Impact of Body Composition Indices on Ten-year Mortality After Revascularization of Complex Coronary Artery Disease (From the Syntax Extended Survival Trial)

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Numerous studies have demonstrated a paradoxical association between higher baseline body mass index (BMI) and lower long-term mortality risk after coronary revascularization, known as the "obesity paradox", possibly relying on the single use of BMI. The current study is a post-hoc analysis of the SYNTAX Extended Survival (SYNTAXES) trial, which is the extended follow-up of the SYNTAX trial comparing percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) in patients with left-main coronary artery disease (LMCAD) or three-vessel disease (3VD). Patients were stratified according to baseline BMI and/or waist circumference (WC). Out of 1,800 patients, 1,799 (99.9%) and 1,587 (88.2%) had available baseline BMI and WC data, respectively. Of those, 1,327 (73.8%) patients had High BMI (≥25 kg/m^2), whereas 705 (44.4%) patients had High WC (>102 cm for men or >88 cm for women). When stratified by both BMI and WC, 10-year mortality risk was significantly higher in patients with Low BMI/Low WC (adjusted hazard ratio [HR]: 1.65; 95% confidence interval [CI]: 1.09 to 2.51), Low BMI/High WC (adjusted HR: 2.74; 95% CI: 1.12 to 6.69), or High BMI/High WC (adjusted HR: 1.59; 95% CI: 1.11 to 2.27) compared to those with High BMI/Low WC. In conclusion, the "obesity paradox" following coronary revascularization would be driven by low long-term mortality risk of the High BMI/Low WC group. Body composition should be assessed by the combination of BMI and WC in the appropriate evaluation of the long-term risk of obesity in patients with LMCAD or 3VD. **(Am J Cardiol 2021;151:30−38)**

Obesity is a major health problem worldwide and contributes to progression of cardiovascular disease, including coronary artery disease (CAD), leading to poor prognosis.[1] Nevertheless, numerous studies have demonstrated in patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) a paradoxical association between high baseline body mass index (BMI) and a low mortality risk, the so-called "obesity paradox".[2-6] Although the exact biological and prognostic significance of the "obesity paradox" remains unclear thus far, one major hypothesis is that BMI itself would be a poor and indirect indicator of obesity-related cardiovascular risk

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See page 37 for disclosure information.

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since it does not necessarily reflect total body adiposity.[7] Therefore, to combine BMI with other body composition indices such as waist circumference (WC) may achieve better predictive performance than single use of BMI, and may provide insights into the obesity paradox. The aim of the present subgroup analysis of the SYNTAX Extended Survival (SYNTAXES) study is to investigate the impact of body composition on very long-term clinical outcomes by using BMI and WC as two different anthropomorphic indices in patients with severe CAD who underwent PCI or CABG.

Methods

The present study is a post-hoc subgroup analysis of the SYNTAXES study (NCT03417050), which was an investigator-driven extended 10-year follow-up of the SYNTAX trial (NCT00114972) beyond its original final follow-up of 5 years.[8,9] In brief, the SYNTAX trial was a multicenter, randomized controlled trial done in 85 hospitals across 18 North American and European countries. A total of 1,800 patients with de novo three-vessel disease (3VD) and/or left main CAD (LMCAD), who were deemed eligible for both PCI and CABG based on clinical judgement and the consensus of a Heart Team, were enrolled and randomized in a 1:1 fashion either to receive PCI (n = 903) with a uniform use of TAXUS Express paclitaxel-drug eluting stents (Boston Scientific Corporation, Marlborough, MA, USA) or CABG (n = 897). Patients who had only one of the two revascularization options were excluded from randomization and were entered into nested registries for PCI or CABG.

The main result of the SYNTAXES study has been already reported.[10] Both SYNTAX and SYNTAXES trials were approved by the ethics committees at each investigating center, and all patients provided their written informed consent prior to participation in the SYNTAX trial. Follow-up was performed in accordance with local law and regulations of each participating institution and complied with the Declaration of Helsinki.

Both BMI and WC measurements were collected at the time of randomization, prior to the index procedure. The patient's baseline BMI was calculated as weight in kilograms divided by height in meters squared. Patients were stratified according to their baseline BMI; Low BMI (<25 kg/m^2) and High BMI (≥25 kg/m^2) on the basis of World Health Organization and National Institutes of Health guidelines,[11] in which patients with BMI ≥25 kg/m^2 were classified as overweight (25.0 to 29.9 kg/m^2) or obese (≥30 kg/m^2).

The patient's baseline WC was measured according to the protocol of the National Cholesterol Education Program (NCEP),[12] in which WC was measured at the level of the upper margin of the iliac crest. Patients were also stratified according to their baseline WC at the time of randomization; Low WC (≤102 cm [40 inches] for men or ≤88 cm [35 inches] for women) and High WC (>102 cm [40 inches] for men or >88 cm [35 inches] for women).[11,12] Finally, patients were divided into 4 groups according to both baseline BMI and baseline WC; Low BMI/Low WC, Low BMI/High WC, High BMI/Low WC, and High BMI/High WC (Figure 1).

Baseline hemoglobin A1c (HbA1c) and C-reactive protein (CRP) were analyzed in an independent central chemistry laboratory (Covance Incorporated, Indianapolis, US, and Geneva, Switzerland).

