The obesity paradox revisited: body mass index and long-term outcomes after PCI from a large pooled patient-level database

Rafal Wolny[1,2,3], MD; Akiko Maehara[2,3]*, MD; Yangbo Liu[2], MS; Zixuan Zhang[2], MS; Gary S. Mintz[2], MD; Björn Redfors[2,3,4], MD, PhD; Mahesh V. Madhavan[2,3], MD; Pieter C. Smits[5], MD; Clemens von Birgelen[6,7], MD, PhD; Patrick W. Serruys[8], MD; Roxana Mehran[2,9], MD; Martin B. Leon[2,3], MD; Gregg W. Stone[2,9], MD

1. Institute of Cardiology, Warsaw, Poland; 2. Clinical Trials Center, Cardiovascular Research Foundation, New York, NY, USA; 3. Division of Cardiology, Columbia University Medical Center, New York, NY, USA; 4. Sahlgrenska University Hospital, Gothenburg, Sweden; 5. Division of Cardiology, Maasstad Hospital, Rotterdam, the Netherlands; 6. Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands; 7. Department of Health Technology and Services Research, Faculty of Behavioural, Management and Social Sciences, Technical Medical Centre, University of Twente, Enschede, the Netherlands; 8. Centre for International Cardiovascular Health, Imperial College London, London, United Kingdom; 9. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

GUEST EDITOR: Adnan Kastrati, MD; *Deutsches Herzzentrum, Munich, Germany*

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00467

Abstract

Aims: The aim of this study was to evaluate the relationship between body mass index (BMI) and outcomes in patients with coronary artery disease undergoing percutaneous revascularisation.

Methods and results: In 13 randomised trials, 22,922 patients were stratified (in kg/m^2) as underweight (BMI <18.5), normal weight (18.5 ≤BMI <25, used as reference), overweight (25 ≤BMI <30), and obese (Class I [30 ≤BMI <35], Class II [35 ≤BMI <40], or Class III [BMI ≥40]). The primary endpoint was all-cause death at five years. Secondary endpoints were cardiac and non-cardiac death, target (TLR) and non-target lesion revascularisation (NTLR), myocardial infarction (MI), and definite/probable stent thrombosis. Despite adjustment for multiple confounders, overweight and Class I obesity were associated with lower all-cause mortality versus normal weight (HR 0.83, 95% CI: 0.71-0.96, and HR 0.83, 95% CI: 0.69-0.96, respectively); however, non-cardiac death was the major contributor to this effect (HR 0.77, 95% CI: 0.63-0.94 for overweight). Conversely, cardiac mortality was higher in severely obese individuals (HR 1.62, 95% CI: 1.05-2.51 for Class III obesity). Obesity was associated with higher rates of NTLR (HR 1.28, 95% CI: 1.04-1.58 for Class II obesity) but not with TLR, MI and stent thrombosis.

Conclusions: Moderately increased BMI is associated with improved survival post PCI, mostly due to lower non-cardiac but not cardiac mortality.

Corresponding author: Columbia University Medical Center, Cardiovascular Research Foundation, 1700 Broadway, 9th Floor, New York, NY 10019, USA. E-mail: amaehara@crf.org

Abbreviations

BMI   body mass index
CAD   coronary artery disease
CI   confidence interval
DES   drug-eluting stent
HR   hazard ratio
NTLR   non-target lesion revascularisation
PCI   percutaneous coronary intervention
RCT   randomised controlled trial
STEMI   ST-elevation myocardial infarction
TIMI   Thrombolysis In Myocardial Infarction
TLR   target lesion revascularisation

Introduction

It is estimated that high body mass index (BMI) contributes to 4.0 million deaths per year worldwide and the prevalence of obesity continues to increase[1]. Obesity and excess body fat are strong risk factors of premature cardiovascular and non-cardiovascular diseases; yet, in patients with known coronary artery disease (CAD) and in those undergoing percutaneous coronary intervention (PCI), being overweight is associated with a significant all-cause mortality benefit[2,3]. Despite previous reports describing the so-called "obesity paradox", there is still a need for more data on the exact causes and durability of the observed mortality benefit and its association with certain clinical and procedural characteristics, especially the extent of the cardiac and non-cardiac mortality effect and the relationship between body size and other cardiovascular outcomes. Thus, we investigated five-year cardiovascular outcomes in relation to baseline BMI using pooled patient-level data from randomised controlled trials (RCTs).

Methods

STUDY POPULATION

Individual patient-level data from 21 PCI RCTs performed and reported between 1999 and 2016 were pooled in a centralised database at the Cardiovascular Research Foundation (New York, NY, USA). For the present analysis, 13 studies with available BMI at the time of PCI were included **(Supplementary Table 1)**. All but three trials (ACUITY, HORIZONS-AMI, SPIRIT IV) reported five-year outcomes. The trials compared different types of stent (bare metal stents, first- and second-generation drug-eluting stents [DES]) and various antithrombotic regimens (heparin with or without glycoprotein IIb/IIIa inhibitors, or bivalirudin) in patients with a spectrum of clinical presentations. All studies complied with the Declaration of Helsinki and were approved by the institutional review boards at each participating centre; written informed consent was obtained from all patients at the time of enrolment.

Patients were stratified into six groups using the National Heart, Lung, and Blood Institute definitions according to their BMI (kg/m^2) at the time of PCI: underweight (BMI <18.5), normal weight (18.5 ≤BMI <25), overweight (25 ≤BMI <30), obesity Class I (30 ≤BMI <35), obesity Class II (35 ≤BMI <40), and obesity Class III (BMI ≥40)[4].

STUDY ENDPOINTS

The primary outcome of the study was all-cause death at five-year follow-up. Secondary outcomes included cardiac and non-cardiac death, ischaemia-driven target lesion revascularisation (TLR), non-target lesion revascularisation (NTLR) in the target vessel and non-target vessel, myocardial infarction (MI), and definite/probable stent thrombosis as defined by the Academic Research Consortium[5]. All MIs within three days post PCI were classified as periprocedural and were excluded because of the variable definitions used. Definitions of cardiac and non-cardiac death were similar across studies, with deaths of unknown cause considered cardiac. All outcomes were reported in all studies included in the analysis, except for NTLR which was not available in ACUITY, TAXUS II, IV, V and PLATINUM.

STATISTICAL ANALYSIS

Patient-level data were pooled as one structured data set. Baseline demographics, core lab reported quantitative coronary angiography results, and procedural characteristics are presented as mean and standard deviation and were tested with the Student's t-test (after normal distribution was confirmed with the Kolmogorov-Smirnov test). Multiple group comparisons were performed using analysis of variance. Categorical variables are presented as counts and percentages and were tested with the χ^2 test. Because we expected less than one false positive test on average if all BMI pairs tested positive at a 5% type I error, no adjustment of p-values for *post hoc* pairwise testing was done. Cumulative five-year event rates are presented as Kaplan-Meier estimates and were tested with the log-rank test. A multivariable Cox proportional hazards model was adjusted for patient and lesion characteristics with each RCT as a random effect using normal weight individuals as a reference. Selection of covariates was based on their historical and pathophysiologic association with risk of ischaemic events and differences across BMI subgroups. The following covariates were included in the model: age, sex, diabetes mellitus, current smoker, hypertension, hyperlipidaemia, previous coronary artery bypass grafting, previous PCI, previous MI, clinical presentation with MI (non-ST-elevation myocardial infarction [NSTEMI] or ST-elevation myocardial infarction [STEMI]) versus stable CAD or unstable angina, stent type (bare metal stents, first-generation DES, second-generation DES), stent length, reference vessel diameter, calcification, and number of treated lesions. All study outcomes were tested for interaction with age, sex, clinical presentation, and stent type. Two-sided p-values <0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Overall, 22,922 patients (mean age 62.8 years, 27.8% female) were included. BMI was 29.0±5.4 kg/m^2. When divided into BMI subgroups, 137 (0.5%) were classified as underweight, 4,997 (21.8%) as normal weight, 9,665 (42.2%) as overweight, and 8,123 (35.4%) as obese, including 5,318 (23.2%) Class I, 1,903

(8.3%) Class II, and 902 (3.9%) Class III. Baseline patient clinical characteristics are summarised in **Table 1**. Overweight and obese patients were younger than those of normal weight. Higher BMI was associated with more cardiovascular risk factors (diabetes mellitus, hypertension, and hyperlipidaemia) as well as higher rates of prior MI and prior revascularisation (both PCI and surgery), while current smoking had a lower prevalence across higher BMI subgroups. Higher BMI was associated with more frequent stable CAD than normal BMI and underweight individuals.

Core lab angiographic findings and procedural characteristics are presented in **Table 2**. Overall, 80% of patients underwent single-vessel PCI (1.2±0.6 lesions), and 86% of stents were DES (58.5% second-generation). Reference vessel size and minimal lumen diameter were larger in higher BMI patients versus normal weight counterparts. In overweight and obese patients, lesions were shorter, less calcified, and less frequently ACC/AHA type C versus normal weight patients. PCI procedures in obese, but not overweight patients were associated with significantly shorter stents, but greater residual diameter stenosis versus normal weight individuals.

At five-year follow-up, 1,450 (9.2%) deaths were reported (683 [47.1%] cardiac and 767 [52.9%] non-cardiac) along with 1,762 (9.4%) ischaemia-driven TLR, 1,543 (14.6%) NTLR, 876 (4.8%) MIs, and 385 (2.1%) definite/probable stent thrombosis **(Supplementary Table 2)**.

Kaplan-Meier curves for outcomes across BMI subgroups are presented in **Figure 1** with unadjusted and adjusted hazard ratios (HR) summarised in **Figure 2**, **Figure 3** and **Supplementary Table 3**. Spline curves representing the association of BMI with unadjusted and adjusted risk of study outcomes are shown in **Supplementary Figure 1** and **Supplementary Figure 2**. Unadjusted all-cause mortality was twofold higher in underweight (HR 2.15, 95% confidence interval [CI]: 1.38-3.33) and was lower in overweight (HR 0.75, 95% CI: 0.66-0.85), obese Class I (HR 0.67, 95% CI: 0.57-0.78), and obese Class II patients (HR 0.70, 95% CI: 0.57-0.87) versus normal weight individuals. After adjustment, overweight and Class I obesity remained related with lower all-cause mortality (HR 0.83, 95% CI: 0.71-0.96, and HR 0.83, 95% CI: 0.69-0.99, respectively).

