	1.28 (0.98–1.68)	0.067	1.47 (1.09–1.99)	0.012
BMI per 1 kg/m^2	0.93 (0.89–0.96)	< 0.001	0.95 (0.91–0.99)	0.008
Hypertension	1.48 (1.15–1.92)	0.003	1.53 (1.12–2.07)	0.007
Diabetes	1.46 (1.16–1.83)	0.001	1.15 (0.88–1.50)	0.317
Chronic renal failure	2.84 (2.10–3.86)	< 0.001	1.80 (1.23–2.62)	0.002
Previous CVA	1.68 (1.23–2.30)	0.001	1.38 (0.96–1.99)	0.079
Acute coronary syndrome	1.42 (1.13–1.79)	0.003	1.36 (1.05–1.77)	0.021
LVEF < 40%	2.92 (2.22–3.86)	< 0.001	2.34 (1.71–3.19)	< 0.001
Severe calcification	2.24 (1.65–3.04)	< 0.001	2.03 (1.42–2.88)	< 0.001
Total stent length ≥28 mm	1.64 (1.29–2.09)	< 0.001	1.72 (1.31–2.25)	< 0.001
Mortality predictors				
Age ≥75 years	3.55 (2.53–4.98)	< 0.001	3.00 (2.03–4.33)	< 0.001
Male	1.28 (0.98–1.68)	0.067	1.71 (1.12–2.61)	0.014
BMI per 1 kg/m^2	0.87 (0.82–0.92)	< 0.001	0.93 (0.88–0.99)	0.023
Hypertension	1.43 (0.98–2.10)	0.065	1.22 (0.79–1.89)	0.376
Diabetes	2.07 (1.47–2.91)	< 0.001	1.54 (1.06–2.26)	0.025
Chronic renal failure	4.27 (2.86–6.38)	< 0.001	2.57 (1.63–4.06)	< 0.001
Previous CVA	1.94 (1.26–3.00)	0.003	1.28 (0.91–1.80)	0.150
Acute coronary syndrome	1.94 (1.36–2.77)	< 0.001	1.62 (1.10–2.39)	0.015
LVEF < 40%	4.34 (2.98–6.34)	< 0.001	2.84 (1.91–4.23)	< 0.001
Severe calcification	2.74 (1.80–4.18)	< 0.001	1.92 (1.22–3.01)	0.005
Total stent length ≥28 mm	1.30 (1.01–1.83)	0.042	1.31 (0.90–1.91)	0.162

BMI, body mass index; CRF, chronic renal failure; CVA, cerebrovascular accident; DES, drug eluting stent; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular event.

variable (per 1 kg/m^2), a higher BMI was significantly associated with a lower incidence of MACCE (HR, 0.95; 95% CI, 0.91–0.99; $p = 0.008$) (Table 3). Other important predictors for MACCEs included age, male sex, hypertension, chronic renal failure, acute coronary syndrome, left ventricular systolic dysfunction, severe coronary artery calcification, and total stent length > 28 mm. As for all-cause mortality, BMI remained a significant independent predictor (HR, 0.93; 95% CI, 0.88–0.99; $p = 0.023$) along with age, male sex, diabetes, chronic renal failure, acute coronary syndrome, left ventricular systolic dysfunction, and severe coronary artery calcification.

From the cubic spline analysis plotting, increase of MACCE began below a BMI of 24 kg/m^2 (Fig. 2A). When patients were categorized into low- and high-BMI groups based on this cutoff value, the low-BMI group had a higher incidence of MACCEs (HR, 1.32; 95% CI, 1.06–1.66; $p = 0.015$) (Fig. 2B) and all-cause mortality (HR, 1.75; 95% CI, 1.24–2.46; $p < 0.001$) (Fig. 2C) than the high-BMI group.

In the subgroup analysis of the occurrence of MACCE, the effects of a low-BMI (BMI < 24 kg/m^2) *versus* a high-BMI (BMI ≥24 kg/m^2) were consistent across the various subgroups (Supplemental Fig. 3). However, a significant interaction was observed between BMI and diabetes,