The primary endpoint of the present study is all-cause death at 10 years. Vital status was confirmed by using electronic healthcare record review and national death registries. Patients with missing vital status were included in the analysis and censored at the time of "lost to follow-up" or at 5 years when recruiting centers did not participate in the SYNTAXES study for 10-year extended follow-up (a total of 5 patients in 2 centers).

Continuous variables are expressed as median and interquartile range (IQR) and are compared using the Mann-Whitney U test. Categorical variables are presented as counts and percentage and are compared using chi-square test or Fisher's exact test as appropriate. Kaplan-Meier method is used to estimate the cumulative rates of events and log-rank test was performed to examine the differences between groups. A scatter plot was drawn between BMI and WC, and the Pearson correlation was used to quantify the relation between BMI and WC.

The incidence of all-cause death up to 10 years was assessed in comparison either among BMI groups or WC groups using unadjusted and adjusted Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). The covariables in the adjusted models included randomization (PCI or CABG), age, sex, medically treated diabetes, hypertension, dyslipidemia, current smokers, previous myocardial infarction (MI), previous cerebrovascular disease, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), creatinine clearance, hemoglobin, left ventricular ejection fraction (LVEF), clinical presentation (silent ischemia, stable angina or unstable angina), achievement of complete revascularization, disease type (LMCAD or 3VD), and anatomical SYNTAX score. The estimated HRs were plotted for each observed pair BMI and WC values as a heat map. The reference for plotted HRs was the hazard at the median values of BMI and WC.

For exploratory purposes, patients were also stratified according to their baseline BMI as follows; underweight/normal weight (≤24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), and obesity (≥30 kg/m^2).[11] The primary endpoint of all-cause death was assessed in these BMI groups with or without WC as sensitivity analysis. Ten-year mortality was also assessed according to the waist-to-height ratio (WHtR) in the following subgroups: low WHtR (<0.50), intermediate WHtR (≥0.50 and <0.60), and high WHtR (≥0.60).[13]

Statistical significance was considered if two-sided p value ≤0.05. All analyses were performed in SPSS Statistics version 26 (IBM Corp., Armonk, 281 N.Y., USA) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Out of 1,800 patients, 1,799 patients (99.9%) had available baseline BMI data with a median value of 27.3 kg/m^2 (IQR: 24.9 to 30.6 kg/m^2). On the other hand, 1,587 patients (88.2%) had available baseline WC data with a median value of 98.0 cm (IQR: 90.0-106.7 cm).

