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ORIGINAL ARTICLE
Coronary Intervention

Body Mass Index and Major Adverse Events During Chronic Antiplatelet Monotherapy After Percutaneous Coronary Intervention With Drug-Eluting Stents

— Results From the HOST-EXAM Trial —

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Background: This study evaluated the association of body mass index (BMI) with adverse clinical outcomes during chronic maintenance antiplatelet monotherapy after percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

Methods and Results: Overall, 5,112 patients were stratified (in kg/m^2) into underweight (BMI ≤18.4), normal weight (18.5–22.9), overweight (23.0–24.9), obesity (25.0–29.9) and severe obesity (≥30.0) categories with randomized antiplatelet monotherapy of aspirin 100 mg or clopidogrel 75 mg once daily for 24 months. The primary endpoint was the composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome and major bleeding of Bleeding Academic Research Consortium type ≥3. Compared with normal weight, the risk of primary composite outcomes was higher in the underweight (hazard ratio [HR] 2.183 [1.199–3.974]), but lower in the obesity (HR 0.730 [0.558–0.954]) and severe obesity (HR 0.518 [0.278–0.966]) categories, which is partly driven by the difference in all-cause death. The risk of major bleeding was significantly higher in the underweight (HR 4.140 [1.704–10.059]) than in the normal weight category. A decrease in categorical BMI was independently associated with the increased risk of primary composite outcomes.

Conclusions: Lower BMI is associated with a higher risk of primary composite outcomes, which is primarily related to the events of all-cause death or major bleeding during chronic maintenance antiplatelet monotherapy after PCI with DES.

Key Words: Antiplatelet; Body mass index; Drug-eluting stents; Percutaneous coronary intervention; Prognosis

Obesity is a substantial public health issue due to its close relationship with cardiovascular (CV) disease and adverse clinical outcomes in the general population.[1,2] However, several studies on patients with chronic disease suggested that an increase of body mass index (BMI), which estimates a relative weight for height and is frequently used to assess the excess body fat and obesity, is associated with improved short- and long-term prognosis, showing either an inverse linear or U-shaped association between BMI and mortality.[3–5] This phenomenon is called the "obesity paradox" or 'reverse epidemiology'. An inverse relationship between BMI and adverse

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Table 1. Baseline Characteristics