Table 1. Baseline characteristics and clinical presentation.

| | Underweight n=137, 0.5% | Normal weight n=4,997, 21.8% | Overweight n=9,665, 42.2% | Obese | | | Overall p-value |
				Class I n=5,318, 23.2%	Class II n=1,903, 8.3%	Class III n=902, 3.9%	
Body mass index, kg/m^2	17.0±1.5	23.1±1.5	27.4±1.4	32.1±1.4	37.1±1.4	44.4±4.6	<0.0001
Weight, kg	50.3±7.0	68.2±9.1	82.1±9.6	95.4±11.5	107.8±14.1	124.4±19.1	<0.0001
Height, cm	172.0±11.3	171.4±9.5	172.7±9.1	172.1±9.9	170.2±10.8	167.2±11.9	<0.0001
Body surface area, m^2	1.6±0.2*	1.8±0.2	2.0±0.2#	2.1±0.2‡	2.2±0.2§	2.3±0.3¶	<0.0001
Age, years	66.5±11.8	64.8±11.5	63.4±10.9#	61.5±10.5‡	60.0±10.6§	58.3±10.0¶	<0.0001
Male	70 (51.1)*	3,399 (68.0)	7,496 (77.6)#	3,892 (73.2)‡	1,210 (63.6)§	473 (52.4)¶	<0.0001
Risk factors							
Diabetes mellitus	15 (10.9)	660/4,995 (13.2)	1,919/9,656 (19.9)#	1,590/5,316 (29.9)‡	876/1,902 (46.1)§	503/900 (55.9)¶	<0.0001
Insulin-treated	5 (3.6)	165/4,995 (3.3)	489/9,656 (5.1)#	471/5,316 (8.9)‡	299/1,902 (15.7)§	194/900 (21.6)¶	<0.0001
Current smoker	58/136 (42.6)*	1,704/4,970 (34.3)	2,621/9,590 (27.3)#	1,344/5,258 (25.6)‡	438/1,885 (23.2)§	197/884 (22.3)¶	<0.0001
Hypertension	69 (50.4)	2,660/4,991 (53.3)	5,938/9,652 (61.5)#	3,829/5,314 (72.1)‡	1,516/1,902 (79.7)§	775/901 (86.0)¶	<0.0001
Hyperlipidaemia	70/136 (51.5)	2,661/4,969 (53.6)	5,897/9,603 (61.4)#	3,586/5,274 (68.0)‡	1,346/1,887 (71.3)§	681/896 (76.0)¶	<0.0001
Clinical history							
Prior CABG	10 (7.3)	331/4,994 (6.6)	782/9,663 (8.1)#	491/5,317 (9.2)‡	170/1,902 (8.9)§	81 (9.0)¶	<0.0001
Prior PCI	25/136 (18.4)	901/4,981 (18.1)	2,034/9,617 (21.2)#	1,233/5,293 (23.3)‡	481/1,891 (25.4)§	220/897 (24.5)¶	<0.0001
Prior MI	25 (18.2)	991/4,962 (20.0)	2,114/9,565 (22.1)#	1,189/5,264 (22.6)‡	430/1,884 (22.8)§	206/887 (23.2)¶	0.009
Clinical presentation							
Acute coronary syndromes	86/132 (65.2)	3,008/4,809 (62.5)	5,417/9,230 (58.7)#	2,728/5,022 (54.3)‡	910/1,751 (52.0)§	389/817 (47.6)¶	<0.0001
STEMI	38 (27.7)	1,206 (24.1)	1,868/9,663 (19.3)#	811 (15.3)‡	180 (9.5)§	51 (5.7)¶	<0.0001
NSTEMI	18 (13.1)	812 (16.2)	1,519/9,663 (15.7)	694 (13.1)‡	229 (12.0)§	90 (10.0)¶	<0.0001
Unstable angina	30/132 (22.7)	990/4,809 (20.6)	2,030/9,230 (22.0)	1,223/5,022 (24.4)‡	501/1,751 (28.6)§	248/817 (30.4)¶	<0.0001
Stable CAD	46/132 (34.8)	1,801/4,809 (37.5)	3,813/9,230 (41.3)#	2,294/5,022 (45.7)‡	841/1,751 (48.0)§	428/817 (52.4)¶	<0.0001

Values are mean±standard deviation, n (%), or otherwise indicated. *p<0.05 for comparison between underweight and normal weight patients; #p<0.05 for comparison between overweight and normal weight patients; ‡p<0.05 for comparison between patients with Class I obesity and normal weight patients; §p<0.05 for comparison of patients with Class II obesity and normal weight patients; ¶p<0.05 for comparison of patients with Class III obesity and normal weight patients. CABG: coronary artery bypass grafting; CAD: coronary artery disease; IQR: interquartile range; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

Table 2. Quantitative coronary angiography and procedural characteristics.

		Underweight n=137, 0.5%	Normal weight n=4,997, 21.8%	Overweight n=9,665, 42.2%	Obese Class I n=5,318, 23.2%	Obese Class II n=1,903, 8.3%	Obese Class III n=902, 3.9%	Overall p-value
Baseline								
Reference vessel diameter, mm		2.76±0.53	2.73±0.71	2.76±0.81#	2.78±0.52‡	2.77±0.51§	2.78±0.51¶	0.01
Minimum lumen diameter, mm		0.71±0.48	0.68±0.46	0.70±0.46	0.73±0.45‡	0.76±0.44§	0.81±0.44¶	<0.0001
Diameter stenosis, %		74.6±16.5	76.1±17.0	75.8±16.4	75.0±15.9‡	73.4±15.2§	71.3±14.5¶	<0.0001
Lesion length, mm		16.9±10.7	17.5±11.9	17.5±11.8	16.7±10.6‡	15.9±9.6§	15.1±8.3¶	<0.0001
Tortuosity		5/75 (6.7)	127/2,074 (6.1)	254/3,854 (6.6)	153/2,281 (6.7)	72/869 (8.3)§	42/457 (9.2)¶	0.11
Calcification		54/126 (42.9)	1,544/4,358 (35.4)	2,760/8,491 (32.5)#	1,453/4,801 (30.3)‡	472/1,747 (27.0)§	208/853 (24.4)¶	<0.0001
ACC/AHA type C lesion		57/125 (45.6)	1,960/4,526 (43.3)	3,636/8,877 (41.0)#	1,891/4,983 (37.9)‡	597/1,781 (33.5)§	247/859 (28.8)¶	<0.0001
TIMI 3 flow		89/125 (71.2)	3,436/4,528 (75.9)	6,868/8,880 (77.3)	4,025/4,986 (80.7)‡	1,514/1,783 (84.9)§	768/860 (89.3)¶	<0.0001
Final								
Number of treated lesions	1	114/136 (83.8)	3,976/4,978 (79.9)	7,639/9,623 (79.4)	4,232/5,300 (79.8)	1,543/1,897 (81.3)	760/899 (84.5)¶	0.004
	2	19/136 (14.0)	792/4,978 (15.9)	1,575/9,623 (16.4)	872/5,300 (16.5)	294/1,897 (15.5)	113/899 (12.6)¶	0.07
	≥3	3/136 (2.2)	209/4,978 (4.2)	409/9,623 (4.3)	195/5,300 (3.7)	60/1,897 (3.2)	26/899 (2.9)	0.052
Stent type	Bare metal	23/136 (16.9)	686/4,956 (13.8)	1,193/9,593 (12.4)#	636/5,280 (12.0)‡	212/1,888 (11.2)§	92/888 (10.4)	0.003
	Drug-eluting	111/136 (81.6)	4,196/4,956 (84.7)	8,263/9,593 (86.1)#	4,567/5,280 (86.5)‡	1,639/1,888 (86.8)§	778/888 (87.6)	0.02
	First-generation	50/136 (36.8)	1,722/4,956 (34.7)	3,325/9,593 (34.7)	1,919/5,280 (36.3)	744/1,888 (39.4)§	347/888 (39.1)	0.0003
	Second-generation	61/136 (44.9)	2,474/4,956 (49.9)	4,938/9,593 (51.5)	2,648/5,280 (50.2)	60/1,888 (47.4)	431/888 (48.5)	0.01
Total stent length, mm		29.1±19.7	32.1±22.8	32.3±23.5	29.9±20.5‡	28.5±18.7§	25.8±14.8¶	<0.0001
Minimum lumen diameter, mm		2.26±0.50	2.27±0.72	2.30±0.89	2.33±0.92‡	2.31±0.65§	2.30±0.54	0.051
Diameter stenosis, %		17.1±11.4	16.6±11.7	16.6±11.3	16.7±11.1	16.9±10.2	18.0±10.2¶	0.04
TIMI 3 flow		120/124 (96.8)	4,392/4,525 (97.1)	8,636/8,869 (97.4)	4,864/4,977 (97.7)‡	749/1,780 (98.3)§	844/858 (98.4)¶	0.03

Values are mean±standard deviation or n/N (%). *p<0.05 for comparison between underweight and normal weight patients; #p<0.05 for comparison between overweight and normal weight patients; ‡p<0.05 for comparison between patients with Class I obesity and normal weight patients; §p<0.05 for comparison of patients with Class II obesity and normal weight patients; ¶p<0.05 for comparison of patients with Class III obesity and normal weight patients. ACC: American College of Cardiology; AHA: American Heart Association; TIMI: Thrombolysis In Myocardial Infarction

Rates of cardiac death were higher in underweight (HR 2.65, 95% CI: 1.44-4.89) and lower in obese Class I patients (HR 0.79, 95% CI: 0.63-0.99) versus normal weight individuals. After multivariable adjustment, excess body weight was associated with higher cardiac mortality, statistically most significant for Class III obesity (HR 1.62, 95% CI: 1.05-2.51).

Unadjusted non-cardiac death was markedly lower in overweight (HR 0.67, 95% CI: 0.56-0.80) and obese Class I to III patients (HR 0.57, 0.65, and 0.48, respectively) versus normal weight patients. The trend persisted after adjustment, and overweight remained associated with improved non-cardiac mortality (HR 0.77, 95% CI: 0.63-0.94).

There were no differences in unadjusted and adjusted rates of ischaemia-driven TLR across BMI subgroups; however, rates of NTLR were higher for overweight (HR 1.16, 95% CI: 1.01-1.35) and Class I to III obesity subgroups (HR 1.41, 1.85, and 1.47, respectively). After adjustment, obesity Class II was an independent predictor of NTLR (HR 1.28, 95% CI: 1.04-1.58). No differences were found in rates of MI across BMI categories. The unadjusted risk of definite/probable stent thrombosis was lower in the Class II obesity versus normal weight subgroups (HR 0.60,

95% CI: 0.37-0.96). After adjustment, none of the BMI subgroups was associated with a risk of stent thrombosis. The unadjusted and adjusted adverse event rates were similar when only studies with five-year follow-up were included **(Supplementary Table 4, Supplementary Table 5, Supplementary Figure 3)**.