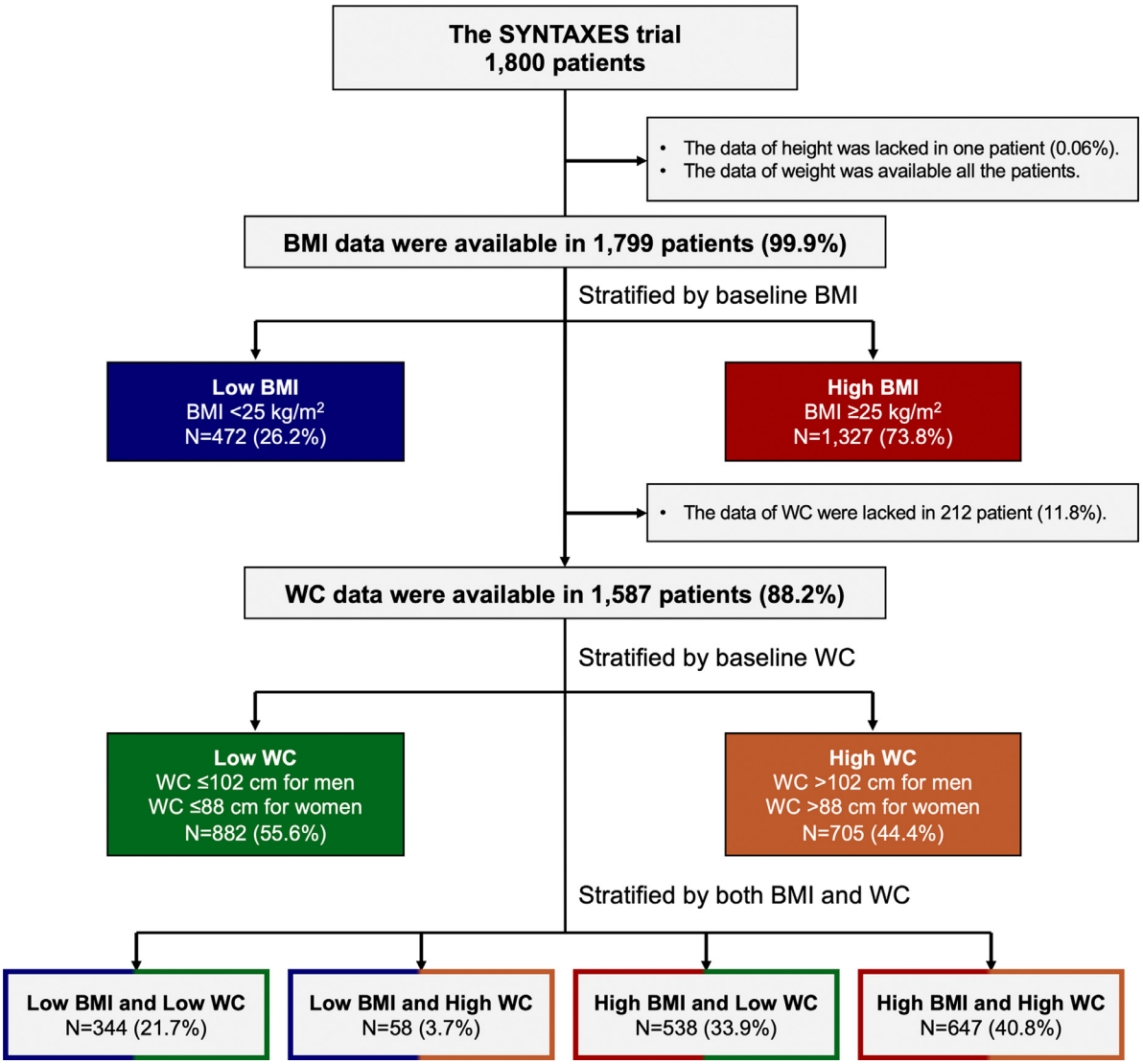


Figure 1. Flowchart of the present study. In the randomized cohort of the SYNTAX trial (N = 1,800), patients were stratified according to baseline BMI and/or WC. BMI: body mass index; WC: waist circumference.

Among 1,799 patients with available BMI data, 472 (26.2%) and 1,327 patients (73.8%) were classified as Low BMI and High BMI, respectively. Whereas, among 1,587 patients with available WC data, 882 (55.6%) and 705 patients (44.4%) were classified as Low WC and High WC, respectively. When stratified by both BMI and WC, 344 (21.7%), 58 (3.7%), 538 (33.9%), and 647 patients (40.8%) were categorized as Low BMI/Low WC, Low BMI/High WC, High BMI/Low WC, and High BMI/High WC, respectively (Figure 1).

The baseline characteristics in patients stratified by the combination of BMI and WC are shown in Table 1 **and Online Table 1**. When compared to patients with High BMI/Low WC, patients with High BMI/High WC were more frequently female, had a higher prevalence of medically treated diabetes as well as insulin dependant diabetes, metabolic syndrome and hypertension, had higher hemoglobin A1c (HbA1c) level and C-reactive protein (CRP) level, had lower creatinine clearance and LVEF, had higher EuroSCORE and Parsonnet SCORE, had lower number of lesions, had lower prevalence of any bifurcational lesions and took angiotensin-coverting enzyme inhibitor and angiotensin receptor blocker more frequently (all $p < 0.05$). There was no significant difference in terms of age between patients with High BMI/Low WC and those with High BMI/High WC.

The scatterplot of BMI and WC is shown in Figure 2. There was a significant though modest correlation between BMI and WC (Pearson r coefficient 0.675; R^2 0.46; $p < 0.001$).

The median durations of the 10-year were 3,653 days (interquartile range [IQR]: 2,796 to 3,653 days). At 10 years, the crude incidence of all-cause death was significantly lower in patients with High BMI compared with those with low BMI, however, after adjustment there was no longer significant difference between 2 groups (Figure 3 **and** Table 2). In contrast, patients with High WC had a significantly higher crude rate of all-cause death at 10 years compared with those with Low WC. The increased mortality risk in High WC over Low WC was consistent even after