	Underweight	Normal weight	Overweight	Obesity	Severe obesity	
	BMI ≤18.4 kg/m² (n=76)	BMI 18.5–22.9 kg/m² (n=1,293)	BMI 23.0–24.9 kg/m² (n=1,395)	BMI 25.0–29.9 kg/m² (n=2,076)	BMI ≥30.0 kg/m² (n=272)	P value
Age, years	70.1±12.5	65.5±10.4	64.1±10.3	61.9±10.4	59.2±12.0	<0.001
Male	46 (60.5)	912 (70.5)	1,091 (78.2)	1,576 (75.9)	191 (70.2)	<0.001
BMI, kg/m²	17.6±0.8	21.5±1.1	24.0±0.6	26.8±1.3	32.5±3.7	<0.001
Hypertension	42 (55.3)	708 (54.8)	837 (60.0)	1,363 (65.7)	204 (75.0)	<0.001
Diabetes	32 (42.1)	400 (30.9)	453 (32.5)	731 (35.2)	125 (46.0)	<0.001
Dyslipidaemia	52 (68.4)	868 (67.1)	962 (69.0)	1,527 (73.6)	216 (79.4)	<0.001
Current smoking	12 (15.8)	257 (19.9)	275 (19.7)	447 (21.5)	58 (21.3)	0.503
Chronic kidney disease	23 (30.3)	170 (13.1)	176 (12.6)	259 (12.5)	22 (8.1)	<0.001
Previous myocardial infarction	15 (19.7)	216 (16.7)	231 (16.6)	342 (16.5)	36 (13.2)	0.606
Previous cerebrovascular accident	6 (7.9)	65 (5.0)	57 (4.1)	97 (4.7)	13 (4.8)	0.520
High bleeding risk*	33 (47.8)	303 (26.7)	244 (20.4)	311 (17.3)	37 (15.7)	<0.001
Clinical indication of PCI						
Silent ischemia	2 (2.6)	29 (2.2)	42 (3.0)	45 (2.2)	3 (1.1)	0.303
Stable angina	19 (25.0)	330 (25.5)	387 (27.7)	517 (24.9)	79 (29.0)	0.289
Unstable angina	23 (30.3)	455 (35.2)	457 (32.8)	783 (37.7)	103 (37.9)	0.031
NSTEMI	18 (23.7)	221 (17.1)	256 (18.4)	426 (20.5)	47 (17.3)	0.085
STEMI	14 (18.4)	258 (20.0)	253 (18.1)	305 (14.7)	40 (14.7)	0.001
Medications						
Aspirin	36 (47.4)	676 (52.3)	696 (49.9)	1,014 (48.8)	138 (50.7)	0.397
Clopidogrel	40 (52.6)	617 (47.7)	699 (50.1)	1,062 (51.2)	134 (49.3)	0.397
β-blocker	32 (42.1)	576 (44.5)	668 (47.9)	1,114 (53.7)	146 (53.7)	<0.001
ACEI	11 (14.5)	189 (14.6)	181 (13.0)	320 (15.4)	42 (15.4)	0.378
ARB	22 (28.9)	383 (29.6)	463 (33.2)	787 (37.9)	121 (44.5)	<0.001
Calcium-channel blocker	16 (21.1)	301 (23.3)	369 (26.5)	615 (29.6)	108 (39.7)	<0.001
Nitrate	4 (5.3)	102 (7.9)	120 (8.6)	197 (9.5)	29 (10.7)	0.291
Statin	64 (84.2)	1,078 (83.4)	1,190 (85.3)	1,766 (85.1)	238 (87.5)	0.406
Laboratory findings						
Haemoglobin, g/dL	12.6±1.8	13.3±1.7	13.8±1.6	14.0±1.6	14.2±1.6	<0.001
Creatinine, mg/dL	1.2±1.3	1.0±0.8	1.0±0.6	1.0±0.5	0.9±0.2	0.027
Total cholesterol, mg/dL	138.3±36.7	137.3±30.3	136.1±29.9	137.5±29.9	144.1±28.6	0.006
Triglycerides, mg/dL	96.6±47.2	109.7±68.5	122.0±69.9	134.5±82.5	158.8±114.3	<0.001
HDL cholesterol, mg/dL	52.2±15.8	48.9±13.1	46.2±11.2	44.9±11.6	44.6±11.3	<0.001
LDL cholesterol, mg/dL	65.9±22.9	69.9±23.1	70.8±23.6	71.9±23.4	76.2±23.3	0.001
Hemoglobin A1c, %	6.6±1.3	6.4±1.2	6.5±1.1	6.5±1.1	6.7±1.1	0.051
Angiographic and procedural characteristics						
Extent of CAD						
One-vessel disease	29 (38.2)	659 (51.0)	702 (50.4)	1,036 (49.9)	144 (52.9)	0.231
Two-vessel disease	23 (30.3)	403 (31.2)	436 (31.3)	661 (31.8)	84 (30.9)	0.990
Three-vessel disease	24 (31.6)	231 (17.9)	256 (18.4)	379 (18.3)	44 (16.2)	0.041
Left main disease	7 (9.2)	64 (4.9)	82 (5.9)	99 (4.8)	7 (2.6)	0.073
PCI for bifurcation lesion	10 (13.2)	114 (8.8)	164 (11.8)	252 (12.1)	25 (9.2)	0.026
PCI for CTO lesion	9 (11.8)	100 (7.7)	119 (8.5)	219 (10.5)	23 (8.5)	0.051
Mean diameter of stents, mm	3.0±0.4	3.1±0.4	3.1±0.4	3.1±0.4	3.1±0.4	0.271
Minimum diameter of stents, mm	2.9±0.4	3.0±0.4	3.0±0.5	3.0±0.5	3.0±0.5	0.495
Total length of stents, mm	33.2±20.8	34.8±22.8	36.5±24.7	36.4±24.8	33.7±19.3	0.094
Total number of stents	1.4±0.7	1.4±0.8	1.5±0.8	1.5±0.9	1.4±0.7	0.194
Generation of DES						0.678
First-generation DES	0 (0.0)	23 (1.8)	32 (2.3)	38 (1.8)	4 (1.5)	
Second-generation DES	75 (98.7)	1,262 (97.6)	1,348 (96.6)	2,018 (97.2)	264 (97.1)	
Unknown generation	1 (1.3)	8 (0.6)	15 (1.1)	20 (1.0)	4 (1.5)	

Data are presented as mean±standard deviation or n (%). *High bleeding risk was defined according to the Academic Research Consortium for High Bleeding Risk definition. Data were available for 4,433 (86.7%) participants. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CTO, chronic total occlusion; DES, drug-eluting stents; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Table 2. Clinical Outcomes