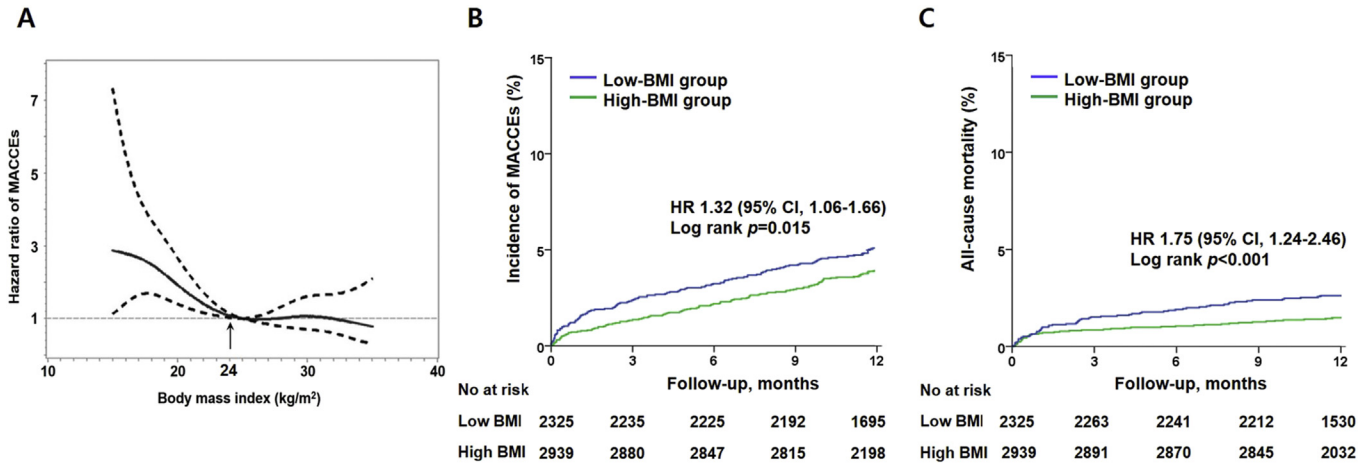

Fig. 2. Cutoff for increasing MACCE and outcomes using its cutoff value.
(A) From the cubic spline analysis plotting, increase of MACCE began below a BMI of 24 kg/m^2. Arrow indicates the cutoff value that begins an increase of MACCE. Solid line and dashed lined indicate hazard ratio and 95% confidence interval, respectively. The low-BMI group based on 24 kg/m^2 of BMI value had higher 12-month cumulative MACCE (B) and all-cause mortality (C) than the high-BMI group. BMI = body mass index; MACCE = major adverse cardiac and cerebrovascular event.

suggesting a worse clinical outcome in the diabetic patients of the low-BMI group (p-interaction = 0.005).

4. Discussion

To our knowledge, this is the first study to report the obesity paradox phenomenon after new-generation DES implantation. In this analysis of real-world Korean new-generation DES registries, we found that a lower BMI was significantly associated with a higher MACCE rate, mainly driven by increases in all-cause mortality and TVR. These associations were maintained even after adjustment for age, sex, and other potential confounders. Finally, BMI as a continuous variable remained an independent predictor of MACCE at 12 months. Our findings suggest that the obesity paradox phenomenon is still present after PCI using new-generation DES in an Asian population.

Anthropometric differences including body physique and BMI exist between Western and Asian individuals. In this study, the mean BMI was 24.5 kg/m^2 and the prevalence of overweight or obesity was 41.6%, which is similar to those in previous studies conducted in Asian countries [4,13,14]. However, the proportion of overweight and obesity was much lower than that of Western-population studies, which reaches approximately 70% [5,15]. Some Western studies describing an inverse J-shaped relationship between BMI and mortality demonstrated that underweight (BMI < 18.5 kg/m^2) and severely obese (BMI ≥ 35 kg/m^2) patients are at a higher risk of death [16–18]. However, in the present study, only 28 patients (0.05%) had a BMI ≥ 35 kg/m^2. Thus, we could not categorize and analyze a severely obese group, but we found that a higher BMI could be a significant protective factor for the occurrence of MACCE and all-cause mortality, and we identified the best cutoff value of BMI for predicting worse outcomes without a J-shaped relationship. In the present study, the incidence of all-cause death, MACCE, and TVR was highest in underweight patients. BMI as a continuous variable was an independent predictor of all-cause mortality with an HR demonstrating a 7% lower risk of death at 1 year. Our findings are largely consistent with those of previous reports of the obesity paradox and provide further evidence supporting their results in an Asian population, at least over the short term. Other than for patients with the highest BMI, the clinical impact of BMI on short-term outcomes after PCI should be similar between Korean populations and other Western countries. For a more precise understanding of the J-curve theory in an Asian population, the clinical outcomes of severely obese patients treated using new-generation DES, even with an extremely low incidence in Asian populations, should be investigated further in the future.