Table 1
Baseline characteristics in patients stratified by BMI and WC

Variable	Low BMI		P value	High BMI		P value
	Low WC(N = 344)	High WC(N = 58)		Low WC(N = 538)	High WC(N = 647)	
Body mass index (kg/m^2)	23.2 (21.9-24.2)	23.6 (22.5-24.4)	0.08	27.3 (26.2-29.1)	30.7 (28.3-33.6)	<0.001
Height (cm)	171 (165-178)	167 (160-178)	0.028	170 (166-175)	170 (164-177)	0.64
Weight (kg)	68.0 (62.0-73.0)	64.6 (59.8-75.0)	0.33	81.0 (75.0-86.0)	90.0 (80.0-100.0)	<0.001
Waist circumference (cm)	87 (81-92)	100 (92-104)	<0.001	94 (89-98)	108 (104-115)	<0.001
Randomization			0.48			0.68
PCI	50.9 (175/344)	44.8 (26/58)		50.4 (271/538)	51.6 (334/647)	
CABG	49.1 (169/344)	55.2 (32/58)		49.6 (267/538)	48.4 (313/647)	
Age (year)	67 (60-74)	73 (67-78)	<0.001	65 (57-71)	65 (58-72)	0.85
Sex			<0.001			<0.001
Male	80.8 (278/344)	37.9 (22/58)		90.3 (486/538)	67.9 (439/647)	
Female	19.2 (66/344)	62.1 (36/58)		9.7 (52/538)	32.1 (208/647)	
Medically-treated diabetes	15.1 (52/344)	29.3 (17/58)	0.013	20.1 (108/538)	33.4 (216/647)	<0.001
On insulin	7.0 (24/344)	6.9 (4/58)	1.00	6.3 (34/538)	14.7 (95/647)	<0.001
Hemoglobin A1c (%)	5.8 (5.5-6.2)	6.1 (5.6-6.7)	0.048	5.8 (5.5-6.2)	6.0 (5.6-6.7)	<0.001
C-reactive protein (mg/dl)	0.23 (0.09-0.80)	0.33 (0.12-0.83)	0.23	0.30 (0.11-0.73)	0.42 (0.16-0.93)	<0.001
Metabolic syndrome	15.9 (46/290)	68.6 (35/51)	<0.001	24.6 (111/452)	75.9 (415/547)	<0.001
Hypertension	64.2 (221/344)	67.2 (39/58)	0.77	63.2 (340/538)	69.6 (450/647)	0.022
Dyslipidemia	73.2 (251/343)	75.4 (43/57)	0.87	79.3 (424/535)	78.0 (497/637)	0.62
Current smoking	26.8 (92/343)	17.2 (10/58)	0.14	19.0 (102/537)	18.4 (118/643)	0.82
Previous MI	34.0 (116/341)	46.6 (27/58)	0.08	29.5 (157/533)	33.4 (213/638)	0.16
Previous cerebrovascular disease	14.0 (48/343)	15.5 (9/58)	0.84	13.2 (71/536)	15.1 (97/643)	0.40
Previous stroke	3.5 (12/343)	0.0 (0/58)	0.23	3.7 (20/534)	5.3 (34/644)	0.26
Previous transient ischemic attack	5.5 (19/343)	6.9 (4/58)	0.76	5.4 (29/537)	4.1 (26/640)	0.33
Previous carotid artery disease	7.3 (25/344)	8.6 (5/58)	0.79	7.8 (42/538)	9.1 (59/647)	0.47
Peripheral vascular disease	10.5 (36/344)	19.0 (11/58)	0.08	8.4 (45/538)	9.3 (60/647)	0.61
Chronic obstructive pulmonary disease	6.4 (22/344)	12.1 (7/58)	0.16	7.6 (41/538)	9.7 (63/647)	0.22
Chronic kidney disease	36.5 (113/310)	46.3 (25/54)	0.17	13.1 (64/489)	13.6 (82/601)	0.86
Creatinine clearance (ml/min)	69.0 (55.9-84.1)	63.3 (51.8-74.2)	0.008	82.6 (68.0-101.1)	91.3 (72.2-116.1)	<0.001
Left ventricular ejection fraction (%)	60 (50-65)	58 (44-63)	0.18	60 (55-70)	60 (50-65)	0.001
Congestive heart failure	3.8 (13/342)	3.5 (2/57)	1.00	4.5 (24/533)	5.8 (37/637)	0.36
Clinical presentation			0.62			0.99
Silent myocardial ischemia	16.6 (57/344)	20.7 (12/58)		13.6 (73/538)	13.8 (89/647)	
Stable angina pectoris	52.9 (182/344)	46.6 (27/58)		58.6 (315/538)	58.1 (376/647)	
Unstable angina pectoris	30.5 (105/344)	32.8 (19/58)		27.9 (150/538)	28.1 (182/647)	
EuroSCORE	4 (2-6)	6 (4-7)	<0.001	3 (1-5)	4 (2-6)	0.009
Parsonnet SCORE	5 (3-12)	10 (4-19)	<0.001	6 (3-10)	8 (6-14)	<0.001
Disease type			0.25			0.72
3VD	58.7 (202/344)	67.2 (39/58)		60.4 (325/538)	61.5 (398/647)	
LMCAD	41.3 (142/344)	32.8 (19/58)		39.6 (213/538)	38.5 (249/647)	
Disease type			0.32			0.09
LMCAD only	4.7 (16/344)	1.8 (1/57)		3.9 (21/538)	6.5 (42/647)	
LMCAD+1VD	9.6 (33/344)	3.5 (2/57)		5.9 (32/538)	7.9 (51/647)	
LMCAD+2VD	14.0 (48/344)	12.3 (7/57)		12.1 (65/538)	10.8 (70/647)	
LMCAD+3VD	13.1 (45/344)	15.8 (9/57)		17.7 (95/538)	13.3 (86/647)	
2VD (No LMCAD)	2.6 (9/344)	0.0 (0/57)		1.7 (9/538)	2.0 (13/647)	
3VD (No LMCAD)	56.1 (193/344)	66.7 (38/57)		58.7 (316/538)	59.5 (385/647)	
SYNTAX score	29 (20-37)	29 (21-38)	0.73	27 (21-37)	27 (20-35)	0.08
SYNTAX score tercile			0.94			0.23
Low	30.7 (105/342)	28.6 (16/56)		30.2 (162/537)	34.6 (223/644)	
Intermediate	33.9 (116/342)	35.7 (20/56)		35.4 (190/537)	34.3 (221/644)	
High	35.4 (121/342)	35.7 (20/56)		34.5 (185/537)	31.1 (200/644)	
Number of lesions	4 (3-6)	4 (3-6)	0.60	4 (3-6)	4 (3-5)	0.007
Any total occlusion	22.9 (78/341)	23.2 (13/56)	1.00	24.2 (130/537)	23.5 (151/643)	0.78
Any bifurcation	71.8 (245/341)	75.0 (42/56)	0.75	76.5 (411/537)	70.3 (452/643)	0.018
Number of stents	4 (3-6)	5 (4-7)	0.52	5 (3-6)	5 (3-6)	0.81
Total stent length per patient	80 (48-117)	88 (76-132)	0.12	82 (52-112)	80 (52-112)	0.88
Off pump coronary bypass	14.5 (23/159)	21.9 (7/32)	0.29	14.2 (37/261)	19.8 (60/303)	0.09
Complete revascularization	59.5 (198/333)	54.4 (31/57)	0.47	58.1 (309/532)	61.2 (390/637)	0.28

(*continued*)

Table 1 (*Continued*)

Variable	Low BMI		P value	High BMI		P value
	Low WC(N = 344)	High WC(N = 58)		Low WC(N = 538)	High WC(N = 647)	
Medication at discharge						
Any antiplatelet therapy						
Aspirin	95.1 (312/328)	94.5 (52/55)	0.74	93.6 (494/528)	94.4 (594/629)	0.54
Thienopyridine	60.4 (198/328)	49.1 (27/55)	0.14	59.7 (315/528)	61.2 (385/629)	0.63
Statin	82.0 (269/328)	78.2 (43/55)	0.57	82.2 (434/528)	82.0 (516/629)	1.00
Beta blocker	78.7 (258/328)	76.4 (42/55)	0.72	79.7 (421/528)	83.6 (526/629)	0.09
ACEI	52.7 (173/328)	43.6 (24/55)	0.24	47.7 (252/528)	55.0 (346/629)	0.015
ARB	7.3 (24/328)	18.2 (10/55)	0.018	8.5 (45/528)	13.0 (82/629)	0.018

Data are presented as median (interquartile range) or percentage (number).