Subgroup analyses of patients treated with second-generation DES and other stents were performed **(Supplementary Table 6, Supplementary Table 7)**. We found no significant interaction between the use of second-generation DES and adjusted study outcomes at five years, except for ischaemia-driven TLR ($p_{interaction}$=0.04) **(Supplementary Table 8)**. Similarly, no significant interaction regarding study outcomes was found with age (<65 vs ≥65 years), sex, BMS (vs DES) and clinical presentation (STEMI and NSTEMI vs stable and unstable angina) with the exception of stent thrombosis that was more prevalent in patients with biomarker-positive presentation ($p_{interaction}$<0.001) **(Supplementary Table 8, Supplementary Table 9)**. Comparison of clinical and procedural characteristics, as well as unadjusted five-year outcomes of patients with and without available BMI data, are shown in **Supplementary Table 10-Supplementary Table 12**.
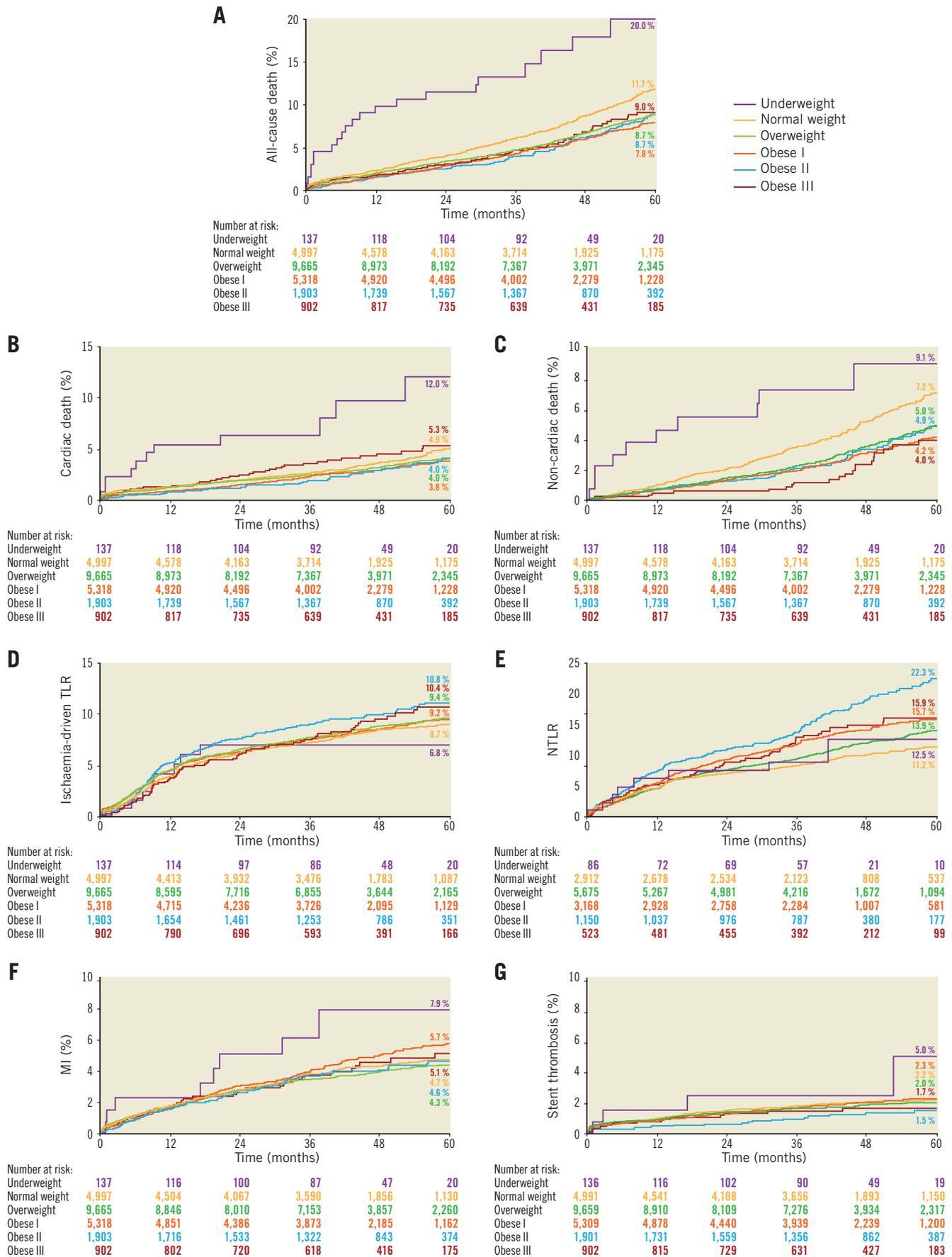
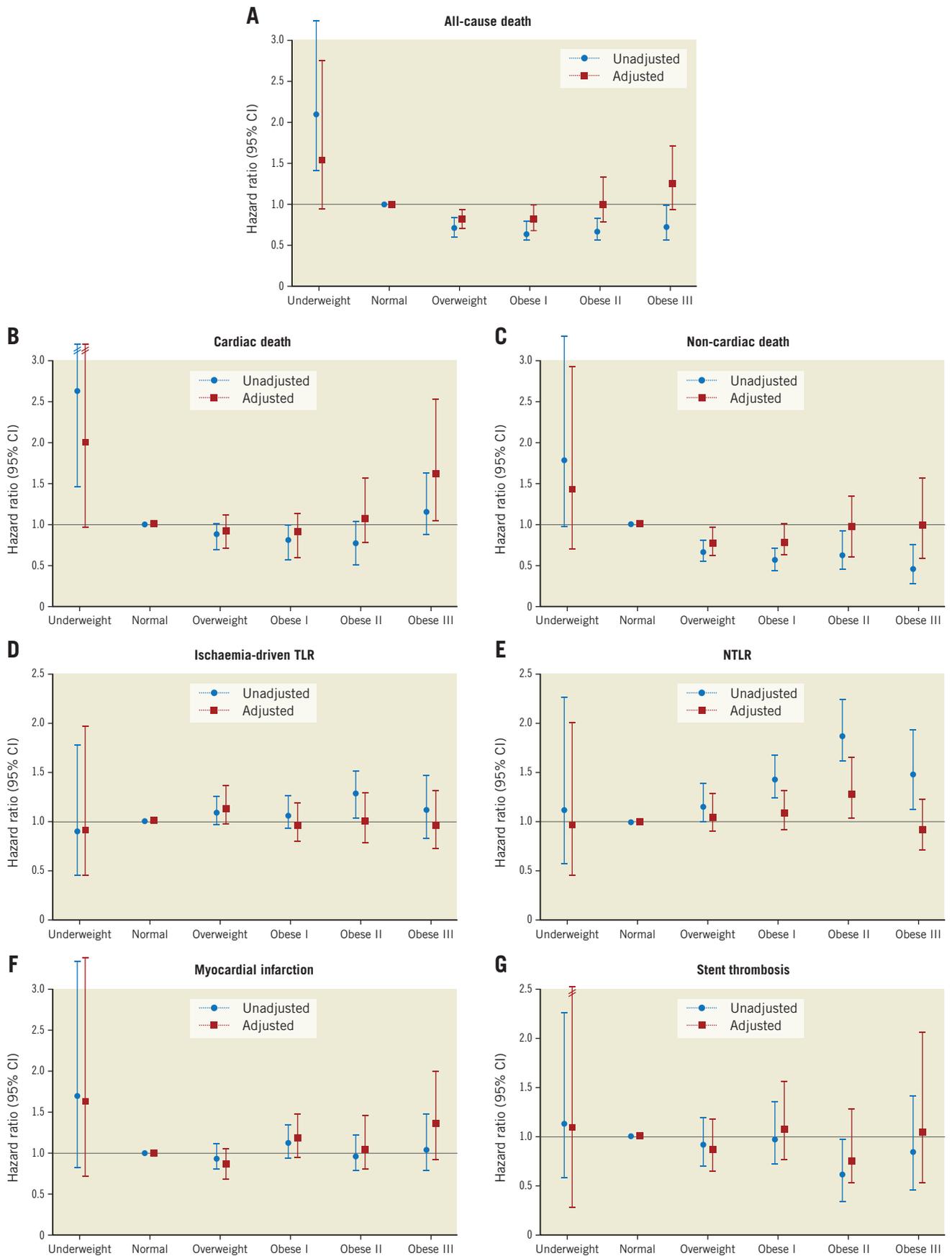**Figure 1.** *Kaplan-Meier curves stratified by body mass index.*

Figure 2. *Unadjusted and adjusted risk of study outcomes according to body mass index. Normal weight was used as a reference. CI: confidence interval*
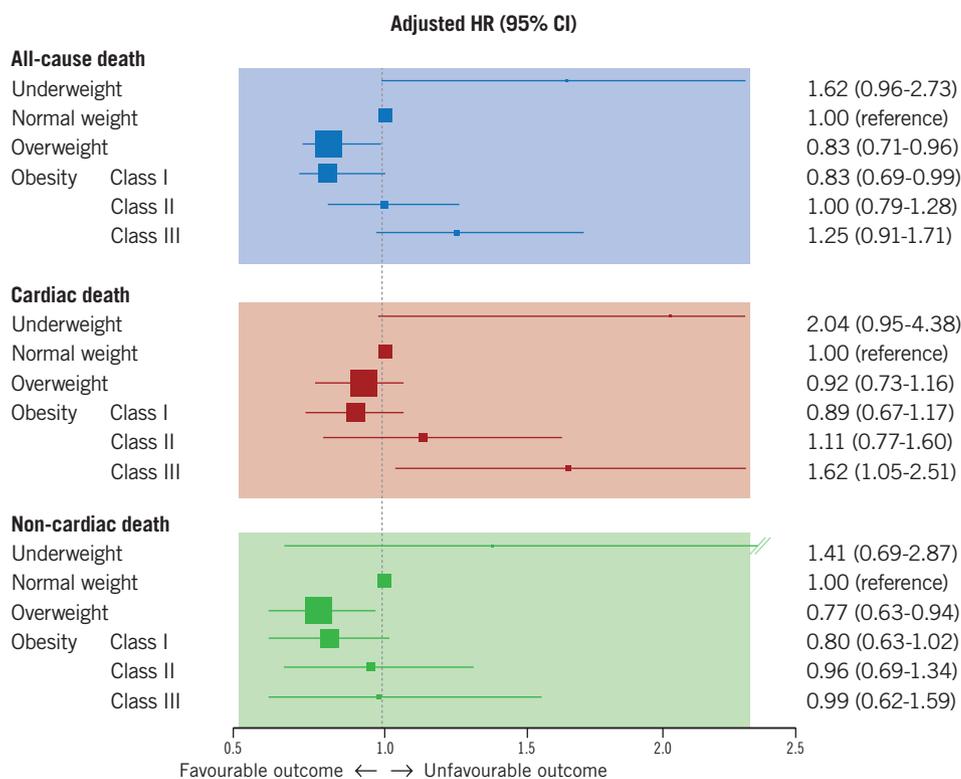
Figure 3. *Adjusted all-cause, cardiac and non-cardiac mortality five years after percutaneous coronary intervention. Box sizes represent number of patients in each BMI subgroup. HR: hazard ratio*