	Underweight	Normal weight	Overweight	Obesity	Severe obesity	P value
	BMI ≤18.4 kg/m² (n=76)	BMI 18.5–22.9 kg/m² (n=1,293)	BMI 23.0–24.9 kg/m² (n=1,395)	BMI 25.0–29.9 kg/m² (n=2,076)	BMI ≥30.0 kg/m² (n=272)	
Primary endpoint	12 (15.8)	99 (7.7)	102 (7.3)	117 (5.6)	11 (4.0)	0.001
All-cause death	4 (5.3)	30 (2.3)	27 (1.9)	20 (1.0)	1 (0.4)	0.001
Cardiac death	2 (2.6)	9 (0.7)	10 (0.7)	8 (0.4)	1 (0.4)	0.100
Non-cardiac death	2 (2.6)	21 (1.6)	17 (1.2)	12 (0.6)	0 (0)	0.007
Non-fatal myocardial infarction	1 (1.3)	7 (0.5)	17 (1.2)	17 (0.8)	1 (0.4)	0.317
Stroke	2 (2.6)	16 (1.2)	13 (0.9)	25 (1.2)	2 (0.7)	0.622
Ischemic stroke	1 (1.3)	8 (0.6)	9 (0.6)	17 (0.8)	2 (0.7)	0.917
Hemorrhagic stroke	1 (1.3)	8 (0.6)	4 (0.3)	8 (0.4)	0 (0)	0.335
Readmission due to ACS	4 (5.3)	46 (3.6)	53 (3.8)	57 (2.7)	7 (2.6)	0.313
Major bleeding (BARC type ≥3)	6 (7.9)	26 (2.0)	18 (1.3)	30 (1.4)	2 (0.7)	<0.001
Any revascularization	0 (0.0)	33 (2.6)	42 (3.0)	36 (1.7)	7 (2.6)	0.081
Target lesion revascularization	0 (0.0)	17 (1.3)	23 (1.6)	13 (0.6)	2 (0.7)	0.039
Target vessel revascularization	0 (0.0)	25 (1.9)	31 (2.2)	20 (1.0)	3 (1.1)	0.020
Definite or probable stent thrombosis	0 (0.0)	5 (0.4)	12 (0.9)	5 (0.2)	0 (0)	0.054

Data are presented as n (%). ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; BMI, body mass index.

clinical outcomes has also been reported in the era of percutaneous coronary intervention (PCI) even after focusing on clinical condition, PCI indication, lesion complexity and generation of drug-eluting stents (DES).[6–8] In patients treated using PCI with DES, chronic antiplatelet monotherapy with aspirin or clopidogrel after the initial 6–12 months of dual antiplatelet therapy (DAPT) is essential for secondary prevention of adverse CV events.[9–11] However, there is a paucity of data on this phenomenon during the controlled chronic antiplatelet monotherapy after PCI with DES. The HOST-EXtended Antiplatelet Monotherapy (HOST-EXAM) is the first randomized trial to compare aspirin and clopidogrel as a chronic antiplatelet monotherapy after PCI with DES.[12] In this study, >5,000 patients who were event-free under DAPT for an average of 1 year after PCI with DES were enrolled and then treated with antiplatelet monotherapy for another 2 years. Thus, by using this huge cohort with a long follow-up duration at the chronic phase after PCI, we evaluated the association between BMI and risk of major adverse events during chronic antiplatelet monotherapy after PCI.

Methods

Study Design and Populations

Details regarding the design of the HOST-EXAM trial have been described previously.[13] Briefly, the HOST-EXAM was an investigator-initiated, prospective, randomized, open-label, multicentre trial conducted at 37 study sites in South Korea. All participants were randomly assigned in consecutive order to either the aspirin group (100 mg once daily) or clopidogrel group (75 mg once daily) in a ratio of 1:1. Initially, a total of 5,530 patients were enrolled in the current study. Of these, 418 patients who met the exclusion criteria and had unavailable BMI information were excluded. Finally, 5,112 patients — comprising 2,560 patients with aspirin monotherapy and 2,552 patients with clopidogrel monotherapy for 24 months — were included. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m²).[14] All patients were categorized into BMI groups with the Asian-Pacific cut-offs as follows: underweight (<18.5 kg/m²), normal weight (18.5–22.9 kg/m²), overweight (23–24.9 kg/m²), obesity (≥25.0–29.9 kg/m²) and severe obesity (≥30.0 kg/m²).[14,15]

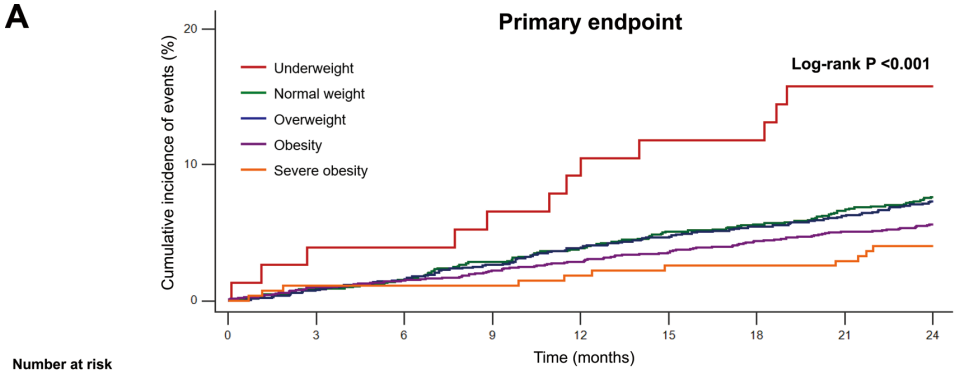
Clinical follow up was scheduled at 12 and 24 months (each with a window of ±3 months). Any additional visits were at the discretion of attending physicians. On each visit, active surveillance for any adverse clinical events was performed, with the assessment of adherence to the study drug. Participants and study investigators were not blinded to the assigned group. This study was conducted following the standards specified in the International Council for Harmonization Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board at each participating site.