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CABG: coronary artery bypass grafting; LMCAD: left main coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; 3VD: three-vessel disease.

adjustment (Figure 3 **and** Table 2). As a continuous variable, WC was an independent predictor of 10-year mortality in adjusted models, whereas BMI was not independently associated with the mortality risk (Table 2).

When patients were divided into 4 groups by both BMI and WC, patients with High BMI/Low WC showed the lowest crude rate of death at 10 years (19.4%), followed by those with High BMI/High WC (29.7%), Low BMI/Low WC (31.7%), and Low BMI/High WC (38.6%) (Figure 4). After adjusting for potential confounders, the risks of all-cause death at 10 years were significantly higher in patients with Low BMI/Low WC, Low BMI/High WC, or High BMI/High WC compared to those with High BMI/Low WC (Figures 5 **and** 6). **Online Table 2** presents the results in the variant adjusted models including different potential confounders, showing the consistency of the results. The heat map of adjusted risk for all-cause death at 10 years demonstrated that patients with higher BMI but lower WC had lower mortality risk, and in contrast, patients with lower BMI but higher WC had higher mortality risk (Figure 6).

When stratified by revascularization mode, similar trends were observed either in PCI or CABG arm (**Online Figure 1 and 2**). The results according to BMI <25.0 kg/m^2 (underweight or normal weight), 25.0 to 29.9 kg/m^2 (overweight), or ≥30 kg/m^2 (obesity), with combination of WC are presented in **Online Figure 3 and 4**. When compared to overweight patients with low WC, overweight patients with high WC had significantly higher risks of all-cause death at 10 years. There were no significant difference in all-cause death among those 3 WHtR groups (**Online Figure 5**).

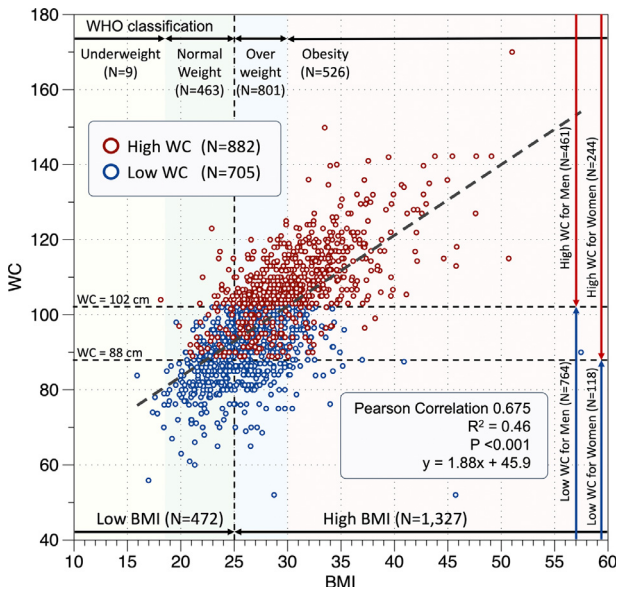


Figure 2. The correlation between BMI and WC. Red and Blue circle indicate High and Low WC, respectively. Yellow, Green, Blue, and Red area indicate Underweight, Normal Weight, Overweight, and Obesity, respectively, according to the definition from WHO. WHO: world health organization; Other abbreviations as in Figure 1.

Discussion

In our study, BMI had a modest correlation with WC (Figure 2), however, BMI and WC showed diverging and opposite associations with crude mortality rate at 10 years (Figure 3). When stratified by both BMI and WC, patients with High BMI/Low WC had the lowest crude 10-year mortality rate, which contributed to the favorable outcome of High BMI group (Figure 4). It can be assumed that the High BMI/Low WC patients might have more lean body mass including organs, bones, and muscle mass, than fat mass. In fact, patients with High BMI/Low WC were more frequently male (90.3%), were less frequently diabetes (especially on insulin), and had significantly lower levels of HbA1c and CRP, compared to those with High BMI/High WC (Table 1), indicating that the High BMI/High WC patients may be the "true obesity" group with more metabolic risks including insulin resistance and proinflammatory conditions, possibly contributing to the worse outcomes compared to High BMI/Low WC group.[14] Recently, Beyhoff et al reported that increased high-sensitivity CRP (hsCRP) level was associated with increase in BMI from normal weight toward severely obese in patients undergoing PCI,[15] and in the all BMI strata, the risk of major adverse cardiac events was significantly higher in those with hsCRP >3.0 mg/L, potentially suggesting the heterogeneity of the obesity group defined only by BMI.