Discussion

The main findings of this large study using pooled patient-level data from 13 RCTs evaluating long-term outcomes after PCI are as follows. (i) Despite adjustment for multiple clinical, angiographic, and procedural confounders, BMI-determined overweight and moderate obesity were associated with a significantly lower long-term all-cause and non-cardiac mortality versus normal weight patients undergoing PCI. (ii) Conversely, cardiac death was not reduced in overweight and moderately obese patients but was significantly higher in morbidly obese individuals. (iii) A high BMI was associated with an increased risk of NTLR, but not with rates of ischaemia-driven repeat target lesion PCI, spontaneous MI, or stent thrombosis. (iv) Underweight patients comprised a small fraction of PCI subjects; they had the highest long-term mortality.

The advantage of the present study over previously published reports is in providing data not only on all-cause mortality, but also on centrally adjudicated cardiac and non-cardiac causes of death. Moreover, the large amount of clinical and procedural information available for patients enrolled in the analysed RCTs allowed adequate statistical adjustment. In the largest single study to date (N=345,192), Holroyd et al[6] reported that overweight and obesity (BMI >30 kg/m^{2}) were independent predictors of lower all-cause five-year mortality. However, the study did not distinguish between cardiac and non-cardiac death, similar to the study by Hastie et al[7] which reported significantly lower adjusted five-year

all-cause mortality of overweight, but not obese patients undergoing elective PCI. All-cause and cardiac mortality were evaluated in a pooled patient-level analysis of women undergoing PCI in 26 RCTs reported by Faggioni et al[8], revealing the association of higher BMI with lower all-cause, but not cardiac mortality.

Likewise, we reported a significant overall (cardiac and non-cardiac) mortality benefit to being overweight or obese. However, unlike these studies we revealed that only non-cardiac mortality was significantly lower; we found higher cardiac mortality in the highest BMI (>40 kg/m^{2}) versus normal weight individuals. This finding confirms the results of a large meta-analysis (N=250,152) showing that severe obesity (BMI >35 kg/m^{2}) was an independent predictor of higher cardiovascular mortality versus normal weight (relative risk 1.88, 95% CI: 1.05-3.34)[2]. Thus, the obesity paradox applies only to non-cardiac mortality, but not to cardiac mortality post PCI.

Aside from providing clarification on mortality patterns, our analysis revealed an association between BMI and higher rates of NTLR, a surrogate of CAD progression. This explanation seems plausible, given the higher prevalence of comorbidities and cardiovascular risk factors in obese patients as well as the previously reported association between obesity and accelerated development of CAD[9]. Conversely, the reduced anatomical complexity of CAD in obese patients was probably due to younger age of presentation versus normal weight counterparts. Closer medical attention and potentially a lower threshold for follow-up in secondary prevention of obese patients may also contribute to this effect[10].

In the current analysis there was no association between BMI and long-term risk of ischaemic TLR. Several previous trials assessing outcomes post PCI reported significant associations between higher BMI and increased risk of TLR and target vessel revascularisation[11,12]; however, the studies comprised mostly data on patients treated with bare metal stents. In studies reporting outcomes post DES, a high BMI was not associated with an increased risk of TLR or target vessel revascularisation[13,14]. One meta-analysis combining 15 studies (N=49,002) revealed a linear relationship between a higher BMI and any repeat revascularisation without categorisation into TLR and NTLR; however, again this was no longer significant when only patients treated with DES were included[15]. In the only previous study that distinguished TLR from NTLR, Wang et al[16] analysed outcomes of 6,083 patients (median 26-month follow-up) undergoing elective PCI with DES and reported a significant association of a higher BMI with higher risk of NTLR, but not TLR, concordant with our results. Moreover, fewer calcifications, shorter lesion length, and larger reference vessel size in high BMI patients may contribute to good acute and long-term stent results.

The higher long-term mortality observed in our study in underweight versus normal weight individuals was largely consistent with previous reports[2,6-8]. The underweight population was characterised by the most advanced age, highest proportion of women, current smokers, and unstable clinical presentation, and the most coronary calcification. These are known predictors of worse outcomes following PCI. We hypothesise that underweight patients bear either advanced cardiovascular disease (e.g., chronic insulin-dependent diabetes) or some non-cardiovascular comorbidities affecting nutrition status (i.e., illness-related weight loss) despite the fact that patients diagnosed with cancer or other severe chronic illnesses were not included in most stent trials. Low BMI is also associated with greater response to antiplatelet and anticoagulant pharmacotherapy, leading to increased risk of bleeding events, which might have contributed to higher mortality[10,17].

The absence of significant interaction between second-generation DES and study outcomes indicated that the observed relationships of BMI and all-cause, cardiac, and non-cardiac mortality as well as NTLR can be applied to contemporary clinical practice, largely dominated by newer DES platforms. The only significant interaction of stent type was with ischaemia-driven TLR. However, it seemed to be driven mainly by differences in the BMI <18.5 group **(Supplementary Table 4, Supplementary Table 5)**, the group with the smallest sample size, thus possibly occurring by chance.

Finally, hazard ratios of all-cause, cardiac, and non-cardiac death across BMI subgroups form U-shaped curves **(Figure 2)**, with the lowest number of events corresponding to overweight patients (25 ≤BMI <30 kg/m²). Many potential reasons for this apparent survival benefit have been suggested. The first is purely mechanistic and includes statistical explanations such as unmeasured confounders, reverse causation, and collider stratification bias, all described in detail elsewhere[18]. Despite selecting multiple covariates with potential impact on ischaemic outcomes for the multivariate Cox regression model, it is likely that some were not accounted for. However, as the adjustment revealed significant reduction of the point estimates observed in the unadjusted data, we hypothesise that most causes of improved survival in overweight patients are favourable differences in comorbidities, clinical presentation, and procedural factors. Second is the inherent limitation of BMI as a measure of obesity, as it does not differentiate whether the excess weight comes from fat or muscle. Other anatomical measures such as waist circumference or waist-to-hip ratio might give a better estimation of abdominal obesity because they have been shown to predict adverse outcomes independently of BMI; however, to date there are no studies assessing long-term prognosis of patients with CAD in relation to those indices. Third, the overweight subgroup was by far the largest (42.2%), twice the size of the normal weight reference (21.8%); therefore, it may be argued that this represents the "new normal".

Study limitations

First, the studied cohort included only patients enrolled in RCTs who usually represent a lower-risk population. Second, no data on renal function, non-cardiac comorbidities, medications, PCI access site, or bleeding outcomes were available in our pooled data set. Third, possible changes in BMI at follow-up were not accounted for. Fourth, MI definitions varied among the studies, not surprising considering the time course in which these studies were conducted. Some of the associations might have occurred by chance due to multiple testing. Finally, we used BMI as a measure of obesity, reflecting body size, but could not assess its composition, including the amount of fatty tissue.

Conclusions

Our results from a large pooled patient-level analysis confirm the long-term survival benefit seen in overweight and moderately obese patients versus normal weight controls post PCI. The main contributor to the overall survival benefit was non-cardiac death; we found no protective effect of high BMI on cardiac death. Patients with high BMI represented a higher risk of NTLR, but not TLR.

Impact on daily practice

Interventional cardiologists should no longer consider obese patients with stable CAD being at lower risk of adverse cardiovascular outcomes versus normal weight individuals. Even though patients with moderately increased BMI have improved long-term all-cause mortality post PCI, this results mostly from lower non-cardiac mortality as there was no significant association of BMI and the risk of MI, TLR, and stent thrombosis. Conversely, patients with severe obesity were at higher risk of both cardiac death and NTLR. Obese patients undergoing PCI should therefore receive adequate information on their risk of cardiovascular events and professional counselling about safe and effective ways to lose weight.

Guest Editor

Funding

Conflict of interest statement

A. Maehara reports research grants and personal fees from Boston Scientific and Abbott Vascular. C. von Birgelen reports institutional research grants from Abbott Vascular, Biotronik, Boston Scientific and Medtronic, outside the submitted work. P.W. Serruys reports personal fees from Abbott Laboratories, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sino Medical Sciences Technology, Société Europa Digital & Publishing, Stentys France, Svelte Medical Systems, Philips/Volcano, St. Jude Medical, Qualimed, and Xeltis, outside the submitted work. R. Mehran reports grants from Abbott Vascular, Boston Scientific, Medtronic, AstraZeneca, Bayer, BMS, CSL, DSI, Novartis, OrbusNeich, Osprey Medical, and PLC/Renal Guard, and personal fees from Abbott Vascular, Medtronic, Medscape/Web MD, Siemens Medical Solutions, Philips/Volcano/Spectranetics, Roviant Sciences, Sanofi (ITA), Bracco Group, Beth Israel Deaconess, Janssen, Watermark Research, Medintelligence (Janssen), ACC, Bayer, and AMA, outside the submitted work. G. Stone reports personal fees from Terumo, Amaranth, Shockwave, Valfix, TherOx, Reva, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Matrizyme, Miracor, Neovasc, V-wave, Abiomed, Claret, Sirtex, Ancora, Qool Therapeutics, SpectraWave, and MAIA Pharmaceuticals, and other from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, MedFocus family of funds, SpectraWave, and Orchestra Biomed, outside the submitted work. The other authors have no conflicts of interest to declare. The Guest Editor has no conflicts of interest to declare.

References

1. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Ärnlöv J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ, Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Fürst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang YH, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirrakhimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin MJ, Shiri R, Shiue I,

Roba HS, Silva DAS, Silverberg JI, Singh JA, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med.* 2017;377:13-27.

2. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet.* 2006;368:666-78.