Clinical Outcomes

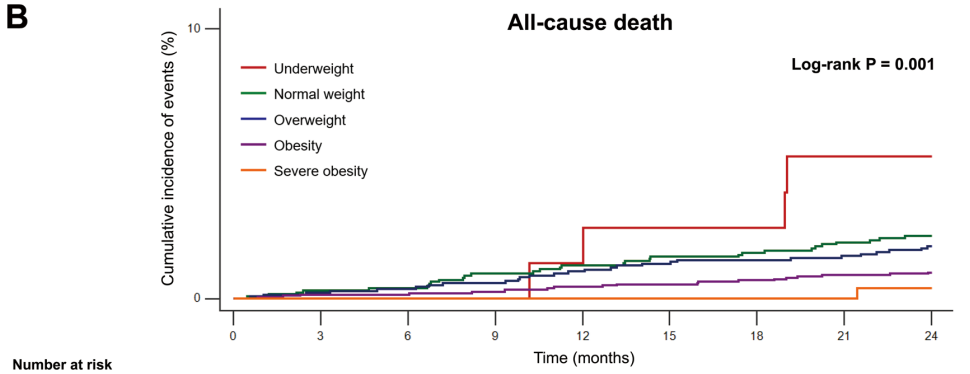
The primary endpoint was the composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome (ACS) and major bleeding of Bleeding Academic Research Consortium (BARC) type ≥3, as previously defined in the HOST-EXAM trial.[12,13] The status of all patients was cross-checked using the National Health Insurance Service System of South Korea and the South Korea National Statistics System. The definite cause of death was confirmed by the recorded data classified by the International Classification of Disease, 10th Revision, Clinical Modification codes. All serious adverse events were monitored at each site.

Statistical Analysis

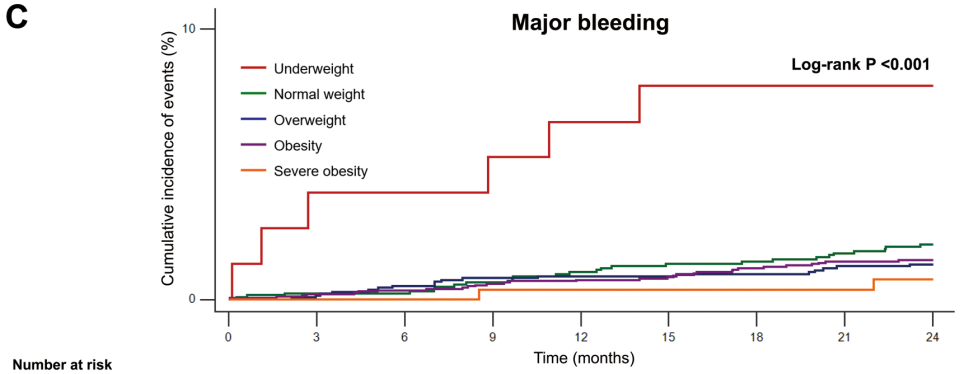
Continuous variables were presented as the mean±standard deviation and compared using the one-way analysis of variance. Categorical variables were presented as absolute values and percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. The primary endpoint was analysed by a Cox proportional hazard model and Kaplan-Meier survival curves to estimate the risk of clinical events. A Cox proportional hazard model was also



Number at risk (Number censored)									
Underweight	76 (0)	73 (0)	73 (0)	71 (0)	69 (0)	67 (0)	67 (0)	63 (1)	63 (2)
Normal weight	1293 (0)	1281 (0)	1273 (0)	1256 (0)	1243 (0)	1227 (0)	1220 (0)	1207 (0)	1195 (17)
Overweight	1395 (0)	1384 (0)	1374 (0)	1357 (1)	1340 (1)	1329 (1)	1318 (1)	1307 (1)	1292 (18)
Obesity	2076 (0)	2055 (0)	2045 (0)	2030 (0)	2016 (0)	2001 (1)	1984 (1)	1969 (1)	1958 (18)
Severe obesity	272 (0)	269 (0)	269 (0)	269 (0)	265 (0)	267 (0)	265 (0)	264 (0)	261 (4)



Number at risk (Number censored)									
Underweight	76 (0)	76 (0)	76 (0)	76 (0)	75 (0)	74 (0)	74 (0)	71 (1)	71 (2)
Normal weight	1293 (0)	1289 (0)	1288 (0)	1281 (0)	1277 (0)	1272 (1)	1270 (1)	1263 (3)	1260 (22)
Overweight	1395 (0)	1392 (0)	1390 (0)	1386 (1)	1380 (1)	1376 (1)	1374 (1)	1368 (5)	1363 (23)
Obesity	2076 (0)	2073 (0)	2073 (0)	2071 (0)	2067 (0)	2064 (1)	2060 (2)	2055 (3)	2053 (20)
Severe obesity	272 (0)	272 (0)	272 (0)	272 (0)	272 (0)	272 (0)	272 (0)	270 (2)	269 (6)