In the present study, the increase of WC was independently associated with an increased 10-year mortality risk,

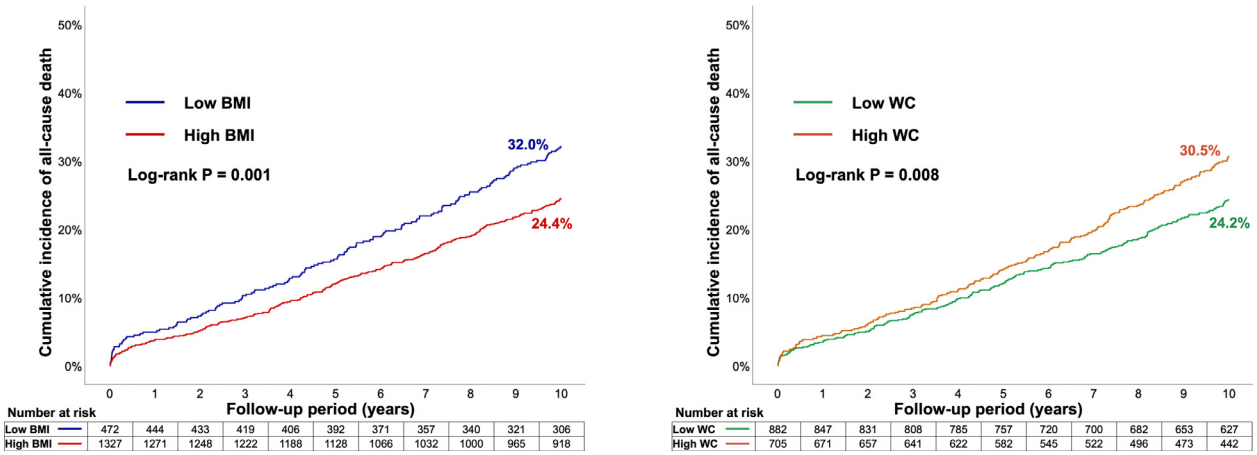


Figure 3. Kaplan-Meier curves for 10-year all-cause death in the BMI groups or WC groups. Kaplan-Meier curves in patients with Low or High BMI (Left), or those with Low or High WC (Right). Abbreviations as in Figure 1.

which was in line with past studies,[16] indicating that WC has a better prognostic performance than BMI in CAD patients. However, patients with Low BMI/Low WC also had a significantly higher mortality at 10 years when compared to those with High BMI/Low WC (Figures 5 and 6). It is plausible that those population included malnourished and frail patients, as suggested by higher age, higher prevalence of CKD and higher EuroSCORE in the population compared to those with High BMI/Low WC (**Online Table 1**). Therefore, if only one index was used (e.g. WC without BMI), clinicians would not be able to discriminate patients with a significantly higher 10-year mortality risk (i.e. Low WC/Low BMI) from the others. Therefore, for risk stratification, the combined use of BMI and WC (or other body composition indices) should be recommended in patients with complex CAD.[1,11]

A number previous of studies have indicated that overweight CAD patients had the lowest mortality risk among BMI subgroups,[2-6] a fact also observed in the current study (**Online Figure 3**). However, in the current study, overweight patients with High WC had significantly higher mortality risk than those with Low WC (**Online Figure 4**), suggesting that the "overweight" category accidentally include relatively healthy subjects with low fat mass. Nevertheless, there are still some unclarified issues regarding the "obesity paradox". Lavie et al reported that the obesity paradox was still present when used percent body fat [17] or lean mass index[18] on top of BMI in patients with CAD. Lee et al reported that WC but not BMI showed U-shape association with cardiovascular outcomes after PCI.[19] Moreover, it has been reported that the obesity paradox was still present even by using WC especially in patients who had atrial fibrillation,[20] or systolic heart failure.[21] In contrast to our study with very long-term follow-up duration (maximum 14 years), those studies had only short/medium-term results, which may not be sufficient to evaluate obesity-related risk appropriately. In addition, differences of population characteristics and/or adjusted confounding factors may compound the discrepancy.[22,23] Moreover, as an important part of the management of obesity, cardiopulmonary fitness and weight reduction may play a critical role in reducing the mortality risk among obesity patients, and therefore, may contribute to the paradox.[24,25] Further studies with various other measurements of body composition, monitoring carefully confounding factors such as the impact of a long-term fitness program on vital prognosis will be needed in the future. Although the combination of BMI with WC can be viewed as a marginal improvement in gaining insight into patient's body composition, our long-term observation provides a simple and pragmatic prognostic risk stratification by combining two simple parameter indirectly related to body composition.