3. Wang ZJ, Zhou YJ, Galper BZ, Gao F, Yeh RW, Mauri L. Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: a systematic review and meta-analysis. *Heart.* 2015;101:1631-8.

4. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res.* 1998;6 Suppl 2:51S-209S.

5. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel M, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

6. Holroyd EW, Sirker A, Kwok CS, Kontopantelis E, Ludman PF, De Belder MA, Butler R, Cotton J, Zaman A, Mamas MA; British Cardiovascular Intervention Society and National Institute of Cardiovascular Outcomes Research. The Relationship of Body Mass Index to Percutaneous Coronary Intervention Outcomes: Does the Obesity Paradox Exist in Contemporary Percutaneous Coronary Intervention Cohorts? Insights From the British Cardiovascular Intervention Society Registry. *JACC Cardiovasc Interv.* 2017;10:1283-92.

7. Hastie CE, Padmanabhan S, Slack R, Pell ACH, Oldroyd KG, Flapan AD, Jennings KP, Irving J, Eteiba H, Dominiczak AF, Pell JP. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. *Eur Heart J.* 2010;31:222-6.

8. Faggioni M, Baber U, Afshar AE, Giustino G, Sartori S, Sorrentino S, Steg PG, Stefanini GG, Windecker S, Leon MB, Stone GW, Wijns W, Serruys PW, Valgimigli M, Camenzind E, Weisz G, Smits PC, Kandzari DE, Galatius S, Von Birgelen C, Jeger RV, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Kastrati A, Chieffo A, Dangas GD, Morice MC, Mehran R. Effects of Body Mass Index on Clinical Outcomes in Female Patients Undergoing Percutaneous Coronary Intervention With Drug-Eluting Stents: Results From a Patient-Level Pooled Analysis of Randomized Controlled Trials. *JACC Cardiovasc Interv.* 2018;11:68-76.

9. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA.* 1999;282:1523-9.

10. Numasawa Y, Kohsaka S, Miyata H, Kawamura A, Noma S, Suzuki M, Nakagawa S, Momiyama Y, Naito K, Fukuda K. Impact of body mass index on in-hospital complications in patients undergoing percutaneous coronary intervention in a Japanese real-world multicenter registry. *PLoS One.* 2015;10: e0124399.

11. Rana JS, Mittleman MA, Ho KK, Cutlip DE. Obesity and clinical restenosis after coronary stent placement. *Am Heart J.* 2005;150:821-6.

12. Martin JL, Jia G, Martin SS, Shapiro TA, Herrmann HC, Dibattiste PM, Topol EJ, Moliterno DJ. The relationship of obesity to ischemic outcomes following coronary stent placement in contemporary practice. *Catheter Cardiovasc Interv.* 2006;67:563-70.

13. Sarno G, Räber L, Onuma Y, Garg S, Brugaletta S, van Domburg RT, Pilgrim T, Pfäffli N, Wenaweser P, Windecker S, Serruys P. Impact of body mass index on the five-year outcome of patients having percutaneous coronary interventions with drug-eluting stents. *Am J Cardiol.* 2011;108:195-201.

14. Akin I, Tölg R, Hochadel M, Bergmann MW, Khattab AA, Schneider S, Senges J, Kuck KH, Richardt G, Nienaber CA; DES.DE (German Drug-Eluting Stent) Study Group. No evidence of "obesity paradox" after treatment with drug-eluting stents in a routine clinical practice: results from the prospective multicenter German DES.DE (German Drug-Eluting Stent) Registry. *JACC Cardiovasc Interv.* 2012;5:162-9.

15. Wang ZJ, Gao F, Cheng WJ, Yang Q, Zhou YJ. Body Mass Index and Repeat Revascularization After Percutaneous Coronary Intervention: A Meta-analysis. *Can J Cardiol.* 2015;31:800-8.

16. Wang ZJ, Zhou YJ, Zhao YX, Liu YY, Shi DM, Liu XL, Yu M, Gao F. Effect of obesity on repeat revascularization in patients undergoing percutaneous coronary intervention with drug-eluting stents. *Obesity (Silver Spring).* 2012;20:141-6.

17. Jakubowski JA, Angiolillo DJ, Zhou C, Small DS, Moser BA, Ten Berg JM, Brown PB, James S, Winters KJ, Erlinge D. The influence of body size on the pharmacodynamic and pharmacokinetic response to clopidogrel and prasugrel: a retrospective analysis of the FEATHER study. *Thromb Res.* 2014;134:552-7.

18. Banack HR, Stokes A. The 'obesity paradox' may not be a paradox at all. *Int J Obes (Lond).* 2017;41:1162-3.

Supplementary data

Supplementary Figure 1. Spline curves representing the association of BMI and unadjusted risk of study outcomes. Hazard ratios are referenced to normal BMI.

Supplementary Figure 2. Spline curves representing the association of BMI and adjusted risk of study outcomes. Hazard ratios are referenced to normal BMI.

Supplementary Figure 3. Kaplan-Meier curves according to BMI in 10 studies with 5-year follow-up (n=13,752).

Supplementary Table 1. Clinical trial characteristics.

Supplementary Table 2. Adverse event rates at 5-year follow-up.

Supplementary Table 3. Unadjusted and adjusted hazard ratios of adverse outcomes at 5-year follow-up for BMI subgroups with normal weight individuals as the reference.

Supplementary Table 4. Adverse event rates at 5-year follow-up for 10 studies with 5-year follow-up (n=13,752).

Supplementary Table 5. Unadjusted and adjusted hazard ratios of adverse outcomes at 5-year follow-up for BMI subgroups with normal weight individuals as the reference for 10 studies with 5-year follow-up (n=13,752).

Supplementary Table 6. Adverse event rates at 5-year follow-up in patients treated with second-generation DES.

Supplementary Table 7. Adverse event rates at 5-year follow-up in patients treated with BMS and first-generation DES.

Supplementary Table 8. Interaction of BMI with sex and stent type for study outcomes at 5-year follow-up.

Supplementary Table 9. Interaction of BMI with age and clinical presentation for study outcomes at 5-year follow-up.

Supplementary Table 10. Baseline characteristics and clinical presentation in patients with and without available BMI data.

Supplementary Table 11. Quantitative coronary angiography and procedural characteristics in patients with and without available BMI data.

Supplementary Table 12. Adverse event rates at 5-year follow-up in patients with and without available BMI data.

The supplementary data are published online at:
https://eurointervention.pcronline.com/
doi/10.4244/EIJ-D-19-00467
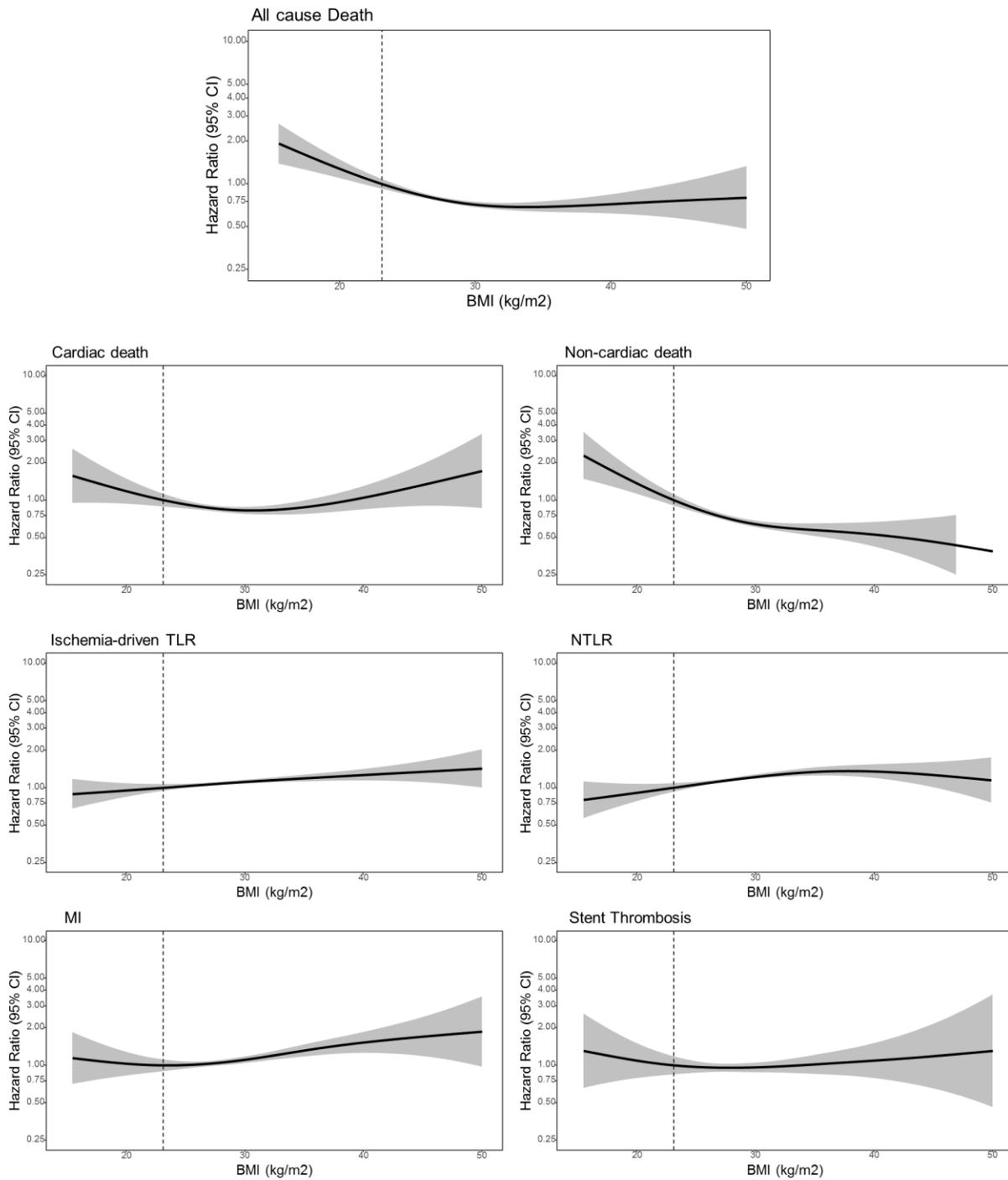
Supplementary data