Number at risk (Number censored)									
Underweight	76 (0)	73 (0)	73 (0)	72 (0)	71 (0)	69 (1)	69 (1)	66 (4)	66 (5)
Normal weight	1293 (0)	1287 (3)	1286 (4)	1276 (9)	1268 (12)	1260 (16)	1258 (17)	1248 (23)	1242 (42)
Overweight	1395 (0)	1390 (3)	1383 (5)	1375 (9)	1369 (14)	1366 (17)	1364 (18)	1355 (23)	1349 (45)
Obesity	2076 (0)	2069 (3)	2066 (3)	2059 (5)	2052 (9)	2048 (11)	2040 (12)	2031 (16)	2028 (35)
Severe obesity	272 (0)	272 (0)	272 (0)	271 (0)	271 (0)	271 (0)	271 (0)	269 (2)	267 (7)

Figure 1. Two-year cumulative incidence of the (**A**) primary endpoint, (**B**) all-cause death and (**C**) major bleeding of the Bleeding Academic Research Consortium (BARC) type ≥3 is shown according to categorical body mass index (BMI) groups.

Table 3. Categorical BMI Groups and the Risk of Major Adverse Events

	HR	95% CI	P value
Primary endpoint			
Normal weight	1	–	–
Underweight	2.183	1.199–3.974	0.011
Overweight	0.954	0.724–1.258	0.739
Obesity	0.730	0.558–0.954	0.021
Severe obesity	0.518	0.278–0.966	0.039
Individual components			
All-cause death			
Normal weight	1	–	–
Underweight	2.293	0.808–6.509	0.119
Overweight	0.833	0.495–1.410	0.490
Obesity	0.412	0.234–0.726	0.002
Severe obesity	0.157	0.021–1.149	0.068
Non-fatal myocardial infarction			
Normal weight	1	–	–
Underweight	2.457	0.302–19.971	0.400
Overweight	2.255	0.935–5.438	0.070
Obesity	1.506	0.625–3.631	0.362
Severe obesity	0.671	0.083–5.458	0.709
Stroke			
Normal weight	1	–	–
Underweight	2.166	0.498–9.422	0.303
Overweight	0.751	0.361–1.562	0.443
Obesity	0.967	0.516–1.811	0.916
Severe obesity	0.589	0.135–2.561	0.480
Readmission due to ACS			
Normal weight	1	–	–
Underweight	1.510	0.543–4.194	0.429
Overweight	1.068	0.720–1.585	0.744
Obesity	0.765	0.519–1.128	0.176
Severe obesity	0.712	0.321–1.576	0.402
Major bleeding (BARC type ≥3)			
Normal weight	1	–	–
Underweight	4.140	1.704–10.059	0.002
Overweight	0.641	0.351–1.168	0.146
Obesity	0.714	0.422–1.207	0.208
Severe obesity	0.361	0.086–1.519	0.165

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 2.

used to analyse the prespecified subgroups. Multiple Cox proportional hazard models were used to identify the association between BMI and the risk of primary endpoint; the forced entry method was used to enter independent variables into the multiple Cox proportional hazard models (Model 1, unadjusted; Model 2, adjusted for clinical risk factors including age, sex, hypertension, diabetes, dyslipidemia, current smoking and chronic kidney disease; Model 3, adjusted for clinical risk factors and procedural factors including left main disease, multivessel disease, PCI for acute myocardial infarction, bifurcation lesion, and chronic total occlusion (CTO) lesion, a minimum diameter of stents, the total length of stents and generation of DES; and Model 4, adjusted for clinical risk factors, procedural factors and medical therapy including aspirin, clopidogrel, β-blocker, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), calcium-channel blocker, nitrate and statin). All statistical analyses were performed using SAS (version 9.1.3; SAS Institute Inc., Cary, NC, USA). A P value <0.05 was considered significant for all analyses.

Results

Baseline Characteristics

The baseline clinical and procedural characteristics of the overall population are shown in **Table 1**. In the present study, the proportion of patients who underwent PCI with second-generation DES was 97.2%. The mean BMI for the study population was 24.8±3.2 kg/m^2. When divided into BMI groups, 76 (1.5%) were underweight, 1,293 (25.3%) had normal weight, 1,395 (27.3%) were overweight, and 2,076 (40.6%) were obese and 272 (5.3%) were severely obese. Patients with higher BMI were significantly younger and less likely to have chronic kidney disease and high bleeding risk assessed by the Academic Research Consortium