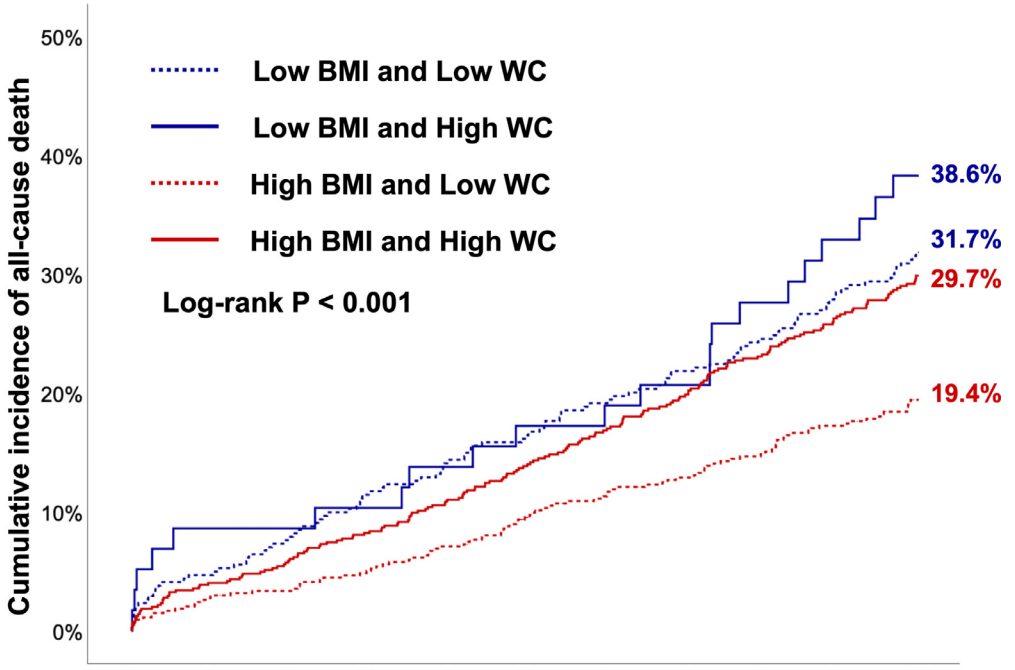
The present study has several strengths, including the prospective characteristic of a randomized trial with minimum exclusion criteria, collection of uniform data by central core laboratory, very long-term follow-up period, and

Table 2
Adjusted hazard ratio for all-cause mortality at 10 years among normal weight, overweight, and obesity patients

	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
High BMI vs. Low BMI	0.73 (0.60-0.88)	0.001	0.86 (0.64-1.15)	0.312
BMI (each 1 kg/m^2 increase)	0.99 (0.97-1.01)	0.267	1.01 (0.98-1.04)	0.535
High WC vs. Low WC	1.30 (1.07-1.57)	0.008	1.45 (1.09-1.93)	0.012
WC (each 1 cm incrase)	1.01 (1.00-1.01)	0.086	1.01 (1.00-1.03)	0.012

* Adjusted covariates are randomization (PCI or CABG), age, sex, medically treated diabetes, hypertension, dyslipidemia, current smokers, previous myocardial infarction, previous cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, creatinine clearance (ml/min), hemoglobin (g/dl), left ventricular ejection fraction, clinical presentation (silent ischemia, stable angina or unstable angina), achievement of complete revascularization, disease type (LMCAD or 3VD), and anatomical SYNTAX score.

Abbreviations as in Table 1.



Number at risk

L-BMI/L-WC	344	324	314	301	291	283	269	260	251	235	224
L-BMI/H-WC	58	53	53	52	50	48	48	46	41	38	34
H-BMI/L-WC	538	523	517	507	494	474	451	440	431	418	403
H-BMI/H-WC	647	618	604	589	572	534	497	476	455	435	408

Figure 4. Kaplan-Meier curves for all-cause death at 10 years in patients stratified by both BMI and WC. Cumulative incidencde of all-cause death up to 10 years in patients with Low BMI/Low WC, Low BMI/High WC, High BMI/Low WC, and High BMI/High WC. Abbreviations as in Figure 1.

high follow-up rate of 93.8% for 10-year vital status (1,688 out of 1,799 included patients). There are also several limitations of the present study that warrant discussion. First, this is a post-hoc analysis of the SYNTAXES study. Although we adjusted a number of confounding variables, the effect of other possible confounding factors cannot be excluded. Second, the number of patients included in our study was relatively smaller than in other past studies assessing the association of BMI with mortality risk in epidemiological studies. Particularly in the Low BMI/High WC group, we might not be able to assess appropriately the relative risks due to the limited prevalence (3.7%), hence the statistical significance of this group might be a play of chance. However, we focused on a specific population with complex CAD (LMCAD or 3VD), who were at high-risk of mortality. Therefore, it would be desirable to dispel the obesity paradox among those high-risk CAD patients with better stratification relying on body compositions.[26] Third, BMI and WC data were only measured at the time of randomization. BMI and WC can change depending on weight gain or loss during the follow-up, which might have an impact on the clinical outcomes.[23] It would have been useful to verify proper group assignment by obtaining BMI and WC at a time close to the patient's death or at termination of the 10-year surveillance period. Fourth, the protocol did not implement other measurements of

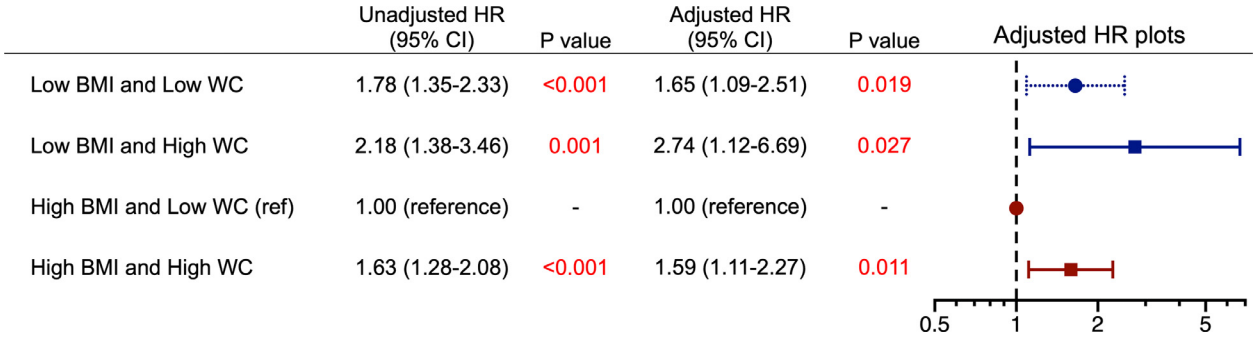


Figure 5. Hazard ratios of all-cause death at 10 years. Adjusted covariates are listed in Table 2. HR: hazard ratio; CI: confidence interval; Other abbreviations as in Figure 1.