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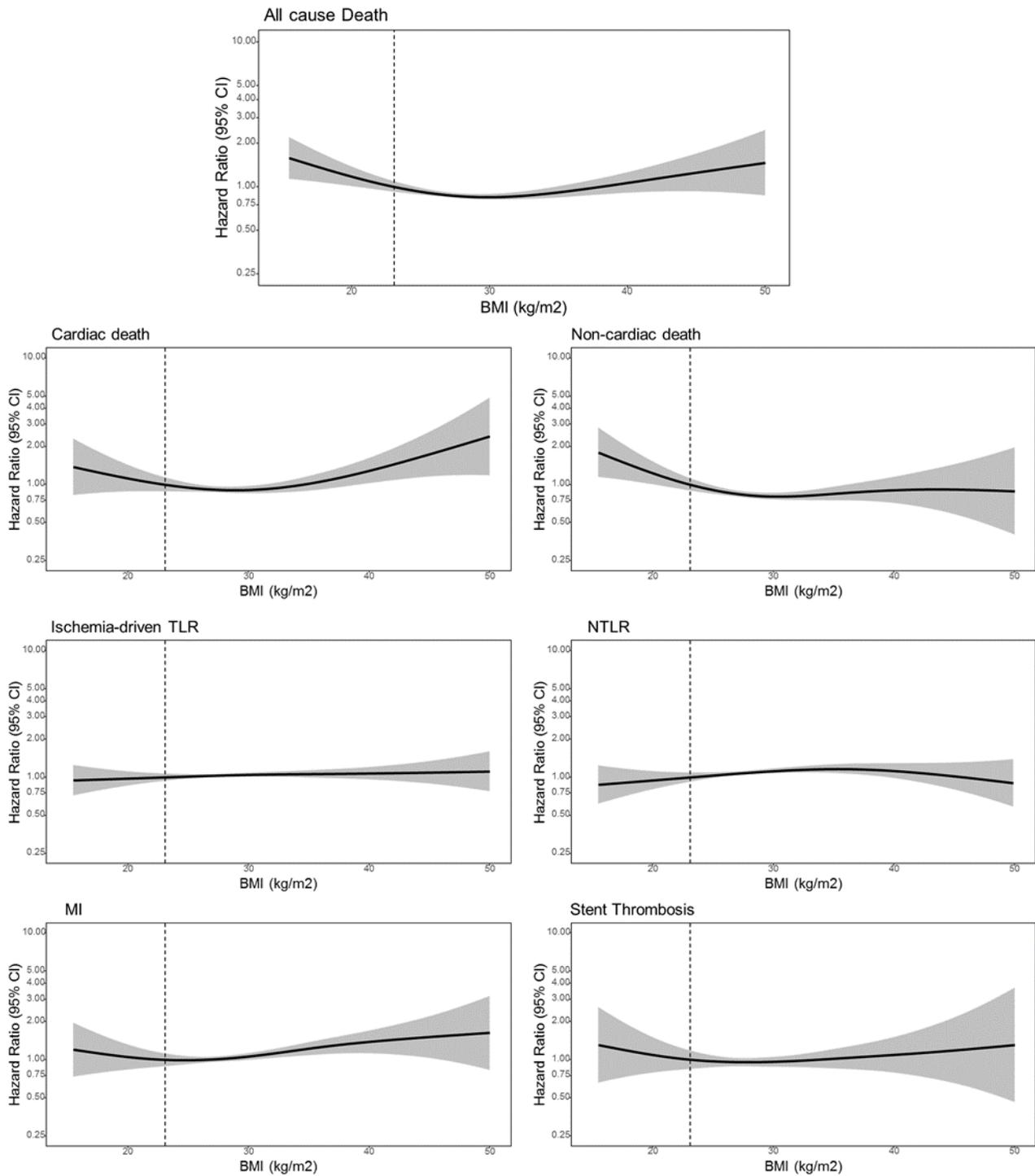
Supplementary Figure 2. Spline curves representing the association of BMI and adjusted risk of study outcomes. Hazard ratios are referenced to normal BMI.
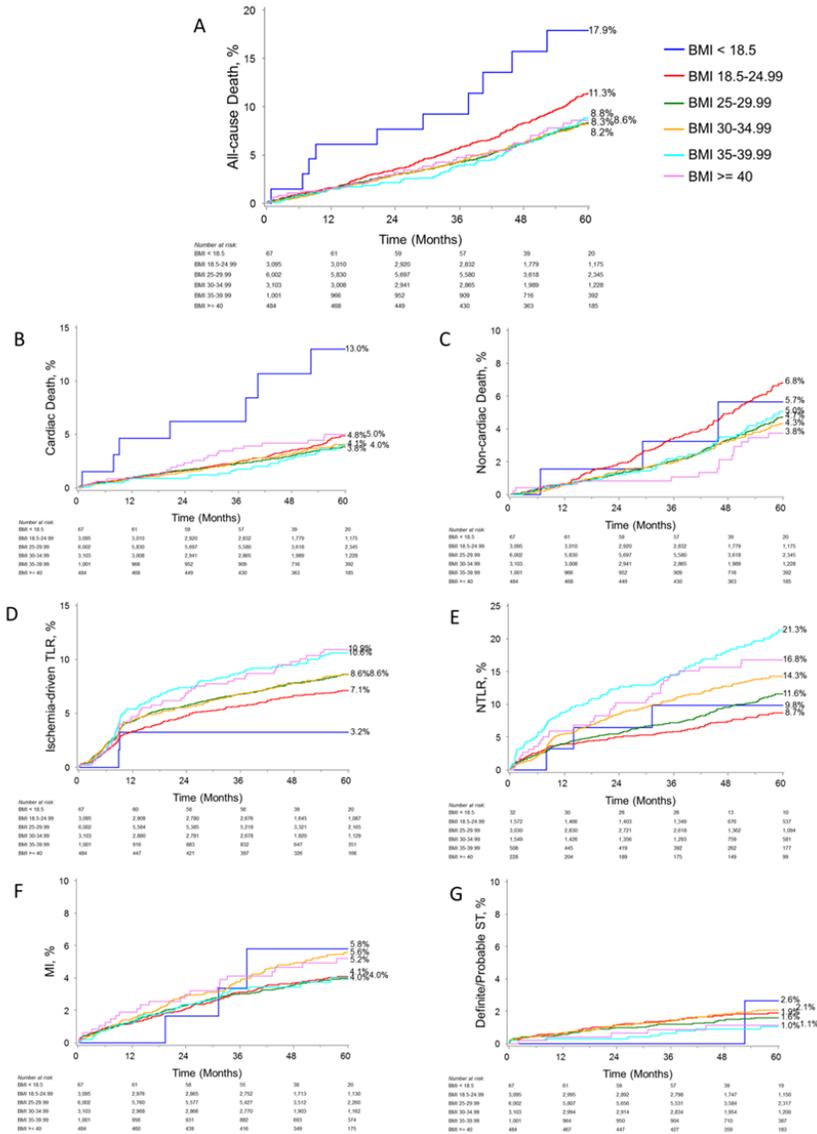
Supplementary Figure 3. Kaplan-Meier curves according to body mass index in 10 studies with 5-year follow-up (n=13,752).

Unadjusted Kaplan-Meier curves (5-year follow-up) according to body mass index for (A) all-cause death; (B) cardiac death; (C) non-cardiac death; (D) ischaemia-driven target lesion revascularisation (TLR); (E) non-target lesion revascularisation (NTLR); (F) myocardial infarction (MI); and (G) definite/probable stent thrombosis.

Supplementary Table 1. Clinical trial characteristics.

Trial	N	Patients with BMI data	Clinical presentation	Stents used	Follow-up, yrs	Any revascularisation reported	NTLR reported
TAXUS II	399	380	Stable CAD	TAXUS, BMS	5	Yes	No
TAXUS IV	1,314	1,277	Stable CAD or UA	TAXUS, BMS	5	No	No
TAXUS V	1,156	1,116	Stable CAD or UA	TAXUS, BMS	5	Yes	No
SPIRIT III	1,002	974	Stable CAD or UA	XIENCE, TAXUS	5	Yes	Yes
ACUITY	7,789	2,575	NSTEMI or UA	TAXUS, CYPHER, BMS	1	No	No
HORIZONS-AMI	3,006	2,968	STEMI	TAXUS, BMS	3	Yes	Yes
COMPARE	1,800	1,760	Stable CAD, UA, NSTEMI, or STEMI	XIENCE, TAXUS	5	Yes	Yes
ENDEAVOR IV	1,548	1,522	Stable CAD or UA	Endeavor, TAXUS	5	Yes	Yes
SPIRIT IV	3,687	3,627	Stable CAD or UA	XIENCE, TAXUS	3	Yes	Yes
COMPARE II	2,707	2,663	Stable CAD, UA, NSTEMI, or STEMI	Nobori, XIENCE, PROMUS	5	Yes	Yes
PLATINUM	1,530	1,515	Stable CAD or UA	PROMUS, XIENCE	5	No	No
TWENTE	1,391	1,141	Stable CAD, UA, or NSTEMI	Resolute, XIENCE	5	Yes	Yes
TWENTE II	1,811	1,404	Stable CAD, UA, NSTEMI, or STEMI	Resolute, PROMUS	5	Yes	Yes

BMS: bare metal stent; CAD: coronary artery disease; NTLR: non-target lesion revascularisation; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

Supplementary Table 2. Adverse event rates at 5-year follow-up.

	Underweight	Normal weight	Overweight	Obese			Overall *p*-value
				Class I	Class II	Class III	
All-cause death	20% (21)*	11.7% (391)	8.7% (584)†	7.8% (288)‡	8.7% (109)§	9.0% (57)	<0.0001
Cardiac death	12% (11)*	4.9% (164)	4.0% (279)	3.8% (143)‡	4.0% (50)	5.3% (36)	0.0004
Non-cardiac death	9.1% (10)	7.2% (227)	5.0% (305)†	4.2% (145)‡	4.9% (59)§	4.0% (21)‖	<0.0001
Ischaemia-driven TLR	6.8% (8)	8.7% (355)	9.4% (750)	9.2% (406)	10.8% (170)§	10.4% (73)	0.28
NTLR	12.5% (8)	11.2% (259)	13.9% (601)†	15.7% (409)‡	22.3% (194)§	15.9% (72)‖	<0.0001
Myocardial infarction	7.9% (8)	4.7% (188)	4.3% (343)	5.7% (231)	4.6% (70)	5.1% (36)	0.16
Stent thrombosis#	5.0% (4)	2.2% (90)	2.0% (162)	2.3% (95)	1.5% (21)§	1.7% (13)	0.24

Values are presented as Kaplan-Meier estimate (number of events). *p<0.05 for comparison between underweight and normal weight patients; †p<0.05 for comparison between overweight and normal weight patients; ‡p<0.05 for comparison between patients with Class I obesity and normal weight patients; §p<0.05 for comparison of patients with Class II obesity and normal weight patients; ‖p<0.05 for comparison of patients with Class III obesity and normal weight patients; #definite or probable according to the Academic Research Consortium.