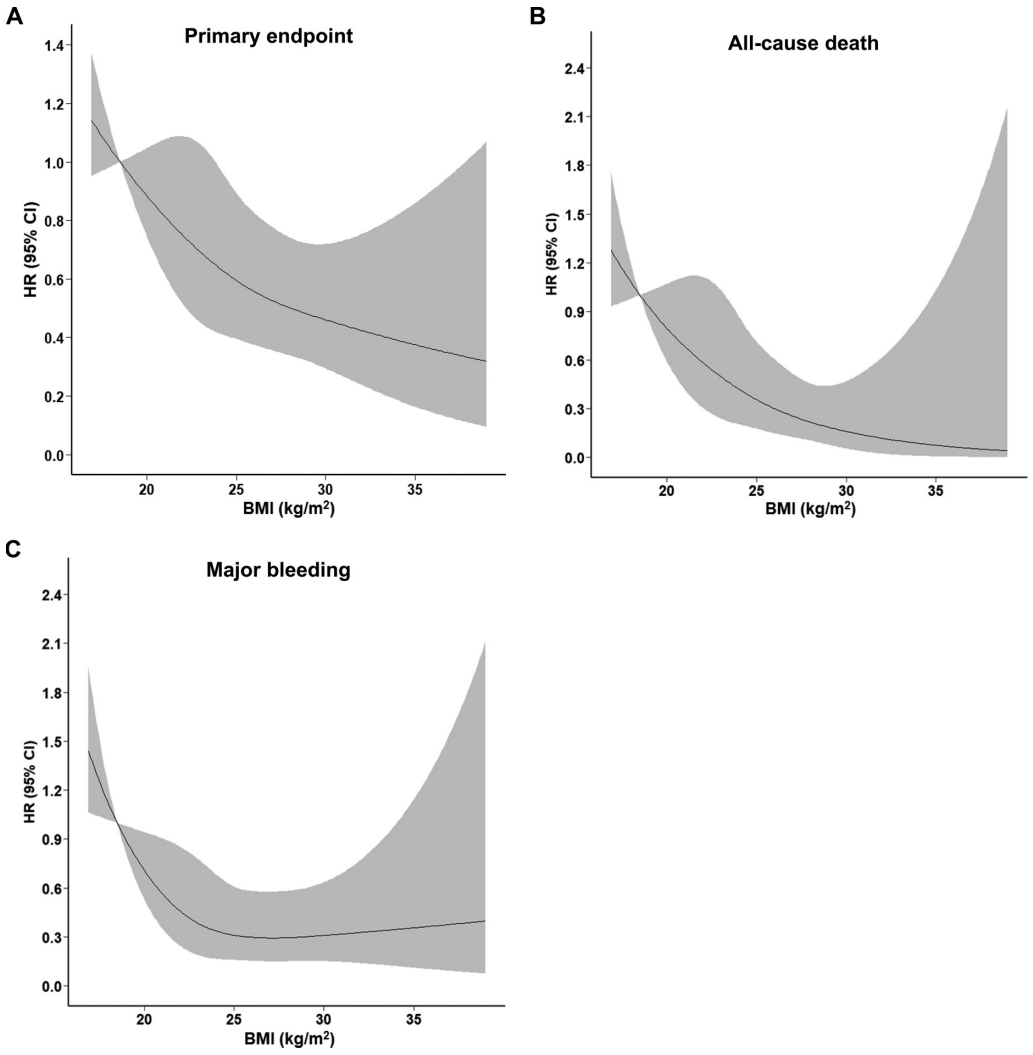


Figure 2. Restricted cubic spline analysis for the association between body mass index (BMI) and the risk of (**A**) primary endpoint, (**B**) all-cause death and (**C**) major bleeding. Reference BMI for the analysis is 18.5 kg/m^2.

for High Bleeding Risk definition. Those with a higher BMI were more likely to have hypertension and dyslipidemia. The rate of history of myocardial infarction and the cerebrovascular accident was not different among BMI groups. Regarding the medical therapy, no significant difference was observed in medications of aspirin, clopidogrel, ACEI, nitrate and statin among the BMI groups; however, patients with higher BMI were more likely to take β-blockers, ARB and calcium-channel blockers. Patients with higher BMI showed higher triglyceride and low-density lipoprotein (LDL) cholesterol levels and lower high-density lipoprotein (HDL) cholesterol levels. No significant differences were observed in the mean and minimal diameters of stents, total length and number of stents and DES generation among BMI groups; however, the percentage of 3-vessel disease was more prevalent in the underweight group than in the other groups.

Clinical Outcomes

The incidence of clinical events is shown in **Table 2**. During the 24-month follow up, events of primary composite outcomes developed in 341 (6.7%) patients. The incidence of primary composite outcomes in the underweight, normal weight, overweight, obesity and severe obesity groups was 15.8%, 7.7%, 7.3%, 5.6% and 4.0%, respectively. The incidence of all-cause death was the highest in the underweight group and decreased in other groups with higher BMI. Further, the incidence of major bleeding was the highest in the underweight patients and decreased in other groups with higher BMI. No significant differences were observed among the 5 groups of different BMI in terms of clinical outcomes, such as non-fatal myocardial infarction, ischemic and hemorrhagic stroke, readmission due to ACS, any revascularization and definite or probable stent thrombosis. The Kaplan-Meier survival analysis (**Figure 1**) showed that the cumulative incidence of primary composite outcomes was the highest in the underweight group and that it decreased with higher BMI. The cumulative incidence of all-cause death and major bleeding showed the same results as the primary outcomes.