Although obesity is a well-known cardiometabolic risk factor, a high BMI has been reported to have cardiovascular protective effects in many large observational studies and meta-analyses [16,17,19]. Some possible reasons for this paradoxical phenomenon of obesity have been proposed; underweight can be a surrogate marker for a patient's frail condition such as malnutrition and combined non-cardiovascular comorbidities such as malignancy, autoimmune disease, inflammatory disease, and psychiatric disease, which can be related to high mortality [16,20]. In addition, underweight patients are more often elderly, and fragile, owing to these conditions, and less responsive to conservative treatments [21]. Despite the absence of detailed data regarding the exact causes of non-cardiac death, our results showed that BMI could affect not only all-cause mortality but also ischemic outcomes such as cardiac mortality, TVR, and total MACCE after adjustment for confounders. Our findings suggest that there might be some more harmful risk factors for cardiovascular disease in underweight patients rather than the factors related to obesity. Dangas et al. reported an inverse relationship between body weight and coronary calcification in patients with CAD using intravascular ultrasonography [22]. A higher prevalence of carotid plaque [20] and a more severe carotid plaque burden [23] in underweight patients undergoing PCI has also been reported. These data suggest that underweight patients with CAD are likely to have more severe and complex pathologic features in their total vasculature, including coronary lesions, than obese patients. Similarly, in the present DES cohort, the patients with a low BMI were likely to have more severe calcification in stenotic lesions, a more frequent presentation of MI, and a lower ejection fraction than those with a high BMI. These findings are in agreement with prior reports demonstrating a higher atherosclerotic burden in underweight patients with CAD and might be related to a higher prevalence of ischemic adverse events in the low-BMI group after PCI. We presented plausible factors of adverse clinical outcomes in underweight group patients in Supplementary Fig. 4. In the future, accurate atherosclerotic plaque burden according to BMI categories should be confirmed using intravascular imaging tools to address this issue.

As shown in subgroup analyses of the current study, clinical outcome was worse in diabetic patients of the low-BMI group than the high-BMI group. The exact pathophysiology explaining this observation is not understood but this result suggests lean diabetes may be related to more atherosclerotic burden or higher mortality. In addition, patients with a high BMI may present symptoms at an earlier stage of CAD because of the more severe symptoms and functional impairment caused by excess body weight [24]. Furthermore, physicians tend to use more aggressive optimal medical therapy [25,26] and enforce cessation

of smoking, dietary counseling, and cardiac rehabilitation more frequently for younger and obese patients than lean patients. These factors could also be the underlying causes of the obesity paradox phenomenon.

Most previous studies reporting the obesity paradox after PCI included patients who underwent first-generation DES or bare-metal stent implantation [5,13,16]. Currently, new-generation DESs have demonstrated superior clinical outcomes over the first-generation DESs or bare metal stents [27,28], which might attenuate the effects of clinical risk factors including BMI. The present study focused on all patients with CAD who underwent PCI with a new-generation DES and demonstrated that the obesity paradox phenomenon still exists and that BMI could affect major clinical outcomes, both TVR and all-cause mortality, even after new-generation DES implantation. However, because there could be residual confounding factors or collider stratification bias in this observation, additional larger long-term studies to validate the precise mechanism of the obesity paradox and to investigate the relationship between BMI and other clinical, angiographic, and procedural risk factors is necessary in the future.

4.1. Limitations

This study has several limitations. First, REVOLUTE, NOBORI, and CONSTANT registries were not primarily designed to investigate the prognostic implication of BMI on clinical outcomes. In addition, because this study was performed by prospective registry-based analyses, there could be a lack of some detailed data, whether complete or incomplete revascularization, measure of frailty, or other important confounding variables. Second, BMI may not distinguish the amount of muscle mass and adipose tissue and is limited for assessing body fat distribution. Alternative measurements of obesity, such as waist circumference or waist-to-hip ratio, which are more specific for abdominal adiposity, were not evaluated in the present study. In addition, fluctuations or changes in BMI during the observation period, which could have influenced the occurrence of adverse events, was not evaluated. Third, the detailed analyses for the causes of mortality and bleeding events were lacking. Finally, the follow-up duration was too short to investigate the long-term role of BMI after PCI.

4.2. Conclusions

Independent of age, sex, and other confounders, BMI had a significant inverse relationship with adverse clinical outcomes in this observational study, suggesting an obesity paradox is still evident in the contemporary new-generation DES era. To identify longer-term effects of obesity and elucidate the underlying causes of the paradox, further well-designed mechanistic studies should be performed.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.08.047.

Kaplan-Meier curves showing the cumulative 12-month rates of MACCE (A) and all-cause mortality (B) according to BMI categories. BMI = body mass index; MACCE = major adverse cardiac and cerebrovascular event.

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