NTLR: non-target lesion revascularisation; TLR: target lesion revascularisation

Supplementary Table 3. Unadjusted and adjusted hazard ratios of adverse outcomes at 5-year follow-up for BMI subgroups with normal weight individuals as the reference.

	Underweight HR (95% CI)	Normal weight	Overweight HR (95% CI)	Class I HR (95% CI)	Obese Class II HR (95% CI)	Class III HR (95% CI)
All-cause death						
Unadjusted	2.15 (1.38-3.33)*	1.00	0.75 (0.66-0.85)†	0.67 (0.57-0.78)‡	0.70 (0.57-0.87)§	0.76 (0.58-1.01)
Adjusted	1.62 (0.96-2.73)	1.00	0.83 (0.71-0.96)†	0.83 (0.69-0.99)‡	1.00 (0.79-1.28)	1.25 (0.91-1.71)
Cardiac death						
Unadjusted	2.66 (1.44-4.89)*	1.00	0.86 (0.71-1.04)	0.79 (0.63-0.99)‡	0.77 (0.55-1.05)	1.16 (0.81-1.67)
Adjusted	2.04 (0.95-4.38)	1.00	0.92 (0.73-1.16)	0.89 (0.67-1.17)	1.11 (0.77-1.60)	1.62 (1.05-2.51)‖
Non-cardiac death						
Unadjusted	1.77 (0.94-3.33)	1.00	0.67 (0.56-0.80)†	0.57 (0.47-0.71)‡	0.65 (0.49-0.87)§	0.48 (0.31-0.75)‖
Adjusted	1.41 (0.69-2.87)	1.00	0.77 (0.63-0.94)†	0.80 (0.63-1.02)	0.96 (0.69-1.34)	0.99 (0.62-1.59)
Ischaemia-driven TLR						
Unadjusted	0.89 (0.44-1.79)	1.00	1.08 (0.95-1.21)	1.05 (0.92-1.22)	1.25 (1.04-1.49)§	1.11 (0.87-1.43)
Adjusted	0.91 (0.43-1.93)	1.00	1.12 (0.97-1.29)	0.97 (0.82-1.14)	1.01 (0.81-1.26)	0.96 (0.72-1.28)
NTLR						
Unadjusted	1.12 (0.56-2.27)	1.00	1.16 (1.01-1.35)†	1.41 (1.22-1.67)‡	1.85 (1.53-2.22)§	1.47 (1.14-1.92)‖
Adjusted	0.94 (0.44-1.99)	1.00	1.06 (0.91-1.24)	1.09 (0.92-1.29)	1.28 (1.04-1.58)§	0.91 (0.69-1.21)
Myocardial infarction						
Unadjusted	1.68 (0.83-3.42)	1.00	0.93 (0.78-1.11)	1.12 (0.93-1.37)	0.96 (0.73-1.27)	1.04 (0.73-1.49)
Adjusted	1.61 (0.71-3.66)	1.00	0.86 (0.69-1.05)	1.18 (0.94-1.49)	1.04 (0.75-1.44)	1.35 (0.90-2.03)
Stent thrombosis#						
Unadjusted	1.12 (0.56-2.27)	1.00	0.92 (0.71-1.19)	0.97 (0.73-1.30)	0.60 (0.37-0.96)§	0.79 (0.44-1.41)
Adjusted	1.09 (0.27-4.44)	1.00	0.87 (0.65-1.17)	1.11 (0.80-1.56)	0.73 (0.42-1.27)	1.07 (0.55-2.10)

Multivariable Cox proportional hazards model based on: age, sex, diabetes, smoking, hypertension, hyperlipidaemia, prior coronary artery bypass grafting, prior percutaneous coronary intervention, prior myocardial infarction, presentation with myocardial infarction (non–ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction), type and length of implanted stents, reference vessel diameter, moderate or severe calcifications, and number of treated lesions. *p<0.05 for comparison between underweight and normal weight patients;

†p<0.05 for comparison between overweight and normal weight patients; ‡p<0.05 for comparison between patients with Class I obesity and normal weight patients; §p<0.05 for comparison of patients with Class II obesity and normal weight patients; ‖p<0.05 for comparison of patients with Class III obesity and normal weight patients; #definite or probable according to the Academic Research Consortium.

CI: confidence interval; HR: hazard ratio; NTLR: non-target lesion revascularisation; TLR: target lesion revascularisation

Supplementary Table 4. Adverse event rates at 5-year follow-up for 10 studies with 5-year follow-up (n=13,752).

	Underweight	Normal weight	Overweight	Obese Class I	Class II	Class III	Overall p-value
All-cause death	17.9% (10)	11.3% (282)	8.3% (409)†	8.2% (214)‡	8.8% (75)§	8.6% (37)	0.0001
Cardiac death	13.0% (7)*	4.8% (117)	3.8% (190)	4.1% (107)	4.0% (33)	5.0% (22)	0.01
Non-cardiac death	5.7% (3)	6.8% (165)	4.7% (219)†	4.3% (107)‡	5.0% (42)	3.8% (15)	0.0003‖
Ischaemia-driven TLR	3.2% (2)	7.1% (196)	8.6% (462)†	8.6% (241)‡	10.6% (98)§	10.9% (48)	0.005‖
NTLR	9.8% (3)	8.7% (110)	11.6% (278)†	14.3% (192)‡	21.3% (93)§	16.8% (35)	<0.0001‖
Myocardial infarction	5.8% (3)	4.1% (110)	4.0% (210)	5.6% (149)‡	4.0% (37)	5.2% (23)	0.07
Stent thrombosis#	2.6% (1)	1.9% (51)	1.6% (84)	2.1% (55)	1.0% (9)	1.1% (5)	0.30

Values are presented as Kaplan-Meier estimate (number of events). *p<0.05 for comparison between underweight and normal weight patients; †p<0.05 for comparison between overweight and normal weight patients; ‡p<0.05 for comparison between patients with Class I obesity and normal weight patients; §p<0.05 for comparison of patients with Class II obesity and normal weight patients; ‖p<0.05 for comparison of patients with Class III obesity and normal weight patients; #definite or probable according to the Academic Research Consortium.

NTLR: non-target lesion revascularisation; TLR: target lesion revascularisation

Supplementary Table 5. Unadjusted and adjusted hazard ratios of adverse outcomes at 5-year follow-up for BMI subgroups with normal weight individuals as the reference for 10 studies with 5-year follow-up (n=13,752).

	Underweight HR (95% CI)	Normal weight	Overweight HR (95% CI)	Obese Class I HR (95% CI)	Class II HR (95% CI)	Class III HR (95% CI)
All-cause death						
Unadjusted	1.68 (0.89-3.15)	1.00	0.73 (0.63-0.85)†	0.72 (0.61-0.86)†	0.75 (0.58-0.97)§	0.76 (0.54-1.06)
Adjusted	1.55 (0.80-3.03)	1.00	0.80 (0.67-0.96)†	0.90 (0.73-1.11)	1.08 (0.81-1.43)	1.25 (0.86-1.82)
Cardiac death						
Unadjusted	2.82 (1.32-6.06)*	1.00	0.82 (0.64-1.03)	0.88 (0.68-1.14)	0.79 (0.54-1.18)	1.10 (0.69-1.72)
Adjusted	2.73 (1.19-6.28)*	1.00	0.89 (0.68-1.17)	0.96 (0.70-1.33)	1.15 (0.75-1.77)	1.64 (0.97-2.75)
Non-cardiac death						
Unadjusted	0.86 (0.28-2.70)	1.00	0.67 (0.55-0.82)†	0.62 (0.48-0.79)‡	0.72 (0.51-1.01)	0.52 (0.31-0.88)‖
Adjusted	0.84 (0.27-2.64)	1.00	0.74 (0.59-0.94)†	0.85 (0.64-1.12)	1.03 (0.70-1.52)	0.97 (0.56-1.70)
Ischaemia-driven TLR						
Unadjusted	0.48 (0.12-1.93)	1.00	1.22 (1.03-1.43)†	1.22 (1.01-1.47)‡	1.54 (1.20-1.96)§	1.54 (1.11-2.08)‖
Adjusted	0.49 (0.12-1.98)	1.00	1.19 (0.99-1.43)	1.00 (0.80-1.24)	1.07 (0.82-1.42)	1.02 (0.72-1.45)
NTLR						
Unadjusted	1.36 (0.43-4.27)	1.00	1.30 (1.04-1.61)†	1.75 (1.37-2.22)‡	2.56 (1.96-3.44)§	2.08 (1.43-3.03)‖
Adjusted	1.29 (0.41-4.09)	1.00	1.07 (0.84-1.36)	1.15 (0.89-1.49)	1.39 (1.02-1.89)§	0.94 (0.62-1.43)
Myocardial infarction						
Unadjusted	1.30 (0.41-4.10)	1.00	0.97 (0.78-1.22)	1.32 (1.03-1.69)‡	1.01 (0.69-1.44)	1.30 (0.83-2.04)
Adjusted	1.54 (0.49-4.90)	1.00	0.84 (0.64-1.10)	1.30 (0.98-1.74)	0.93 (0.61-1.43)	1.47 (0.89-2.41)
Stent thrombosis#						
Unadjusted	N/A	1.00	0.84 (0.59-1.19)†	1.05 (0.71-1.54)	0.52 (0.26-1.05)	0.60 (0.24-1.5)
Adjusted	N/A	1.00	0.71 (0.47-1.06)	1.03 (0.66-1.62)	0.45 (0.20-1.03)	0.72 (0.27-1.91)

Multivariable Cox proportional hazards model based on: age, sex, diabetes, smoking, hypertension, hyperlipidaemia, prior coronary artery bypass grafting, prior percutaneous coronary intervention, prior myocardial infarction, presentation with myocardial infarction (non–ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction), type and length of implanted stents, reference vessel diameter, moderate or severe calcifications, and number of treated lesions. *p<0.05 for comparison between underweight and normal weight patients; †p<0.05 for comparison between overweight and normal weight patients; ‡p<0.05 for comparison between patients with Class I obesity and

normal weight patients; §p<0.05 for comparison of patients with Class II obesity and normal weight patients; ‖p<0.05 for comparison of patients with Class III obesity and normal weight patients; #definite or probable according to the Academic Research Consortium.

CI: confidence interval; HR: hazard ratio; NTLR: non-target lesion revascularisation; TLR: target lesion revascularisation

Supplementary Table 6. Adverse event rates at 5-year follow-up in patients treated with second-generation DES.