Table 4. Association of BMI (per a Categorical BMI Decrease) With the Risk of Major Adverse Events

	HR	95% CI	P value
Primary endpoint			
Model 1	1.238	1.106–1.385	<0.001
Model 2	1.153	1.027–1.294	0.016
Model 3	1.151	1.025–1.293	0.017
Model 4	1.135	1.010–1.276	0.033
Individual components			
All-cause death			
Model 1	1.621	1.285–2.046	<0.001
Model 2	1.374	1.087–1.737	0.008
Model 3	1.368	1.080–1.734	0.009
Model 4	1.349	1.062–1.713	0.014
Non-fatal myocardial infarction			
Model 1	1.000	0.727–1.376	0.999
Model 2	0.995	0.714–1.387	0.979
Model 3	0.985	0.703–1.381	0.931
Model 4	0.928	0.656–1.311	0.671
Stroke			
Model 1	1.092	0.831–1.435	0.526
Model 2	0.969	0.732–1.282	0.825
Model 3	0.957	0.723–1.268	0.761
Model 4	0.941	0.708–1.250	0.674
Readmission due to ACS			
Model 1	1.162	0.990–1.364	0.067
Model 2	1.141	0.967–1.346	0.119
Model 3	1.143	0.968–1.348	0.115
Model 4	1.126	0.953–1.331	0.163
Major bleeding (BARC type ≥3)			
Model 1	1.376	1.094–1.732	0.006
Model 2	1.240	0.980–1.568	0.073
Model 3	1.249	0.986–1.581	0.065
Model 4	1.248	0.983–1.584	0.069

Abbreviations as in Tables 1–3. Model 1: Unadjusted. Model 2: Adjusted for clinical risk factors including age, sex, hypertension, diabetes, dyslipidemia, current smoking and chronic kidney disease. Model 3: Model 2+adjusted for procedural factors including left main disease, multivessel disease, PCI for acute myocardial infarction, bifurcation lesion and CTO lesion, minimum diameter of stents, total length of stents and generation of DES. Model 4: Model 3+adjusted for medical therapy including aspirin, clopidogrel, β-blocker, ACEI or ARB, calcium-channel blocker, nitrate and statin.

The hazard ratios of the primary endpoint and each component were assessed in 4 different groups, with the normal weight group as the reference (**Table 3**). Compared to patients with normal weight, the underweight group showed a significantly higher risk of experiencing a primary endpoint (HR 2.183) and major bleeding (HR 4.140). The result of the restricted cubic spline analysis showed the continuous association of BMI with the risk of primary endpoint, all-cause death and major bleeding (**Figure 2**). **Table 4** shows the association of BMI with the risk of major adverse events. A decrease in categorical BMI was independently associated with the increased risk of primary endpoint and all-cause death in 4 different models after consecutive adjustment of clinical risk factors, procedural factors and medical treatment. Compared to patients with normal weight, the risk of major bleeding was independently higher in those who were underweight in the same adjustment models (**Table 5**). The results regarding the association of BMI (per 1 kg/m^2 increase) with the risk of major adverse events are described in **Supplementary Table 1**.

Discussion

In this HOST-EXAM substudy, no significant difference was observed across BMI groups in the use of aspirin or clopidogrel for chronic antiplatelet monotherapy during the 24-month follow-up periods. The primary composite outcomes and major bleeding were the highest in the underweight group and then decreased in the other groups with higher BMI. After adjusting for possible confounding variables, a decrease in BMI was continuously associated with the increased risk of primary composite outcomes.

Although several studies reported the phenomenon of "obesity paradox" or "reverse epidemiology" in the era of PCI, there is a paucity of data on the association between BMI and major adverse events under antiplatelet monotherapy during the chronic period after PCI with DES. Compared with East Asians, the cut-offs for BMI categories are somewhat different in the Western population as follows: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obesity (30–

Table 5. Adjusted Risk of Major Bleeding in Categorical BMI Groups

	HR	95% CI	P value
Major bleeding (BARC type ≥3)			
Model 2			
Normal weight	1	–	–
Underweight	3.046	1.239–7.488	0.015
Overweight	0.678	0.371–1.239	0.206
Obesity	0.855	0.500–1.462	0.567
Severe obesity	0.479	0.112–2.045	0.320
Model 3			
Normal weight	1	–	–
Underweight	3.086	1.248–7.629	0.015
Overweight	0.658	0.360–1.204	0.175
Obesity	0.835	0.488–1.428	0.510
Severe obesity	0.497	0.116–2.126	0.346
Model 4			
Normal weight	1	–	–
Underweight	3.084	1.246–7.633	0.015
Overweight	0.657	0.358–1.203	0.173
Obesity	0.841	0.489–1.466	0.531
Severe obesity	0.336	0.114–2.101	0.336

Abbreviations as in Tables 2,3. The result of Model 1 (unadjusted) is described in Table 3. Adjusted variables for each model are the same as that for Table 4.