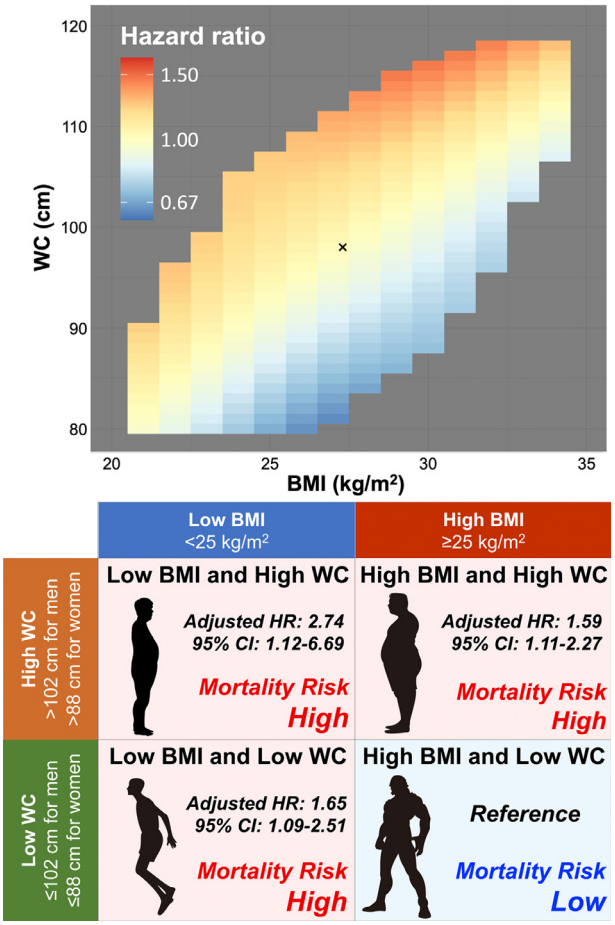


Figure 6. Complementary relationship between BMI and WC in predicting the risk of 10-year mortality. In the heat map of adjusted risk for all-cause mortality at 10 years, "X" indicates the reference point (median value of BMI [27.3 kg/m^2] and WC [98 cm]). Patients with higher BMI but lower WC (the bottom right area of the heat map) had lower mortality risk (bluer), and on the contrast, patients with lower BMI but higher WC (the upper left area of the heat map) had higher mortality risk (redder) at 10 years. When stratified by binary thresholds of BMI (< or ≥25 kg/m^2) and WC (≤ or >102 cm in men or ≤ or >88 cm in women), patients with High BMI/Low WC had the lowest risk of all-cause death at 10 years, whereas the risk was significantly higher in patients with Low BMI/Low WC, Low BMI/High WC, or High BMI/High WC. The adjusted covariates are listed in Table 2. Abbreviations as in Figures 1 and 5.

body composition (e.g. immersion densitometry, skin-fold thicknesses, bioelectrical impedance, or dual energy x-ray absorptiometry bioelectrical impedance)[27] than BMI and WC, which may have been able to provide further insights into the current findings. Finally, the single endpoint in the SYNTAXES study was all-cause death. However, all-cause mortality is the most robust, indisputable (no adjudication needed), and most important outcome for patients which integrates and incorporates all the obesity-related risks, such as oncological and metabolic, and therefore, is an appropriate outcome when considering this type of risk.

In conclusion, when stratified by a combination of BMI and WC, risk of all-cause death at 10 years was significantly higher in patients with Low BMI/Low WC, Low BMI/ High WC, or High BMI/High WC compared to those with High BMI/Low WC.

Credit Author Statement

I (Patrick W. Serruys) is responsible for ensuring that the descriptions are accurate and agreed by all authors.

Authors Contribution

Masafumi Ono gathered, analyzed and interpreted data, wrote the first draft of the article and contributed to all revisions.

Patrick W. Serruys and Yoshinobu Onuma designed the study, gathered and interpreted data and contributed to all revisions.

Michael J. Mack, David R. Holmes, Marie-Claude Morice, Stuart J. Head, Arie Pieter Kappetein, Daniel J.F.M. Thuijs, Friedrick W. Mohr, and Piroze M. Davierwala designed the study, gathered and interpreted data and contributed to critical revision of the manuscript.

Thilo Noack analyzed and interpreted data, wrote the first draft and contributed to revisions.

Hideyuki Kawashima, Hironori Hara, Neil O'Leary, Chao Gao, Rutao Wang, and Kuniaki Takahashi gathered, cleaned data and contributed to revision of the article.

Joanna Wykrzykowska and Jan J. Piek interpreted data and contributed to revision of the article.

John W. McEvoy gathered and interpreted data and contributed to revision of the article.

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Dr. Morice is a shareholder of CERC and ELECTRODUCER, outside the submitted work.

Dr. Head report to work as employee of Medtronic, outside the submitted work.

Dr. Kappetein report to work as employee of Medtronic, outside the submitted work.

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Supplementary materials

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