	Underweight	Normal weight	Overweight	Obese			Overall *p*-value
				Class I	Class II	Class III	
All-cause death	11.8% (6)	10.7% (190)	7.8% (280)†	7.6% (148)‡	8.3% (52)§	9.7% (33)	0.005
Cardiac death	10.3% (5)	4.6% (83)	3.3% (123)†	3.9% (78)	3.8% (25)	5.7% (21)	0.007
Non-cardiac death	1.7% (1)	6.4% (107)	4.7% (157)†	3.8% (70)‡	4.7% (27)	4.2% (12)	0.01
Ischaemia-driven TLR	1.7% (1)	5.9% (116)	6.9% (280)	6.3% (142)	9.1% (67)§	8.5% (32)‖	0.02
NTLR	9.6% (3)	8.1% (93)	12.6% (283)†	14.9% (224)‡	22.4% (110)§	17.0% (46)‖	<0.0001
Myocardial infarction	8.2% (4)*	2.6% (56)	3.4% (137)	4.6% (99)‡	3.7% (26)	4.7% (16)	0.02
Stent thrombosis#	4.2% (1)	1.2% (25)	1.3% (48)	1.7% (35)	1.3% (9)	1.0% (4)	0.80

Values are presented as Kaplan-Meier estimate (number of events). *p<0.05 for comparison between underweight and normal weight patients;

†p<0.05 for comparison between overweight and normal weight patients; ‡p<0.05 for comparison between patients with Class I obesity and

normal weight patients; §p<0.05 for comparison of patients with Class II obesity and normal weight patients; ‖p<0.05 for comparison of patients

with Class III obesity and normal weight patients; #definite or probable according to the Academic Research Consortium.

NTLR: non-target lesion revascularisation; TLR: target lesion revascularisation

Supplementary Table 7. Adverse event rates at 5-year follow-up in patients treated with BMS and first-generation DES.

	Underweight	Normal weight	Overweight	Obese			Overall *p*-value
				Class I	Class II	Class III	
All-cause death	27.0% (14)*	12.7% (199)	9.7% (301)†	8.0% (140)‡	9.3% (57)§	8.2% (24)‖	<0.0001
Cardiac death	12.1% (5)	5.2% (81)	4.6% (153)	3.5% (65)	4.3% (25)	4.7% (15)	0.055
Non-cardiac death	16.9% (9)*	7.9% (118)	5.3% (148)†	4.6% (75)‡	5.2% (32)§	3.7% (9)‖	0.01
Ischaemia-driven TLR	12.2% (7)	11.9% (236)	12.0% (463)	12.2% (259)	12.3% (102)	12.0% (40)	0.94
NTLR	13.0% (5)	14.7% (166)	15.5% (318)	16.9% (185)	21.9% (84)§	14.0% (26)	0.15
Myocardial infarction	6.2% (4)	7.1% (132)	5.5% (205)	6.9% (130)	5.7% (44)	5.2% (19)	0.43
Stent thrombosis#	4.9% (3)	3.4% (65)	2.9% (114)	2.9% (60)	1.8% (12)§	2.4% (9)	0.13

Values are presented as Kaplan-Meier estimate (number of events). *p<0.05 for comparison between underweight and normal weight patients;

†p<0.05 for comparison between overweight and normal weight patients; ‡p<0.05 for comparison between patients with Class I obesity and

normal weight patients; §p<0.05 for comparison of patients with Class II obesity and normal weight patients; ‖p<0.05 for comparison of patients

with Class III obesity and normal weight patients; #definite or probable according to the Academic Research Consortium.

NTLR: non-target lesion revascularisation; TLR: target lesion revascularisation

Supplementary Table 8. Interaction of BMI with sex and stent type for study outcomes at 5-year follow-up.

	p-value for interaction of BMI with sex		*p*-value for interaction of BMI with DES (1ˢᵗ and 2ⁿᵈ generation)		*p*-value for interaction of BMI with 2ⁿᵈ generation DES	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
All-cause death	0.056	0.09	0.13	0.24	0.13	0.39
Cardiac death	0.32	0.13	0.057	0.19	0.12	0.27
Non-cardiac death	0.18	0.13	0.31	0.36	0.30	0.52
Ischaemia-driven TLR	0.25	0.44	0.61	0.06	0.19	0.04
NTLR	0.92	0.50	0.53	0.65	0.05	0.08
Myocardial infarction	0.31	0.62	0.67	0.44	0.053	0.07
Stent thrombosis	0.03	N/A	0.44	0.59	0.68	0.78

NTLR: non-target lesion revascularisation; TLR: target lesion revascularisation

Supplementary Table 9. Interaction of BMI with age and clinical presentation for study outcomes at 5-year follow-up.

	p-value for interaction of BMI with age (<65 vs ≥65 years)		*p*-value for interaction of BMI with clinical presentation (STEMI/NSTEMI vs stable/unstable angina)	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
All-cause death	0.32	0.53	0.15	0.53
Cardiac death	0.10	0.34	0.17	0.29
Non-cardiac death	0.91	0.97	0.06	0.43
Ischaemia-driven TLR	0.04	0.36	0.10	0.18
NTLR	1.00	0.97	0.73	0.53
Myocardial infarction	0.31	0.37	0.09	0.19
Stent thrombosis	0.24	0.43	0.58	<0.001

NTLR: non-target lesion revascularisation; TLR: target lesion revascularisation

Supplementary Table 10. Baseline characteristics and clinical presentation in patients with and without available BMI data.

	BMI n=22,922, 71.5%	No BMI n=9,153, 28.5%	*p*-value
Age, years	62.8±11.0	62.4±11.2	0.003
Male	72.2% (16,540/22,922)	72.3% (23,192/32,070)	0.31
Race			
White	92.0% (14,121/15,345)	92.0% (5,916/6,429)	0.99
Hispanic or Latino	1.8% (271/15,345)	2.8% (183/6,429)	<0.0001
Asian	1.9% (292/15,345)	1.7% (107/6,429)	0.23
Black or African American	4.3% (661/15,345)	3.5% (223/6,429)	0.004
Risk factors			
Diabetes mellitus	24.3% (5,563/22,906)	25.3% (2,302/9,105)	0.06
Insulin-treated	7.1% (1,623/22,906)	7.2% (656/9,105)	0.71
Current smoker	28.0% (6,362/22,723)	28.9% (2,618/9,072)	0.12
Hypertension	64.6% (14,787/22,897)	63.9% (5,812/9,098)	0.24
Hyperlipidaemia	62.6% (14,241/22,765)	62.6% (5,622/8,980)	0.93
Clinical history			
Prior CABG	8.1% (1,865/22,915)	11.9% (1,083/9,074)	<0.0001
Prior PCI	21.5% (4,894/22,815)	29.7% (2,683/9,041)	<0.0001
Prior MI	21.8% (4,955/22,699)	31.3% (2,804/8,951)	<0.0001
Clinical presentation			
Acute coronary syndromes	57.6% (12,538/21,761)	81.7% (6,829/8,363)	<0.0001
STEMI	18.1% (4,154/22,920)	2.3% (215/9,152)	<0.0001
NSTEMI	14.7% (3,362/22,920)	35.0% (3,204/9,152)	<0.0001
Unstable angina	23.1% (5,022/21,761)	40.8% (3,410/8,363)	<0.0001
Stable CAD	42.4% (9,223/21,761)	18.3% (1,534/8,363)	<0.0001

Values are mean±standard deviation or n (%).

CABG: coronary artery bypass grafting; MI: myocardial infarction; NSTEMI: non–ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

Supplementary Table 11. Quantitative coronary angiography and procedural characteristics in patients with and without available BMI data.

	BMI n=22,922, 71.5%	No BMI n=9,153, 28.5%	*p*-value
Baseline angiography			
Reference vessel diameter, mm	2.76 (0.69)	2.76 (0.51)	0.96
Minimum lumen diameter, mm	0.71 (0.46)	0.80 (0.44)	<0.0001
Diameter stenosis, %	75.3 (16.3)	71.0 (14.5)	<0.0001
Lesion length, mm	17.1 (11.3)	15.5 (9.1)	<0.0001
Moderate/severe tortuosity	6.8% (653/9,610)	5.8% (306/5,238)	0.02
Moderate/severe calcification	31.9% (6,491/20,376)	23.2% (1,435/6,181)	<0.0001
ACC/AHA type C lesion	39.7% (8,388/21,151)	31.6% (2,017/6,375)	<0.0001
TIMI 3 flow	78.9% (16,700/21,162)	85.3% (5,485/6,431)	<0.0001
Number of treated lesions			
1	80.0% (18,264/22,833)	80.4% (7,302/9,082)	0.41
2	16.1% (3,665/22,833)	14.3% (1,299/9,082)	0.0001
≥3	4.0% (902/22,833)	5.3% (481/9,082)	<0.0001
Type of implanted stent			
Bare metal	12.5% (2,842/22,741)	35.6% (3,130/8,786)	<0.0001
Drug-eluting	86.0% (19,554/22,741)	56.5% (4,965/8,786)	<0.0001
First-generation	35.6% (8,107/22,741)	36.8% (3,235/8,786)	0.052
Second-generation	50.3% (11,447/22,741)	19.7% (1,730/8,786)	<0.0001
Total stent length, mm	31.1 (22.1)	25.0 (13.2)	<0.0001
Final minimum lumen diameter, mm	2.30 (0.83)	2.28 (0.53)	0.04
Final diameter stenosis, %	16.7 (11.2)	18.6 (10.7)	<0.0001
Final TIMI 3 flow	97.5% (20,605/21,133)	98.3% (6,103/6,211)	0.0005

Values are mean±standard deviation or n (%).

CABG: coronary artery bypass grafting; MI: myocardial infarction; NSTEMI: non–ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

Supplementary Table 12. Adverse event rates at 5-year follow-up in patients with and without available BMI data.

	BMI n=22,922, 71.5%	No BMI n=9,153, 28.5%	*p*-value
All-cause death	9.2% (1,450)	8.9% (461)	0.94
Cardiac death	4.2% (683)	4.1% (221)	1.00
Non-cardiac death	5.2% (767)	4.9% (240)	0.93
Ischaemia-driven TLR	9.4% (1,762)	11.5% (841)	<0.0001
NTLR	14.6% (1,543)	19.9% (371)	<0.0001
Myocardial infarction	4.8% (876)	5.8% (376)	<0.0001
Stent thrombosis#	2.1% (385)	2.0% (138)	0.45