34.9 kg/m^2) and severe obesity (≥35.0 kg/m^2).[14,16] In the recent era of PCI use in the Western population, Wolny et al evaluated the association of BMI with clinical outcomes among 22,922 patients treated with PCI using the data from 13 randomized trials.[17] They found that the 5-year survival rate after PCI was better in overweight and obese patients than in those with normal weight, which was mainly caused by a lower rate of non-cardiac mortality. In the data from 26 randomized trials, Faggioni et al[18] reported that the risk of cardiac events did not differ across BMI groups in 11,557 female patients treated with PCI with DES during the 3-year follow-up period. The risk of all-cause mortality was significantly higher in underweight and lower in overweight patients than in patients with normal weight, with a trend toward increased risk in those with severe obesity. Compared with the current study, these studies had several obvious differences: (1) the large proportion of PCI with bare metal or first-generation DES; (2) no definite exclusion criteria of the acute phase of ACS; (3) mainly focusing on mortality without major bleeding events; (4) no information of medication including antiplatelet agents; (5) a large proportion of patients with a BMI ≥30.0 kg/m^2; and (6) Western participants.

In the current study, when we categorized the patients into 5 different groups based on criteria such as 18.5, 23.0, 25.0 and 30.0 kg/m^2, the incidence of primary composite outcomes was highest in the underweight group and decreased for the normal weight group. Notably, it further decreased in the overweight and other groups. The incidence of all-cause death showed a similar trend in the underweight to obesity groups. The most prominent difference among clinical events was major bleeding that was significantly higher in the underweight group than in other groups. Such a prognosis in the underweight group may well be expected considering the poor baseline profiles: advanced age, prevalent chronic kidney disease and higher proportion of high bleeding risk and 3-vessel disease. After step-wise control of the confounding variables in the 4 different models, a lower BMI was strongly associated with a higher risk of primary endpoint and all-cause death. In particular, the risk of major bleeding was significantly higher in the underweight group compared with the normal weight group in the same adjustment models. Therefore, clinicians should focus on preventing major bleeding in the underweight patients after PCI with DES during chronic antiplatelet monotherapy.

Among categorical BMI groups, the beneficial effect of clopidogrel compared to aspirin in terms of the primary endpoint was obvious in the overweight group; the lower risk of a thrombotic endpoint in patients treated with clopidogrel vs. aspirin was observed in both the overweight and obesity groups (**Supplementary Table 2**). In addition, when we analysed the effect of a categorical BMI decrease on clinical events, the risk of all-cause death significantly increased as BMI decreased by one category. Despite the different cut-offs for the BMI categories according to ethnicity, the beneficial ranges of BMI in terms of mortality in the current study were similar to those of previous studies. Thus, obesity itself may not be a poor prognostic factor in patients during a stabilized period that is under optimal control using appropriate medications in addition to PCI with DES.

This study has several limitations. First, the open-label design has a potential bias in outcome reporting and ascertainment. Second, information on variables comprising measures of fat distribution, physical activity level and serial BMI measures was unavailable. Third, the proportion of underweight participants was extremely low in the current study. However, according to the recent results from large-pooled patient-level analyses in the era of PCI,[17,18] the proportion of underweight patients defined with the same cut-off of a BMI <18.5 kg/m^2 in the Western population was found to be approximately 0.5–1.0%, which is a similar proportion when compared to the HOST-EXAM registry. These findings might imply that the extremely low proportion of underweight patients is an inevitable phenomenon, irrespective of ethnicities in the current era of PCI with DES. Moreover, the studies mentioned above did not include the event of major bleeding in the primary endpoint. Considering that there were limited data regarding the risk of major bleeding in underweight patients during chronic antiplatelet monotherapy after PCI with DES, the findings of present study could be informative in current clinical practice. Fourth, all study populations comprised East Asians. These factors might limit the generalization of the results to other ethnicities. Finally, although the current study endeavored to adjust for possible confounding factors, the collider bias might influence the results of the current study.[19] Despite these limitations, the strength of the current study is that we, for the first time, evaluated the association between BMI and risk of major adverse events in a large sample of patients treated with PCI and DES under a controlled chronic antiplatelet monotherapy.

Conclusions

In this BMI substudy of the HOST-EXAM trial enrolling patients undergoing antiplatelet monotherapy during a

chronic maintenance period after PCI with DES, lower BMI is independently associated with a higher risk of primary composite outcomes, which is primarily related to the events of all-cause death or major bleeding. Thus, clinicians should consider BMI when managing patients undergoing antiplatelet monotherapy during a chronic maintenance period after PCI with DES.

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IRB Information

This study has been approved by the institutional review board at Seoul National University Hospital (reference number: 1208-028-421) and the ethics committees of the respective hospitals. Clinical Trial Registration: ClinicalTrials.gov NCT02044250.

Data Availability

The HOST-EXAM trial is planning to continue follow up until 2025. No individual participant data will be available before this. Any relevant inquiries should be sent to the corresponding author.

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Supplementary Files

Please find supplementary file(s);
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